ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

MENTAL HEALTH

POST ACQUIRED BRAIN INJURY

Cecilia Flores-Sandoval PhD, Swati Mehta PhD, Ujjoyinee Barua MSc, Amber Harnett MSc RN, Laura Rees PhD, Margaret Weiser PhD, Shawn Marshall MD

Disclaimer

This review has been prepared based on the scientific and professional information available up to June 2023. The ERABI information is provided for informational and educational purposes only. If you have or suspect you have a health problem, you should consult your health care provider. The ERABI contributors shall not be liable for any damages, claims, liabilities, costs, or obligations arising from the use or misuse of this material.

Copyright

Flores-Sandoval C, Mehta S, Barua U, Harnett A, Rees L, Weiser M, Marshall S, Teasell R. (2024). Mental Health Post Acquired Brain Injury. In Teasell R, Cullen N, Marshall S, Bayley M, Harnett A editors. Evidence-Based Review of Moderate to Severe Acquired Brain Injury: p1-273.

Funding

This work is supported by the Ontario Ministry of Health. All work produced by ERABI is editorially independent from its funding source.

Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

Contact Information

Evidence-Based Review of Moderate to Severe Acquired Brain Injury

550 Wellington Rd South, London, Ontario, Canada N6C 0A7

Website: www.ERABI.ca

Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of moderate to severe Acquired Brain Injury (ERABI) *Mental Health post Acquired Brain Injury.* Through collaboration of researchers, clinicians, administrators, and funding agencies, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and is committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto) and Dr. Shawn Marshall (University of Ottawa) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

TABLE OF CONTENTS

Preface

About the Authors

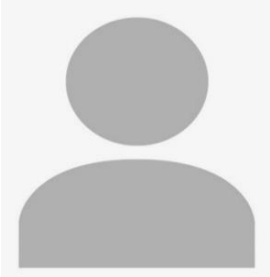
ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

Cecilia Flores-Sandoval, PhD, is the research coordinator of the Evidence-Based Review of Acquired Brain Injury (ERABI). She completed a master's degree and a PhD in Health and Rehabilitation Sciences, field of Health and Aging. Her research interests include aging and rehabilitation, patient engagement and transitional care for older adults.

Swati Mehta, PhD, is a Scientist at Parkwood Institute Research, Lawson Research Institute and Adjunct Assistant Professor in the Department of Physical Medicine and Rehabilitation. She is a registered Psychotherapy with the College of Registered Psychotherapists of Ontario. Her research interest is in improving access to evidence based mental health services for those undergoing rehabilitation through online health programs.

Ujjoyinee Barua, MSc, is a PhD student in the Health and Rehabilitation Sciences program at Western University and is also a Research Assistant at Parkwood Institute. Her primary research area focuses on developing and implementing online mental health programs based on cognitive behavioural therapy (CBT) for caregivers and people with neurological conditions such as traumatic brain injury.

Amber Harnett, MSc, RN, CNF scholar, completed her MSc in pathology and the accelerated BScN program at Western University. Passionate about supporting and advocating for those with acquired brain injuries, she works as a research coordinator to improve healthcare systems through research synthesis, guidelines development, knowledge translation, education, and outreach, in the CORRE lab at Parkwood Institute.



Laura Rees is a neuropsychologist at the Ottawa Hospital.

Margaret Weiser is a clinical psychologist at Parkwood Hospital.

Dr. Shawn Marshall is a physician specializing in Physical Medicine and Rehabilitation (Physiatrist). He is the Division Head of Physical Medicine and Rehabilitation at the University of Ottawa and The Ottawa Hospital where he manages both in-patients and out-patient clinics for patients with concussion to severe traumatic brain injury. Dr. Marshall has a Master's degree in Clinical Epidemiology and is a Full Professor at the University of Ottawa in the Department of Medicine.

Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies.

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amyotrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of

persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Brain Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA). Another factor used to distinguish moderate and severe brain injury is evidence of intracranial injury on conventional brain imaging techniques which distinguish severity of injury from a mild or concussion related brain injury.

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, MEDLINE, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–June 2023 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used

specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the study population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury (as defined in Table 2), and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality randomized controlled trials (RCTs) (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate and the intensity with which it should be provided, based on their individual patient's needs. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with the known limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6

	Prospective Controlled Trial (PCT)	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post Trial	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

MENTAL HEALTH

POST ACQUIRED BRAIN INJURY

Summary of the Evidence

Intervention	Key Point Level of Evidence
MENTAL HEALTH	
Depression	
Non-pharmacological Interventions	
Psychotherapy	Cognitive Behavioural Therapy (CBT) may be an effective treatment for depression following an ABI; however, it may not be more effective than supportive psychotherapy. CBT may be similarly effective when provided in groups or individually over the phone. CBT combined with motivational interviewing or non-directive counselling may be equally effective for the management of depression in individuals with TBI. CBT may improve feelings hopelessness, as well as self-esteem and subjective sexual wellbeing. - *There is 1a evidence (Brenner et al., 2018) that CBT may be an effective treatment for hopelessness post TBI when compared to a waitlist control.* - *There is level 1b evidence (Ponsford et al., 2016) that CBT combined with motivational interviewing or non-directive counselling may be equally effective treatments for depression post TBI when compared to controls.* - *There is level 1b evidence (Fann et al., 2015) and level 2 evidence (Bradbury et al., 2008; Arundine et al., 2012) that CBT may be effective for depression post ABI, and it may be similarly effective when delivered over the phone or in person.* - *There is level 1b evidence (Ashman et al., 2014) that CBT may be no more effective than supportive psychotherapy as a treatment for depression post TBI.* - *There is level 1b evidence (Nguyen et al., 2017) that CBT addressing fatigue and sleep following TBI may reduce depression.* - *There is level 2 evidence (Anson & Ponsford, 2006) that duration of CBT interventions may have no impact on depression in individuals post TBI.* - *There is level 2 evidence (Medd & Tate, 2000) that CBT for anger management may not be effective for depression and self-esteem.* - *There is level 4 evidence (Fraser et al., 2022) that CBT may improve subjective sexuality and self-esteem in individuals with TBI.* Compassion Focused Imagery (CFI) may not be mor effective than Relaxation Imager (RI) for mood, self-compassion and empathy. Compassion Focused Therapy (CFT) may decrease depression symptoms in individuals with ABI.

- *There is level 1b evidence (Campbell et al., 2019) that CFI and RI may not be more effective than RI for the improvement of measures of mood, self-compassion and empathy.*

- *There is level 4 evidence (Ashworth et al., 2015) that CFT may reduce depression post ABI.*

Acceptance and Commitment Therapy (ACT) may reduce depressive symptoms when compared to Befriending Therapy (BT); however, it may not be effective for depression compared to standard care in individuals with moderate to severe TBI.

- *There is level 1b evidence (Sander et al., 2021) that ACT may not be effective for depression when compared to standard care.*

- *There is level 1b evidence (Whiting et al., 2020) that ACT may be effective for depression in individuals with TBI, when compared to Befriending Therapy.*

Positive Psychology may improve happiness post TBI.

- *There is level 2 evidence (Andrewes et al., 2014) that positive psychology may be effective for the improvement of happiness.*

Neuro-Systemic Psychotherapy may be effective for the treatment of depression post TBI.

- *There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may improve depressive mood in individuals with TBI.*

Text message-enhanced behavioural activation therapy may not be different than text message-enhanced attention control for depression post moderate to severe TBI. A telephone intervention combining elements of behavioral activation therapy and problem-solving therapy may improve depression post TBI.

- *There is level 1b evidence (Bombardier et al., 2009) that a telephone intervention incorporating elements of behavioral activation therapy may improve depressive symptoms following a TBI.*

- *There is level 2 evidence (Hart et al., 2020) that text message-enhanced behavioural activation therapy may not be different than attention control session combined with text messages for depressive symptoms in individuals with TBI.*

Mindfulness-Based Stress Reduction (MBSR) may be effective at reducing depressive symptoms in individuals with TBI. However, it may not impact severity.

- *There is level 4 evidence (Combs et al., 2018) that MBSR may be an effective at reducing symptoms of depression post TBI.*

Psychoeducation	Psychoeducation may not be an effective treatment for depression following TBI. - *There is level 1b evidence (Bell et al., 2011) that psychoeducation delivered on the phone may not be more effective than usual care for mood in individuals with TBI.* - *There is level 2 evidence (Sinnakaruppan et al., 2005) that an educational program for individuals with TBI and their caregivers may not decrease depression.* - *There is level 4 evidence (Neumann et al., 2017) that psychoeducation may not be effective for the treatment of depression in individuals with TBI.*
Art Therapy	Art Therapy may be effective for the reduction of depressive symptoms post severe TBI. - *There is level 2 evidence (Di Vita et al., 2022) that art therapy may reduce symptoms of depression in individuals with severe TBI.*
Music Therapy	There is conflicting evidence regarding the use of music therapy to alleviate depression following ABI. - *There is conflicting level 2 evidence (Siponkoski et al., 2022; Thaut et al., 2009) and level 4 evidence (Guétin et al., 2009) regarding the effectiveness of music therapy for depression in individuals with ABI.*
Physical Activity	Aerobic exercise may be effective for depression post ABI. Exercise using an elliptical machine, or a treadmill might not be effective for depression. - *There is level 1b evidence (Bellon et al., 2015) that walking may be effective for improvement of depression.* - *There is level 3 evidence (Gordon et al., 1998), and level 4 evidence (Weinstein et al., 2017) that aerobic exercise may be effective for mood in individuals with TBI.* - *There is level 4 evidence (Chin et al., 2015) that aerobic exercise using an elliptical machine, or a treadmill may not improve depression in individuals with TBI.* Exercise at a fitness center may not be different than exercising at home for depression in individuals with severe TBI. - *There is level 1b evidence (Hassett et al., 2009) that exercising at a fitness center is no more effective than exercising at home for depression and psychological function post severe TBI.* Tai Chi, and Dance therapy may improve symptoms of depression in individuals with ABI. - *There is level 1a evidence (Sarkamo et al., 2021) that dance therapy might reduce symptoms of depression post ABI.*

	- *There is level 1b evidence (Blake & Batson, 2009) that Tai Chi may improve mood compared to wait-list controls following TBI.* A yoga-based mindfulness group intervention may not be effective for depression post TBI. - *There is level 4 evidence (Combs et al., 2018) that a yoga-based mindfulness group intervention may not be effective for the management of depression post TBI.* Cycle ergometer aerobic training may not be more effective than relaxation training for depression in those with severe ABI. - *There is level 1b evidence (Bateman et al., 2001) that cycle ergometer aerobic training may not be effective for depression post severe ABI, compared to relaxation training.*
Rehabilitation Programs	Community-based rehabilitation may not improve depression post TBI. Depression may not mediate cognitive functioning and psychosocial outcomes following post-acute multidisciplinary rehabilitation. - *There is level 1b evidence (Wade et al., 1998), level 2 evidence (Powell et al., 2002) and level 4 evidence (Feigner et al., 2023; Schonberger et al., 2014) that community-based rehabilitation programs alone and specialist follow-up may not improve depression post TBI, and that depression may not mediate cognitive functioning and psychosocial outcomes following post-acute rehabilitation.* Holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for depression than conventional neuropsychological rehabilitation. - *There is 1b evidence (Mendes et al., 2021) that holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for depression than conventional neuropsychological rehabilitation.* Self-awareness training and goal-based rehabilitation may not be effective for depression post TBI. - *There is level 1b evidence (Schmidt et al., 2013) that video feedback for self-awareness rehabilitation may not be different than verbal or experiential feedback for depression post TBI.* - *There is level 1b evidence (Hart & Vaccaro, 2017) that a goal intention intervention with reminders via text messages may not improve depression post severe TBI.*
Cognitive Rehabilitation	Cognitive rehabilitation with the assistance of technology may reduce depressive symptoms in individuals with moderate to severe TBI; however, instant messaging or cognitive training alone may not improve depression in individuals with severe TBI.

- *There is level 1b evidence (Corallo et al., 2022; De Luca et al., 2023) that cognitive rehabilitation with the assistance of a humanoid robot or non-immersive virtual reality may improve depression, coping and well-being in individuals with ABI.*

- *There is level 1b evidence (Bergquist et al., 2009) that cognitive rehabilitation delivered with the assistance of instant messaging may not improve depression post severe TBI.*

- *There is level 1b evidence (Cantor et al., 2014) that a Short-Term Executive Plus (STEP) cognitive Rehabilitation Program may not improve emotion regulation or depression post TBI.*

Intensive cognitive retraining and psychosocial functioning rehabilitation may be equally effective for the reduction of depressed mood post TBI; however, attention training may not be more effective than memory training for depression post TBI.

- *There is level 1b evidence (Ruff & Niemann, 1990) that a cognitive remediation program and a functional rehabilitation program focusing on psychosocial functioning may be equally effective for improving depression in individuals with TBI.*

- *There is level 2 evidence (Ruff et al., 1994) that attention and memory training may not be different for the improvement depression post TBI.*

While Time Management Training, Attentional Training and Modified Short Memory Technique may not improve mood and well-being, problem-solving training seem to have a positive effect.

- *There is level 1b evidence (Chiaravalloti et al., 2016) and level 2 evidence (Dundon et al., 2015; Fasotti et al. 2000; McMillan et al., 2002) that time pressure management training, attentional training and modified short memory technique may not be effective for mood and well-being post TBI.*

- *There is level 2 evidence (Rath et al., 2003) that problem-solving training and attention process training may improve self-esteem and mood post TBI.*

Cognitive didactic-training may not improve depressed mood, compared to functional-experiential treatment. Similarly, errorless learning may not improve mood, compared to error-based learning.

- *There is level 1b evidence (Ownsworth et al., 2017; Vanderploeg et al., 2008) that cognitive-didactic training and errorless learning may not improve depression post TBI, compared to functional-experiential training and error-based training respectively.*

In-hospital cognitive rehabilitation may not be different than home rehabilitation with telephone support for depression post TBI.

- *There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for depression post moderate to severe TBI.*

Transcranial Magnetic Stimulation	Transcranial magnetic stimulation (rTMS) may not be effective for the improvement of symptoms of depression in individuals with moderate to severe TBI. - *There is level 1b evidence (Rodrigues et al., 2020) that repetitive transcranial magnetic stimulation (rTMS) may not be effective for the management of depression post TBI.*
Transcranial direct current stimulation	Transcranial direct current stimulation (tDCS) may not improve depressive symptoms in individuals with moderate to severe TBI. - *There is level 1a evidence (Rushby et al., 2021) and level 2 evidence (Sacco et al., 2016) that transcranial direct current stimulation (tDCS) may not improve depression post TBI.*
Peer Support	Peer support may not be effective for the management of depression post moderate to severe TBI. - *There is level 1b evidence (Levy et al., 2021) and level 2 evidence (Hanks et al., 2012; Struchen et al., 2011) that peer support may not improve depression in individuals with TBI.*
Social Skills Training	Social skills training may not be effective in improving depression in individuals with TBI. - *There is level 1b evidence (McDonald et al., 2008) that a social skills training programs may not improve depression post TBI.*
Light Therapy	Light therapy using bright white light, blue light or yellow light may not be effective for depression in individuals with moderate to severe TBI. - *There is level 1a (Connolly et al., 2021) and level 1b evidence (Bell et al., 2021) that exposure to bright white light may not be effective for the management of depression post TBI.* - *There is level 1b evidence (Sinclair et al., 2014) that blue light may not be different than yellow light for depression following a TBI.* Blue-enriched white light, compared to no light therapy, may improve depressive symptoms with sustained effects at 6 weeks in individuals with moderate to severe TBI. - *There is level 1b evidence (Quera-Salva et al., 2020) that blue enriched white light may improve depression post TBI, compared to no light therapy.*
Biofeedback Training	Biofeedback training may improve depressive symptoms in individuals with moderate to severe TBI. - *There is level 1b evidence (Wearne et al., 2021) that biofeedback may improve depressive symptoms post TBI.*

	- *There is level 4 evidence (Elbogen et al., 2021) that a mobile neurofeedback device may reduce depressive symptoms in individuals with TBI.*
Therapeutic Writing	A writing intervention may not improve depressive symptoms in individuals with moderate to severe TBI. - *There is level 1b evidence (Bugg et al., 2009) that writing as a self-help intervention may not improve depression following a TBI.*
Pharmacological Interventions	
Sertraline	Sertraline may not be effective to treat major depression in individuals with moderate to severe TBI. - *There is level 1b evidence (Ashman et al., 2009; Fann et al., 2017) that sertraline may not be more effective than placebo for managing major depression post TBI.* Sertraline may improve depressive symptoms in the first three months compared to placebo; however, effects may not be sustained after six months. - *There is level 1b (Novack et al., 2009) and level 4 evidence (Kant et al., 1998) that sertraline may improve depression symptoms in the first four weeks to 3 months; however, effects may not be maintained after six months to a year.*
Amantadine	Amantadine may not be effective for depression in individuals with moderate to severe TBI. - *There is level 1b (Hammond et al., 2014) that amantadine may not be effective for the management of depression post TBI.*
Desipramine	Desipramine may be an effective treatment for major depression post TBI; however, further research is required. - *There is level 2 evidence (Wroblewski et al., 1996) that desipramine may improve major depression in moderate to severe TBI compared to placebo. However, more research is needed to determine its effectiveness.*
Huperzine A	Huperzine A may not be an effective treatment for depression in individuals with TBI. - *There is level 1b evidence (Zafonte et al., 2020) that Huperzine A may not improve depression in individuals with TBI.*

Risperidone	Risperidone may not be effective in reducing depressive symptoms post TBI. - *There is level 1b evidence (Deb et al., 2020) that risperidone may not be effective for the management of depression in individuals with TBI.*
Methylphenidate	Further research is needed to determine whether or not methylphenidate may improve mood in individuals with moderate to severe TBI. - *There is level 1a evidence (Gualtieri & Evans, 1988; Jenkins et al., 2019) that methylphenidate may improve mood in individuals with severe TBI; however, more research is needed.*
Cerebrolysin	Cerebrolysin may be effective for depression in individuals with a moderate to severe TBI. - *There is level 1b evidence (Muresanu et al., 2020; Poon et al., 2020) that cerebrolysin may improve depression post TBI.*
Rivastigmine	There is conflicting evidence regarding the effectiveness of rivastigmine for depression following a moderate to severe TBI. Further research is needed. - *There is conflicting level 1a evidence (Tenovuo et al., 2009) and level 1b evidence (Silver et al., 2006; 2009) regarding the efficacy of rivastigmine for the treatment of depression post TBI. Further research is required.*
Dextroamphetamine	Dextroamphetamine may not reduce depressive symptoms post moderate to severe TBI. - *There is level 1b evidence (Hart et al., 2018) that dextroamphetamine may not be effective for depression in individuals with TBI.*
Recombinant Human Growth Hormone	Recombinant human growth hormone (rhGH) may not improve depression, when compared to placebo, in individuals with moderate to severe TBI. - *There is level 1b evidence (Dubiel et al., 2018; High et al., 2010) that recombinant human growth hormone (rhGH) may not be effective for depression post TBI, compared to placebo.*
Melatonin	Melatonin may not be effective for depression following a moderate to severe TBI, compared to placebo or to amitriptyline. - *There is level 1a evidence (Grima et al., 2018) that melatonin may not improve depression post TBI, compared to placebo.* - *There is level 2 evidence (Kemp et al., 2004) that melatonin may not be more effective than amitriptyline for depression post TBI.*

Modafinil	Modafinil may not improve depression in individuals with a moderate to severe TBI. - *There is level 1b evidence (Jha et al., 2008) that modafinil may not improve depression post TBI, compared to placebo.*
Phenytoin	Phenytoin may not be effective for mood and psychosocial functioning, compared to placebo, in individuals with a moderate to severe TBI. Further research is needed. - *There is level 1b evidence (Dikmen et al., 1991) that phenytoin may not improve mood and psychosocial functioning post TBI compared to placebo.*
Bradycor	Bradycor may be ineffective for the management of depression post severe TBI, and it may cause an increase in depressive symptoms. Further research is needed to examine the efficacy and safety of this medication. - *There is level 1b evidence (Marmarou et al., 1999) that bradycor may not improve depression post severe TBI and it may be associated with an increase in depressive symptoms.*
Combination Therapy	Citalopram combined with carbamazepine may improve major depression in individuals with moderate to severe TBI. - *There is level 4 evidence (Perino et al., 2001) that a combination of citalopram and carbamazepine may be an effective treatment for major depression post TBI.*
Fish Oil Supplementation	Enteral nutrition enriched with fish oil supplementation may not prevent the development of depression post ICU discharge in individuals with polytrauma and severe TBI. - *There is level 1b evidence (Kagan et al., 2021) that enteral nutrition with fish oil supplementation may not prevent depression after ICU discharge in individuals with severe TBI.*
Anxiety	
Non-Pharmacological Interventions	
Psychotherapy	Cognitive behavioural therapy (CBT) combined with Motivational Interviewing (MI) and Non-Directive Counselling (NDC) may improve anxiety post TBI, compared to a waitlist control. Cognitive behavioural therapy (CBT) combined with Motivational Interviewing (MI) may be more effective for anxiety and coping skills.

	- *There is level 1a evidence (Ponsford et al., 2006) that CBT combined with MI and NDC may be an effective treatment for anxiety post TBI, compared to waitlist controls.* - *There is level 1b evidence (Hsieh et al., 2012a; 2012b) that CBT combined with MI may be more effective for the management of anxiety and coping skills post TBI.* A 10-week CBT-based coping skills intervention may not be more effective for anxiety than a 5-week intervention. - *There is level 2 evidence (Anson & Ponsford, 2016) that delivering a CBT-based coping skills intervention for 10 weeks may not be more effective for anxiety than a 5-week intervention.* Cognitive behavioural therapy (CBT) delivered in a group or individually over the telephone, may be equally effective for the management of anxiety post ABI. - *There is level 2 evidence (Arundine et al., 2012; Bradbury et al.,2008) that CBT delivered in a group and individually via telephone may be similarly effective in reducing anxiety following ABI.* Neuro-systemic psychotherapy may be effective for the treatment of anxiety post TBI. - *There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may improve anxiety in individuals with TBI.* Acceptance and Commitment Therapy (ACT) may reduce anxiety and psychological distress, compared to standard care. - *There is level 1b evidence (Sander et al., 2021) that ACT may be effective for anxiety and psychological distress when compared to standard care.*
Psychoeducation	Psychoeducation focused on cognitive abilities may not improve anxiety symptoms post moderate to severe TBI. - *There is level 2 evidence (Sinnakaruppan et al., 2005) that an educational program for individuals with TBI and their caregivers focused on cognitive abilities may not decrease anxiety.* Psychoeducation involving emotion recognition and self-awareness training may improve anxiety symptoms following a moderate to severe TBI. - *There is level 4 evidence (Neumann et al., 2017) that psychoeducation that involves emotion recognition and self-awareness may be effective for anxiety in individuals with moderate to severe TBI.*

Transcranial Magnetic Stimulation	Transcranial magnetic stimulation (rTMS) may not be effective for the improvement of anxiety in individuals with moderate to severe TBI. - *There is level 1b evidence (Rodrigues et al., 2020) that repetitive transcranial magnetic stimulation (rTMS) may not be effective for the management of anxiety post TBI.*
Transcranial direct current stimulation	Transcranial direct current stimulation (tDCS) may not improve anxiety in individuals with moderate to severe TBI. - *There is level 1a evidence (Rushby et al., 2021) that transcranial direct current stimulation (tDCS) may not improve anxiety post TBI.*
Biofeedback Training	Biofeedback training may not improve anxiety post severe TBI. - *There is level 1b evidence (Wearne et al., 2021) that Biofeedback training may not improve symptoms of anxiety in individuals with severe TBI.*
Physical Activity	Yoga- based therapy may not improve anxiety in individuals with moderate to severe TBI. - *There is level 1a evidence (Krese et al., 2020) that yoga-based therapy may not improve anxiety post TBI when compared to conventional physical therapy or seated physical activity.* Exercise at a fitness center may not be more effective for anxiety following severe TBI than exercising at home. - *There is level 1b evidence (Hassett et al., 2009) that exercising at a fitness center is no more effective than exercising at home for anxiety post severe TBI.* Cycle ergometer aerobic training may not be more effective than relaxation training for anxiety in those with severe ABI. - *There is level 1b evidence (Bateman et al., 2001) that cycle ergometer aerobic training may not be effective for anxiety post severe ABI, compared to relaxation training.*
Social Skills Training	Social skills training may not be effective in improving anxiety in individuals with TBI. - *There is level 1b evidence (McDonald et al., 2008) that a social skills training programs may not improve anxiety post TBI.*
Rehabilitation Programs	A home-based goal-oriented rehabilitation program may improve anxiety post severe TBI; however, goal intentions delivered via text message may not be effective.

	- *There is 1b evidence (Borgen et al., 2023) that a home-based goal-oriented rehabilitation program delivered via phone call or videoconference may improve symptoms of anxiety at 12 months.* - *There is level 1b evidence (Hart & Vaccaro, 2017) that a goal intention intervention with reminders via text messages may not improve anxiety post severe TBI.* Participation in physiotherapy and occupational therapy may lower the risk of anxiety. - *There is level 2 evidence (Yeh et al., 2020) that participation in physiotherapy and occupational rehabilitation programs post TBI may prevent the development of anxiety post TBI.* Factors such as race, insurance status, and premorbid mental may impact anxiety trajectories following participation in inpatient rehabilitation. - *There is level 2 evidence (Neumann et al., 2022) that factors such as insurance status, race and pre-TBI mental health status may impact anxiety trajectories following inpatient rehabilitation.* Holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for anxiety than conventional neuropsychological rehabilitation. - *There is level 1b evidence (Mendes et al., 2021) that holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for anxiety than conventional neuropsychological rehabilitation.* Self-awareness training may not be effective for anxiety and stress post TBI. - *There is level 1b evidence (Schmidt et al., 2013) that video feedback for self-awareness rehabilitation may not be different than verbal or experiential feedback for stress and anxiety post TBI.* A community outreach program may not be more effective than an information booklet of resources for anxiety post severe TBI. - *There is level 2 evidence (Powell et al., 2002) that an outreach community intervention may not improve anxiety post severe TBI, compared to an information booklet only.*
Cognitive Rehabilitation	Participation in cognitive rehabilitation programs, with or without the assistance of technology, may improve anxiety symptoms post moderate to severe ABI.

	- *There is level 1b evidence (Corallo et al., 2022; De Luca et al., 2023) and level 4 evidence (Afsar et al., 2021) that cognitive rehabilitation, either manualized or with the assistance of a humanoid robot or non-immersive virtual reality, may improve anxiety in individuals with ABI.* Attentional training and modified short memory technique may not improve anxiety post TBI. - *There is level 1b evidence (Chiaravalloti et al., 2016) and level 2 evidence (Dundon et al., 2015; McMillan et al., 2002) that attentional training and modified short memory technique may not be effective for anxiety post TBI.* Errorless learning may not improve anxiety, compared to error-based learning in individuals with severe TBI. - *There is level 1b evidence (Ownsworth et al., 2017) that errorless learning may not improve anxiety post severe TBI, compared to error-based learning.* In-hospital cognitive rehabilitation may not be different than home rehabilitation with telephone support for anxiety post TBI. - *There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for anxiety post moderate to severe TBI.*
Peer Support	Peer support may not be effective for the management of anxiety post moderate to severe TBI. - *There is level 2 evidence (Hanks et al., 2012) that peer support may not improve anxiety symptoms in individuals with TBI.*
Therapeutic Writing	A writing intervention may not improve symptoms of anxiety in individuals with moderate to severe TBI. - *There is level 1b evidence (Bugg et al., 2009) that writing as a self-help intervention may not improve anxiety post TBI.*
Pharmacological Interventions	
Sertraline	Sertraline may not be effective to treat anxiety in individuals with moderate to severe TBI. - *There is level 1b evidence (Ashman et al., 2009; Fann et al., 2017) that sertraline may not be more effective than placebo for anxiety post TBI.*
Amantadine	Amantadine may not be effective for the treatment of anxiety in individuals with moderate to severe TBI.

	- *There is level 1b evidence (Hammond et al., 2014) that amantadine may not be effective for the management of anxiety post TBI.*
Methylphenidate	Methylphenidate may not improve anxiety post TBI; further research is needed. - *There is level 1a evidence (Jenkins et al., 2019) that methylphenidate may not improve anxiety in individuals with severe TBI; however, more research is needed.*
Risperidone	Risperidone may not be effective in reducing symptoms of anxiety post TBI. - *There is level 1b evidence (Deb et al., 2020) that risperidone may not be effective for the management of anxiety in individuals with TBI.*
Cerebrolysin	There is conflicting evidence regarding the efficacy of cerebrolysin for anxiety symptoms post TBI. More research is required. - *There is conflicting level 1b evidence (Muresanu et al., 2020; Poon et al., 2020) that cerebrolysin may have an effect on anxiety; however, further research is needed.*
Melatonin	Melatonin may be effective for anxiety following a moderate to severe TBI compared to placebo; however, it may not decrease anxiety when compared to amitriptyline. - *There is level 1a evidence (Grima et al., 2018) that melatonin may decrease anxiety post TBI, compared to placebo.* - *There is level 1b evidence (Kemp et al., 2004) that melatonin may not decrease anxiety, compared to amitriptyline*.
Fish Oil Supplementation	Enteral nutrition enriched with fish oil supplementation may not prevent the development of anxiety post ICU discharge in individuals with polytrauma and severe TBI. - *There is level 1b evidence (Kagan et al., 2021) that enteral nutrition with fish oil supplementation may not prevent anxiety after ICU discharge in individuals with severe TBI.*
Lisdexamfetamine Dimesylate	Further research is needed to determine the effects of Lisdexamfetamine Dimesylate on depression post moderate to severe TBI. - *There is level 1a evidence (Tramontana et al., 2014) that Lisdexamfetamine Dimesylate may not have an effect on depression post TBI; however, further research is needed.*

Post-Traumatic Stress Disorder	
Non-Pharmacological Interventions	
Interventions for the Management of PTSD	A resilience intervention may help reduce PTSD symptoms post TBI. - *There is level 1b evidence (Assonov et al., 2021) that a resilience intervention may help reduce PTSD symptoms in individuals with TBI.* A writing intervention may not decrease PTSD symptoms in those with a TBI. - *There is level 1b evidence (Bugg et al., 2009) that writing as a self-help intervention may not improve symptoms of PTSD following a TBI.* Cognitive rehabilitation supported by technology may decrease PTSD symptoms among veterans with TBI. - *There is level 2 evidence (Elbogen et al., 2019) that a cognitive rehabilitation intervention supported by technology may decrease PTSD symptoms in veterans with TBI.* Long-term neuropsychological support that includes adaptative coping strategies may promote post-traumatic growth in individuals with ABI. - *There is level 2 evidence (Igoe et al., 2023) that long-term neuropsychological support that includes adaptative coping strategies may promote post-traumatic growth in individuals with ABI who attended post-acute inpatient multidisciplinary rehabilitation.* Mobile neurofeedback with a portable EEG headset may decrease PTSD symptoms post TBI. - *There is level 4 evidence (Elbogen et al, 2021) that mobile neurofeedback using a portable EEG headset linked to an application on a mobile device may reduce PTSD symptoms in individuals with TBI.*
Pharmacological Interventions	
Fish Oil Supplementation	Enteral nutrition enriched with fish oil supplementation may not prevent the development of PTSD post ICU discharge in individuals with polytrauma and severe TBI. - *There is level 1b evidence (Kagan et al., 2021) that enteral nutrition with fish oil supplementation may not prevent PTSD after ICU discharge in individuals with severe TBI.*
Suicidal Ideation	
Non-Pharmacological Interventions	

Interventions for Suicide Ideation	Group-based Cognitive Behavioural Therapy (CBT) may be an effective intervention for reducing feelings of hopelessness, a precursor of suicidal ideation, post TBI. - *There is level 1a evidence (Brenner et al., 2018; Simpson et al., 2011) that CBT may be effective in reducing hopelessness; however, it may not be effective for suicide ideation.* Problem-solving therapy may be a feasible intervention for reducing suicidal ideation post TBI; further research is required to determine its efficacy. - *There is level 4 evidence (Barnes et al., 2017) that problem-solving therapy may be a feasible intervention for suicide prevention post TBI; however more research is needed to determine its efficacy.* Mobile neurofeedback using a portable EEG headset may reduce suicidal ideation in veterans with TBI and PTSD. - *There is level 4 evidence (Elbogen et al., 2021) that mobile neurofeedback may decrease suicidal ideation in veterans with TBI and PTSD.*
Substance Use Disorders	
Non-Pharmacological Interventions	
Programs for the Management of Substance Use	An Adapted Screening and Brief Intervention (ASBI) may not be more effective than a Screening and Education with Attention control (SEA) intervention for number of drinks consumed or alcohol abstinence in individuals with moderate to severe TBI. - *There is level 1b evidence (Bogner et al., 2021) that an Adapted Screening and Brief Intervention (ASBI) may not be more effective than a Screening and Education with Attention control (SEA) intervention for alcohol misuse following a TBI.* Motivational interviewing and education may not reduce substance abuse following a TBI. - *There is level 2 evidence (Ponsford et al., 2012; Sander et al., 2012; Tweedly et al., 2012) that motivational interviewing and education may not reduce frequency or intensity of substance consumption post TBI.* Neuro-systemic therapy may not improve addictive disorders in those with severe TBI. - *There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may not improve addictive disorders post severe TBI.* Long-term substance use programs may reduce substance consumption and may increase abstinence in individuals with TBI.

	- *There is level 4 evidence (Bogner et al., 1997) that a long-term substance abuse program may reduce substance consumptions and may increase abstinence post TBI.*
Peer Support	Peer support may be effective for the management of alcohol use post moderate to severe TBI. However, more research is needed. - *There is level 2 evidence (Hanks et al., 2012) that peer support may decrease alcohol use in individuals with TBI.*
BEHAVIOUR	
Agitation, Anger and Aggression	
Non-Pharmacological Interventions	
Psychotherapy	Cognitive Behavioural Therapy (CBT) may be effective for the management of anger expression and feelings of aggression in individual with moderate to severe TBI. The duration of CBT may not have an impact on anger post TBI. - *There is level 2 evidence (Medd & Tate, 2000) and level 4 evidence (Aboulafia-Brakha et al., 2013; Walker et al., 2010) that CBT may improve anger expression and feelings of aggression post TBI.* - *There is level 2 evidence (Anson & Ponsford, 2006) that duration of CBT interventions may have no impact on depression in individuals post TBI.* Neuro-systemic psychotherapy may improve hostility following a moderate to severe TBI. - *There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may improve hostility in individuals with TBI.* Motivational Interviewing delivered over the phone post discharge may improve behaviour in individuals with moderate to severe TBI. - *There is 1b evidence (Bell et al., 2005) that motivational interviewing via follow-up telephone calls may improve behaviour post TBI.*
Rehabilitation Programs	Anger self-management training programs, comprehensive social and cognitive rehabilitation, as well as behavioural support interventions may be effective for behavioural disorders such as anger and aggression management following TBI, with additional benefits for significant others. - *There is level 1b (Ponsford et al., 2022) that a positive behaviour support intervention with a focus on goal achievement may improve confidence of close others in addressing challenging behaviour.*

	- *There is level 1b evidence (Hart et al., 2017; Aboulafia-Brakha & Ptak, 2016; McDonald et al., 2021; Hart et al., 2012) that anger self-management training may help reduce anger and aggression post TBI.* - *There is level 2 evidence (Carnevale et al., 2006) that behavioural modification programs may improve aggressive behaviour and disinhibition post TBI.* - *There is level 2 evidence (Pachalska et al., 2019) that comprehensive rehabilitation including both social skills and cognitive rehabilitation may be more effective than social or cognitive rehabilitation alone for behavioural disorders associated with TBI.* - *There is level 4 evidence (Feeney & Ylvisaker, 1995; Burke et al., 1988) that a behavioral intervention addressing antecedent conditions may decrease aggressive behaviour post TBI.*
Cognitive Rehabilitation	Cognitive rehabilitation may be effective for behavioral disorders such as anger and disinhibition following TBI. - *There is level 1b evidence (Cantor et al., 2014) and level 2 evidence (Elbogen et al., 2019) that a cognitive rehabilitation may be effective for the management of behaviour, including disinhibition and anger post TBI.* Cognitive-didactic training may not improve anger or irritable behaviour post moderate to severe TBI. - *There is level 1b evidence (Vanderploeg et al., 2008) that cognitive-didactic training may not improve irritability and anger post TBI, compared to functional-experiential training.* Error-based learning may be more effective for behavioural competency in individuals with severe TBI., compared to errorless learning. - *There is level 1b evidence (Ownsworth et al., 2017) that error-based learning may improve behavioral competency post severe TBI, compared to errorless learning.* In-hospital cognitive rehabilitation may not be different than home rehabilitation with telephone support for aggressive behaviour post TBI. - *There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for social behaviour post TBI.*
Emotion Recognition	There is conflicting evidence regarding the effectiveness of facial emotion recognition programs for behaviour post TBI. - *There is conflicting evidence (Neumann et al., 2015; Radice-Neumann et al., 2009) that a program addressing recognition of facial emotions may be effective for irritability and aggression in individuals with TBI.*

Psychoeducation	Psychoeducation may be effective for anger post TBI; however, further research is needed. - *There is level 4 evidence (Neumann et al., 2017) that psychoeducation may be effective for the management of anger in individuals with TBI.*
Music Therapy	Listening to preferred music may decrease agitation in individuals with severe TBI. - *There is level 1a evidence (Park et al., 2016) that preferred music may reduce agitation in individuals with severe TBI who present with agitated behaviour in acute care.* Music therapy may reduce post-coma agitation following ABI. - *There is level 4 evidence (Formisano et al., 2001) that music therapy may reduce post-coma agitation in individuals with ABI; however, further research is needed.*
Biofeedback Training	Biofeedback training may be effective for anger in individuals with moderate to severe TBI. - *There is level 4 evidence (Elbogen et al., 2021) that a mobile neurofeedback device may reduce anger in individuals with TBI.*
Peer Support	Peer support may be effective for the management of behavioural dyscontrol post moderate to severe TBI. However, more research is needed. - *There is level 2 evidence (Hanks et al., 2012) that peer support may decrease behavioural dyscontrol in those with moderate to severe TBI.*
Sensory Stimulation	Auditory and tactile stimulation delivered by a family member may decrease agitation in individuals admitted to the ICU decreased consciousness post severe TBI. - *There is level 1b evidence (Sedghi et al., 2020) that auditory and tactile stimulation may decrease agitation in individuals with decreased consciousness.*
Post-Traumatic Amnesia Interventions	Activities of daily living retraining during or after PTA may not have an effect on agitated behaviour in individuals with severe TBI. - *There is level 1b evidence (Trevena-Peters et al., 2018) that activities of daily living retraining during the period of PTA or after emergence from PTA may not be different for agitation in individuals with TBI.*

Pharmacological Interventions	
Sertraline	Sertraline may be an effective treatment for irritability; however, it may not be effective for the management of aggression and anger in those with moderate to severe TBI. - *There is level 1b evidence (Banos et al., 2010; Fann et al., 2017) that sertraline may not reduce challenging behaviours such as aggression and anger, compared to placebo, post moderate to severe TBI.* - *There is level 4 evidence (Kant et al., 1998) that sertraline may reduce irritability post TBI.* Sertraline may not be effective for agitation post severe TBI. - *There is level 2 evidence (Meythaler et al., 2001) that sertraline may not reduce agitation, compared to placebo, in individuals with severe TBI.*
Amitriptyline	Amitriptyline may be an effective treatment for reducing agitation post TBI; however, further research is needed. - *There is level 4 evidence (Mysiw et al., 1998) that amitriptyline may reduce agitation post TBI.*
Amantadine	Amantadine may be effective for the treatment of aggression in individuals with TBI; however, evidence is conflicting regarding its effectiveness in reducing irritability. Amantadine may not be effective for the management of anger. - *There is level 1b evidence (Hammond et al., 2014; 2015) that amantadine may reduce aggressive behaviour among those with moderate to severe aggression post TBI. However, evidence is conflicting regarding the use of amantadine for the reduction of irritability.* - *There is level 1b evidence (Hammond et al., 2017) that amantadine may not reduce anger post TBI.* Amantadine may not improve agitated behaviour following a moderate to severe TBI. - *There is level 1b evidence (Meythaler et al., 2002) and level 2 evidence (Schneider et al., 1999) that amantadine may not be effective for the management of agitation post TBI.*
Methylphenidate	Further Research is needed to determine whether or not methylphenidate is effective for the management of challenging behaviours following a moderate to severe TBI. - *There is conflicting evidence (Jenkins et al., 2019; Mooney & Haas, 1993) regarding the effectiveness of methylphenidate for the management of challenging behaviours such as disinhibition, executive dysfunction and anger post TBI. Further research is needed.*

Dextroamphetamine	Dextroamphetamine may not reduce agitation post severe TBI. - *There is level 1b evidence (Hart et al., 2018) that dextroamphetamine may not reduce agitated behaviour in individuals with TBI.*
Carbamazepine	Carbamazepine may reduce agitated behaviour, disinhibition and irritability post TBI. However, more research with larger samples is needed. - *There is level 4 evidence (Azouvi et al., 1999) that carbamazepine may reduce agitation, irritability and disinhibited behaviour post TBI.*
Lamotrigine	Lamotrigine may be effective in reducing challenging behaviours in individuals with severe TBI. However, further research with larger samples and standardized outcome measures is needed. - *There is level 4 evidence (Chahine & Chemali, 2006) that lamotrigine may reduce pathological laughter and crying post severe TBI; however, it may not decrease impulsivity.*
Valproic Acid	Valproic acid may be effective in reducing aggression and agitation in individuals with a TBI; however, further research with larger sample sizes and standardized outcome measures is needed. - *There is level 4 evidence (Wroblewski et al., 1997) that valproic acid may reduce aggression post moderate to severe TBI; however, further research is needed.*
Divalproex	Divalproex may be effective in reducing agitation post severe ABI; however, further research is needed. - *There is level 4 evidence (Chatham Showalter & Kimmel, 2000) that divalproex may improve symptoms of agitation in individuals with severe ABI; however, further research is necessary to confirm its effectiveness.*
Risperidone	Risperidone may not be effective in reducing aggression post TBI; further research is needed. - *There is level 1b evidence (Deb et al., 2020) that risperidone may not be effective for the management of aggression in individuals with TBI.*
Rivastigmine	Rivastigmine may not be effective for managing aggression, irritability and impulsivity in individuals with moderate to severe TBI. - *There is level 1a evidence (Tenovuo et al., 2009) and level 1b evidence (Silver et al., 2006) that rivastigmine may not improve aggressive, irritable and impulsive behaviour post TBI.*

Ziprasidone	Ziprasidone may be effective for the management of agitation in those with post-traumatic amnesia following a TBI; however, additional research with larger sample sizes is needed. - *There is level 4 evidence (Noé et al., 2007) that ziprasidone may reduce agitation among those with posttraumatic amnesia. However, additional further research is required to determine its effectiveness.*
Methotrimeprazine	Methotrimeprazine may be effective for the management of agitation post moderate to severe ABI; however, additional research is needed. - *There is level 4 evidence (Maryniak et al., 2001) that methotrimeprazine may reduce agitation post ABI. However, further research is needed.*
Dexmedetomidine	Dexmedetomidine may be more effective for the management of agitation and delirium post moderate to severe TBI. Dexmedetomidine may be more effective for agitation and delirium than haloperidol. - *There is level 1b evidence (Feng et al., 2022; Soltani et al., 2021) and level 4 evidence (Bilodeau et al., 2021) that dexmedetomidine may reduce agitation and delirium post TBI.*
Haloperidol	Compared to haloperidol, dexmedetomidine may be more effective for the treatment of agitated behaviour and delirium in individuals with moderate to severe TBI. - *There is level 1b evidence (Soltani et al., 2021) that haloperidol may not be less effective than dexmedetomidine for the management of agitation and delirium post TBI.*
Propranolol	Propranolol may be effective in reducing the intensity of agitation following a moderate to severe TBI. - *There is level 1b evidence (Brooke et al., 1992) that propranolol may reduce the intensity of agitation episodes in individuals with severe TBI.*
Lithium Carbonate	Lithium carbonate may reduce aggressive behaviour in individuals with ABI; however, further research is needed. - *There is level 4 evidence (Glenn et al., 1989) that lithium carbonate may reduce aggression post ABI.*
Olanzapine	Olanzapine may not be effective for agitated behaviour during post-traumatic amnesia in individuals with severe TBI. Further research is needed. - *There is level 1b evidence (Phyland et al., 2023) that olanzapine may be not effective in reducing agitation during PTA, and it may be associated with poorer cognitive performance.*

Lisdexamfetamine Dimesylate	Further research is needed to determine the effects of Lisdexamfetamine Dimesylate on behaviour following a moderate to severe TBI. - *There is level 1a evidence (Tramontana et al., 2014) that Lisdexamfetamine Dimesylate may not have an effect on behaviour post TBI; however, further research is needed.*
Social Behaviour	
Non-Pharmacological Interventions	
Behavioural Modification Programs	Behavioural modification programs may improve social behaviour and empathy in individuals with ABI. - *There is level 1b evidence (Westerhof-Evers et al., 2017), level 2 evidence (Carnevale et al., 2006), and level 4 evidence (Eames & Wood, 1985) that behavioural modification programs may improve social behaviour and empathy post ABI.*
Cognitive Rehabilitation	In-hospital cognitive rehabilitation may not be different than a home rehabilitation program with telephone support for social behaviour in individuals with moderate to severe TBI. - *There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for social behaviour post TBI.*
Emotion Recognition	Emotion perception training may not improve psychosocial functioning and everyday behaviours in individuals with moderate to severe ABI. - *There is level 1b evidence (McDonald et al., 2013) that an intervention for the identification of emotional prosody may not improve social behaviour or interactions with others post severe ABI.* - *There is level 1b evidence (Bornhofen & McDonald, 2008a) and level 2 evidence (Bornhofen & McDonald, 2008b) that emotion perception training may not improve social behaviour and psychosocial functioning post TBI.* Women may benefit more from an intervention to infer emotions from context, compared to men. - *There is level 1b evidence (Babbage et al., 2018) that women may show greater benefit from an intervention to recognize emotions from context, compared to men.*
Social Skills Training	Social skills training may be effective in improving social behaviour in individuals with TBI.

	- *There is level 1b evidence (McDonald et al., 2008), and level 4 evidence (Brotherton et al., 1988) that a social skills training programs may improve social behaviour post TBI.*
Music Therapy	Music therapy may improve behavioural regulation in individuals with TBI; however, additional research is needed. - *There is level 2 evidence (Siponkoski et al., 2022) that music therapy may improve behavioral regulation in individuals with TBI; however, further research is needed.*
Compassionate Imagery	Compassionate Imagery may not be effective for empathy in individuals with severe TBI. - *There is level 1b evidence (O'Neill & McMillan, 2012) that compassionate imagery may not improve empathy post severe TBI, compared to relaxation only.*
Pharmacological Interventions	
Methylphenidate	Further research is needed to determine whether or not methylphenidate may improve social behaviour in individuals with moderate to severe TBI. - *There is level 1a evidence (Speech et al., 1993) that methylphenidate may not improve social behaviour post TBI. However, further research is needed.*

Introduction

Brain Injuries have been associated with neurobehavioural and mental health problems that can significantly impact function and quality of life in individuals and their families (Howlett et al., 2022). The state of mental health is associated with the ability to maintain social relationships with others, to perform social roles according to the individual's culture and context, and to manage emotions (Bhugra et al., 2013). Individuals who have sustained a TBI commonly report depression and anxiety, with major depression disorder more frequently reported by those with moderate to severe TBI (Pavlovic et al., 2019). A high proportion of TBI survivors often present with psychiatric disorders such as anxiety and depression, as well as major depression disorder (MDD) and post-traumatic stress disorder (PTSD) (Scholten et al., 2016a).

Depression causes a persistent feeling of sadness and loss of interest, as well as irritable mood and some somatic and cognitive changes that significantly impact function and the daily life of individuals (Chand, Arif, et al., 2021). Anxiety is a common disorder in the general population associated with feelings of fear and the anticipation of future circumstances perceived as threatening; anxiety can manifest in specific phobias and social anxiety (Chand, Marwaha, et al., 2021). Suicidal ideation and attempts are also more frequent among individuals post TBI, with rates as high as 23-28% for suicidal ideation (Mackelprang et al., 2014; Simpson & Tate, 2002; Tsaousides et al., 2011) and rates of attempts as high as 26% (Simpson & Tate, 2005). Suicidal ideations describes a range of wishes, contemplations and preoccupations with ideas related to death and suicide that may be exacerbated by existing psychiatric conditions (Harmer et al., 2020).

Challenging behaviours such as agitation and aggression, as well as addictive behaviours such as substance abuse, may also become a significant problem post ABI, and have been associated with worsening of other ABI sequelae and poorer patient outcomes (Bedard et al., 2003; Berthier et al., 2001; Jorge, 2005). Challenging behaviours following ABI occurs with a relatively high frequency (25-50%) (Baguley et al., 2006). Individuals who experience posttraumatic agitation in the acute phase post-injury may also display disinhibited, irritable and aggressive behaviours (Oberholzer & Müri, 2019). In addition, survivors of TBI may also exhibit sexually inappropriate behaviours, including sexual offending and hypersexual behaviour (Turner et al., 2015).

Substance abuse and dependence are often related to pathological changes in reward-related behaviours (Cadet et al., 2014). Substance use disorders can be a serious problem for some individuals post ABI. In TBI populations, pre-injury substance use disorders are more common than the general population (Alway et al., 2016; Hibbard et al., 1998). Pre-injury substance use is a significant predictor of substance abuse after TBI (Alway et al., 2016). Alcohol abuse has also been linked to major depression both before (Dikmen et al., 2004; Seel et al., 2010) and after injury (Jorge, 2005).

MENTAL HEALTH

Depression

Depression is a mood disorder associated with feelings of emptiness and sadness, loss of interest, irritable mood, and somatic and cognitive changes that affect daily function; depressive disorders include major depressive disorder (MDD), disruptive mood dysregulation disorder, dysthymia, premenstrual dysphoric disorder in women and depression due to medical conditions (Chand, Arif, et al., 2021). In Canada, approximately 11% of adults experience depression at some point during their lives, and women are almost twice as likely as men to experience depression (Knoll & MacLennan, 2017). Furthermore, the impact of depression extends beyond individual suffering, affecting interpersonal relationships, work productivity, and overall societal well-being. The economic burden associated with depression, including healthcare costs and loss of productivity, underscores the importance of early detection and effective management strategies (Greenberg et al., 2015)

For those who have sustained an ABI, depression is the most commonly diagnosed mood disorder (Jean-Bay, 2000; Jorge, 2005; Osborn et al., 2018; Seel et al., 2010; Underhill et al., 2003). The development of depression can be related to the location of injury, a pre-existing mental health condition, TBI severity (Scholten et al., 2016a; Singh et al., 2018), personality type, family support, social support, psychological stressors, and/or neurochemical imbalances (Bay & Covassin, 2012; Bombardier et al., 2016; Cnossen et al., 2016; Jorge, 2005; Ownsworth & Oei, 1998; Rosenthal et al., 1998; Sigurdardottir et al., 2013). Depression has been associated with poorer functional recovery and quality of life following an ABI (Anke et al., 2015; Grauwmeijer et al., 2018; Hudak et al., 2012; Kumar et al., 2018). It is often difficult to diagnose depression post ABI due to the complexities of the injury itself (Underhill et al., 2003). Additionally, depression can complicate rehabilitation efforts and impede progress toward functional recovery. Individuals with ABI may face challenges in accessing appropriate mental health care due to limited awareness or resources, further exacerbating the burden of depression in this population (Dikmen et al., 2003). Distinguishing between depression and the behaviours resulting from an ABI can prove to be challenging as there is an overlap between symptoms. For example, the gradual decline in the ability to perform everyday tasks and cope with everyday stressors, as well as an increase in irritability and behavioural issues may be symptoms of either depression or brain injury (Fleminger et al., 2003).

Incidence and Prevalence of Depression

Depression is the most common mental health condition following ABI, surpassing the incidence rates observed in the general population (Gould et al., 2011; Osborn et al., 2014; Osborn et al., 2018; Ouellet et al., 2018; Singh et al., 2018). In two long-term prospective cohorts of patients with moderate to severe

TBI, rates of depression were 4-6 times higher than the general population (Alway et al., 2016), and prevalence was 20% 10 years after TBI (Grauwmeijer et al., 2018). Often, depression presents within the first year post-ABI (Alway et al., 2016; Scholten et al., 2016b). In patients one year post-ABI reports of prevalence are variable, ranging from 13% to 61% (Alway et al., 2016; Fleminger et al., 2003; Gordon et al., 1998; Grauwmeijer et al., 2018; Osborn et al., 2014; Sigurdardottir et al., 2013). Accurately gauging the prevalence of depression post-ABI poses considerable challenges due to diverse patient populations, poorly understood risk factors, and disparate diagnostic methodologies (Osborn et al., 2018). In a meta-analysis, Osborn et al. (2014) reported that 21% to 43% of individuals present with depression within the first five years post-TBI, which then stabilizes to approximately 22% after five years. In a systematic review and meta-analysis, Scholten et al. (2016b) reported that pooled prevalence rates in TBI patients increased over time, with long-term rates of depression estimated at 43%. In another meta-analysis, Osborn et al. (2018) estimated rates at 30%. However, these reviews and most of the literature, are specific to TBI. Contrary to other mood disorders, depression following ABI often endures for years, amplifying the challenges of rehabilitation and reintegration (Hoffman et al., 2010; Ponsford et al., 2018). Comprehensive understanding of the trajectory and determinants of depression post-ABI is imperative to devise tailored interventions and enhance the overall well-being of affected individuals (Alway et al., 2016; Grauwmeijer et al., 2018; Hoffman et al., 2010; Ponsford et al., 2018; Scholten et al., 2016b).

Non-Pharmacological Interventions

Several non-pharmacological Interventions have been used to treat depression in individuals with ABI including cognitive behavioural therapy (CBT), mindfulness-based interventions exercise, music therapy, and brain stimulation. There is preliminary evidence suggesting the benefits of a variety of non-pharmacological interventions for the treatment of mood disorders, particularly depression; however, non-pharmacological interventions are often considered as adjunct interventions to pharmacological treatment.

Psychotherapy

Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) is the primary form of psychotherapy for anxiety and depression in the general population (Butler et al., 2006). CBT focuses on automatic thoughts, cognitive distortions and underlying beliefs to help the individual shape their emotions and actions in response to events, as well as their patterns of thinking and behaviour (Chand et al., 2022).

TABLE 4 | Cognitive Behavioural Therapy for the Management of Depression Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Brenner et al. (2018) USA RCT Crossover PEDro=6 $N_{Initial}$=44, N_{Final}=35	**Population:** TBI; Gender: Male=32, Female=2, Transgender=1. *Experimental Group (n=15)*: Mean Age=47.7yr *Control Group (n=20):* Mean Age=54.6yr. **Intervention:** Participants were randomized to receive a manualized, small-group cognitive behavioural intervention or to a waitlist. The intervention was developed from principles and therapeutic techniques drawn from CBT and focused on alleviating hopelessness. The intervention was 2hr and delivered weekly for 10 wk. Participants were crossed over to the alternate intervention after 10wk. Assessments occurred at baseline, 10wk, and 20wk. **Outcome Measure:** Beck Hopelessness Scale (BHS), Beck Depression Inventory (BDI), Beck Scale for Suicide Ideation (BSSI).	1. After controlling for baseline BHS scores, the intervention group had significantly lower hopelessness post intervention compared to those on the waitlist (p=0.03); these reductions were maintained at follow-up. 2. The waitlist group demonstrated significant reductions on the BHS (p=0.01) and depression (p=0.003) after completing the intervention. 3. There were no significant between-group differences for the BDI or BSSI.
Nguyen et al. (2017) Australia RCT PEDro=8 N=24	**Population:** TBI; *CBT Group* (n=13): Mean Age=45.5yr; Gender: Male=9 (69%), Female=4; Mean Time Post Injury=795d; GCS=6.7. *Control Group* (n=11): Mean Age=41.9yr; Gender: Male=7 (64%), Female=4; Mean Time Post Injury=2093d; Mean GCS=8.13. **Intervention:** Participants received 6 modules of CBT addressing sleep and fatigue secondary to brain trauma over 8 sessions. Controls received treatment as usual. Outcomes were assessed at baseline, 2, and 4mo. **Outcome Measures:** Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Brief Fatigue Inventory (BFI), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS).	1. There was a significant interaction on the HADS depression subscale after treatment (p<0.05) and at follow-up (p<0.01). 2. There was a strong trend toward an interaction effect on the HADS anxiety subscale (p=0.05).
Ponsford et al. (2016) Australia RCT PEDro=7 $N_{Initial}$=75, N_{Final}=51	**Population:** TBI; *CBT+MI Group (n=26):* Mean Age=46.69yr; Gender: Male=18, Female=8; Mean Time Post Injury=4.88yr; Mean GCS=10.43. *CBT+NDC Group (n=26):* Mean Age=39.88yr; Gender: Male=20, Female=6; Mean Time Post Injury=3.58yr; Mean GCS=10.48. *WC Group (n=23):* Mean Age=39.87yr; Gender: Male=17, Female=6; Mean Time Post Injury=2.61yr; Mean GCS=8.23. **Intervention:** Participants diagnosed with depression and/or anxiety were allocated to receive cognitive behavioural therapy (CBT) with either motivational interviewing (CBT+MI) or non-directive counseling (CBT+NDC), or to a waitlist control (WC). MI and NDC were each delivered for 3wk, followed by 9wk of CBT, with three CBT booster sessions 21-30wk from baseline. Assessments were conducted at	1. All groups demonstrated significant improvements in the DASS-Depression, HADS-Anxiety, and SPRS-2 over time. 2. On the DASS-Depression, there was a significantly greater reduction in score over time in CBT+MI versus WC (p<0.005) but not CBT+NDC versus WC; there was no significant difference between CBT+MI and CBT+NDC. 3. Higher baseline DASS-Depression and HADS-Anxiety scores were significantly associated with greater response to treatment (r=0.34, p<0.05 and r=0.37, p<0.05, respectively). 4. When combining CBT+MI and CBT+NDC groups, there were significantly greater improvements on DASS-Depression (p<0.005) in the combined group versus WC.

Author, Year Country Study Design Sample Size	Methods	Outcome
	baseline, 3wk, 12wk, 21wk, and 30wk. **Outcome Measure:** Depression, Anxiety & Stress Scale (DASS), Hospital & Anxiety Depression Scale (HADS), Sydney Psychosocial Reintegration Scale 2 (SPRS-2).	
Fann et al. (2015) USA RCT PEDro=6 $N_{Initial}$=100, N_{Final}=72	**Population:** TBI; Mean Age=45.8yr; Gender: Male=63, Female=37; Mean Time Post Injury=3.33yr; Severity: Moderate=69, Severe=31. **Intervention:** Participants diagnosed with depression received cognitive behavioural therapy (CBT) on telephone (CBT-T), CBT in person (CBT-IP), or usual care (UC). Both CBT treatments consisted of 30-60 min weekly sessions for 12wk, where in-session work and inter-session homework was assigned. UC group received a phone call encouraging them to continue rehabilitation and directing them towards community resources. Assessments were conducted at baseline, 8wk, 16wk, and 24wk. **Outcome Measure**: Structured Clinical Interview for DSM (SCID), Hamilton Rating Scale for Depression (HAM-D), Symptom Checklist-20 (SCL-20), Patient Global Impression (PGI), Satisfaction with Depression Care (SDC).	1. On SCID, there were no significant differences in rate of depression diagnosis for CBT-T versus UC, CBT-IP versus UC, or combined CBT versus UC at 16wk or 24wk (p>0.05). 2. On HAM-D, there were no significant differences for CBT-T versus UC, CBT-IP versus UC, or combined CBT versus UC at baseline, 8wk, 16wk, or 24wk (p>0.05). 3. On SCL-20, CBT-T showed significantly greater improvement than UC at 8wk (p=0.002) and 16wk (p=0.043), but not 24wk (p=0.065). 4. On SCL-20, there were no significant differences between CBT-IP and UC at baseline, 8wk, 16wk, or 24wk (p>0.05). 5. On SCL-20, combined CBT showed significantly greater improvement than UC at 8wk (p=0.001), but not at 16wk (p=0.074) or 24wk (p=0.250). 6. On SDC at 16wk, there was significantly greater satisfaction with combined CBT (p<0.001), CBT-T (p<0.001), and CBT-IP (p=0.007) than UC. 7. Participants without pre-TBI depression had a significantly larger decrease in HAM-D score (p=0.036) and SCL-20 score (p=0.008) when randomized to CBT than UC, whereas those with prior depression did not show a difference.
Ashman et al. (2014) USA RCT PEDro=7 $N_{Initial}$=54, N_{Final}=43	**Population:** TBI. *CBT Group (n=28)*: Mean Age=47.5yr; Gender: Male=10, Female=18; Mean Time Post Injury=7.8yr; Severity: Mild=10, Moderate/Severe=17. *SPT (n=26)*: Mean Age=47.1yr; Gender: Male=12, Female=14; Mean Time Post Injury=13.2yr; Severity: Mild=9, Moderate/Severe=12. **Intervention:** Participants diagnosed with depression were randomized to receive cognitive behavioural therapy (CBT) or supportive psychotherapy (SPT). The CBT group received treatment based on standard techniques with focus on cognitive restructuring and reshaping automatic thoughts. The SPT group received client-centered treatment to improve ability to deal with daily problems effectively. Both groups had 90min sessions 2 day/wk for the first week, followed by 50min sessions 1 day/wk for 3mo. Assessments were conducted before and after	1. Rate of remission of depression between groups was not statistically significant (p=0.16), but 35% in CBT group were no longer depressed at end of treatment compared to 17% in SPT group. 2. Within groups, there was a significant improvement on BDI-II scores in the CBT group (p=0.03) and a marginal improvement in the SPT group(p=0.06). 3. No significant differences in anxiety between groups were found at the end of treatment (p=0.12). 4. No significant differences in quality of life as measured by Life-3 were found at the end of treatment (p>0.05).

Author, Year Country Study Design Sample Size	Methods	Outcome
	each treatment session. **Outcome Measure:** Beck Depression Inventory-Second Edition (BDI-II), State-Trait Anxiety Inventory (STAI), Life-3.	
Anson & Ponsford (2006) Australia RCT PEDro=5 N=33	**Population:** TBI; Gender: Male=27, Female=6. *Group A (n=17)*: Mean Age=38.9yr; Mean Time Post Injury=755.8d. *Group B (n=16)*: Mean Age=37.8yr; Mean Time Post Injury=340.8d. **Intervention:** Participants were randomized to receive a CBT-based Coping Skills Group (CSG) in two groups with different duration. For Group A (n=15), baseline phase was 5wk, followed by 5wk of intervention, and a 5wk follow-up phase. For Group B (n=16), baseline was 10wk, followed by 5wk of intervention and a 10wk follow-up phase. The CSG consisted of 10 group sessions and ran for 900min 2×/wk. **Outcome Measure:** Coping Scale for Adults (CSA), Hospital Anxiety and Depression Scale (HADS), Rosenberg Self Esteem scale (RSE), The Sickness Impact Profile (SIP), The State-Trait Anger Expression Inventory, 2nd ed. (STAXI-2), National Adult Reading Test (NART), Rey Auditory Verbal Learning Test (RAVLT), Six Elements sub-test from the Behavioural Assessment of the Dysexecutive Syndrome (BADS).	1. Although levels of depression and psychosocial dysfunction were significantly different between the two groups ($p<0.05$) participation in the CSG did not have an effect on their scores. 2. Both groups significantly increased their adaptive coping skills following the CSG ($p<0.01$).
Medd & Tate (2000) Australia RCT PEDro=5 N=16	**Population:** TBI; Gender: Male=14, Female=2; *Treatment Group (n=8),* Mean Age=35.88yr; Mean Time Post Injury=37.25mo; *Waitlist Group (n=8),* Mean Age=34yr; Mean Time Post Injury=74.25mo; Mean PTA=2wk. **Intervention:** Participants were randomly allocated to either the treatment group or the waitlist group. The treatment group received 5-8 individualized sessions of cognitive behavioural therapy based on the Commonwealth Rehabilitation Service Anger Management Program. **Outcome Measure:** State-Trait Anger Expression Inventory (STAXI), Hospital Anxiety and Depression Scale (HADS), Self-Esteem Inventories (SEI), Patient Competency Rating Scale (PCRS).	1. No significant differences were found for depression (HADS), or self-esteem (SEI) between groups.
Fraser et al. (2022) Australia Pre-Post $N_{Initial}=9$, $N_{Final}=8$	**Population:** TBI; Gender: Male=4, Female=5; Mean Age=46.33yr; Severity: Mild=4, Moderate=1, Severe=4, Unknown=1. Time post injury range=0.90–33yr. **Intervention:** Participants received a Cognitive Behavioral Therapy (CBT) intervention to treat sexuality problems after TBI for 60min/d, 1d/wk, 8wk. Outcomes were assessed pre-intervention, post-intervention and at 8wk follow-up.	1. In 6 of the 9 participants, subjective sexuality statistically increased from baseline ($p<.001$). 2. Participants who self-reported low self-esteem at pre-treatment demonstrated significantly improved self-esteem at post-treatment, which was maintained at follow-up. 3. No meaningful changes were observed in depression.

Author, Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: Brain Injury Questionnaire of Sexuality (BIQS), Hospital Anxiety and Depression Scale (HADS), Rosenberg self-esteem scale (RSES), Participation Assessment with Recombined Tools-Objective (PART-O), Goal Attainment Scaling (GAS).	
Arundine et al. (2012) Canada PCT $N_{Initial}$=20, N_{Final}=17 Follow up to Bradbury et al. (2008)	**Population:** TBI=10, ABI=10, Severity: Moderate-Severe. *CBT Group (n=10):* Mean age=39.8yr; Gender: Male=5, Female=5; Mean Time Post Injury=7.00yr. *EC Group (n=10):* Mean age=42.5yr; Gender: Male=5, Female=5; Mean Time Post Injury=11.4yr. **Intervention:** Participants with psychological distress were randomized to receive cognitive behavioural therapy (CBT) or education control (EC). CBT involved one individual introductory session, and then 10 sessions either in a group (CBT-G) or individually by telephone (CBT-T). EC group received CBT after initial group. Assessments were conducted at baseline, post treatment, 1mo follow-up, and 6mo follow-up. **Outcome Measure:** Depression Anxiety Stress Scales 21 (DASS-21), Symptom Checklist 90 Revised (SCL-90-R).	1. At 6mo follow-up, all participants showed significant improvements from baseline on DASS-21 ($p<0.01$) and SCL-90-R ($p<0.01$); CBT-G and CBT-T were comparable.
Bradbury et al. (2008) Canada PCT N=20	**Population:** TBI=10, ABI=10, Severity: Moderate-Severe. *CBT Group (n=10):* Mean age=39.8yr; Gender: Male=5, Female=5; Mean Time Post Injury=7.00yr. *EC Group (n=10):* Mean age=42.5yr; Gender: Male=5, Female=5; Mean Time Post Injury=11.4yr. **Intervention:** Participants with psychological distress received cognitive behavioural therapy (CBT) or education control (EC). CBT involved one individual introductory session, and then 10 sessions either in a group (CBT-G) or individually by telephone (CBT-T). Assessments were conducted at baseline, post treatment, and 1mo follow-up. **Outcome Measure:** Depression Anxiety Stress Scales 21 (DASS-21), Symptom Checklist 90 Revised (SCL-90-R).	1. At post treatment and 1mo follow-up, combined CBT showed significantly greater improvement from baseline than EC on DASS-21 ($p<0.001$) and SCL-90-R ($p<0.01$). 2. On DASS-21 and SCL-90-R, there were significant improvements from baseline to post treatment and to 1mo follow-up for CBT-G ($p<0.01$) and CBT-T ($p<0.05$), but there were no significant improvements from post treatment to 1mo follow-up ($p>0.05$). 3. There were no significant differences between CBT-G and CBT-T at any time point on DASS-21 or SCL-90-R ($p>0.05$).

Discussion

In an RCT Crossover, Brenner et al. (2018) found that a small-group cognitive behavioural intervention developed from principles and therapeutic techniques drawn from CBT was effective at improving hopelessness when compared to individuals on a waitlist; however, no significant group differences were

observed in depression, as measured by the Beck Depression Inventory (BDI). Anson and Ponsford (2006) compared the duration of a CBT program in individuals post-TBI. While participants in CBT increased their adaptive coping skills, there were no significant improvements in depressive symptoms. At follow-up, participants who had greater self-awareness and self-esteem, as well as fewer depressive symptoms, showed better outcomes after the program (Anson & Ponsford, 2006). It should be noted that participants in these studies were not formally diagnosed with a depressive disorder, so findings should be interpreted with caution. In the RCT by Medd & Tate (2000), no significant differences were found for depression or self-esteem after CBT for anger management. In another RCT, Nguyen et al. (2017) examined CBT as a treatment for sleep and fatigue secondary to brain trauma. The authors found a significant interaction on the HADS depression subscale following the intervention and at follow-up (Nguyen et al., 2017).

The delivery of CBT either in a group or by telephone was examined in an RCT study and in a PCT (Bradbury et al., 2008; Fann et al., 2015). In the RCT study, Fann et al. (2015) randomized participants into three groups: telephone CBT, in-person CBT and usual care. The authors found no statistically significant differences in depression, as measured by the Hamilton Depression Rating Scale (HAMD-17) between the groups that received in-person or telephone CBT and usual care groups. However, individuals who received CBT reported greater satisfaction with depression care. Similarly, Bradbury et al. (2008) found no differences in terms of CBT delivered in-person versus via telephone.

In an RCT, Ponsford et al. (2016) found improvements in depressive symptoms in favour of CBT, with more significant improvements associated with CBT combined with motivational interviewing (MI) and non-directive counselling (NDC), when compared to the waitlist control group (Ponsford et al., 2016). In the PCT study by Arundine et al. (2012), CBT was also associated with reductions in depression scores in individuals with psychological distress, and individual and group CBT were found to be comparable. In the RCT by Ashman et al. (2014), CBT was compared to supportive psychotherapy was compared to CBT in patients diagnosed with depression following ABI. Overall depression scores decreased from baseline following treatment; however, there were no significant differences in effectiveness between the two treatments (Ashman et al., 2014). Finally, in the pre-post study by Fraser et al. (2022), CBT was found to improve subjective sexuality post-TBI and self-esteem; however, no meaningful changes were found in depression. Most recently, a meta-analysis on the effectiveness of CBT on depression among people with TBI (including mild TBI) found significant improvements in symptoms at post-treatment and at three-month follow-up, suggesting sustainable long-term effects of CBT (Barua et al., 2024).

Conclusions

There is level 1a evidence (Brenner et al., 2018) that CBT may be an effective treatment for hopelessness post TBI when compared to a waitlist control.

There is level 1b evidence (Ponsford et al., 2016) that CBT combined with motivational interviewing or non-directive counselling may be equally effective treatments for depression post TBI when compared to controls.

There is level 1b evidence (Fann et al., 2015) and level 2 evidence (Bradbury et al., 2008; Arundine et al., 2012) that CBT may be effective for depression post ABI, and it may be similarly effective when delivered over the phone or in person.

There is level 1b evidence (Ashman et al., 2014) that CBT may be no more effective than supportive psychotherapy as a treatment for depression post TBI.

There is level 1b evidence (Nguyen et al., 2017) that CBT addressing fatigue and sleep following TBI may reduce depression.

There is level 2 evidence (Anson & Ponsford, 2006) that duration of CBT interventions may have no impact on depression in individuals post TBI.

There is level 2 evidence (Medd & Tate, 2000) that CBT for anger management may not be effective for depression and self-esteem.

There is level 4 evidence (Fraser et al., 2022) that CBT may improve subjective sexuality and self-esteem in individuals with TBI.

KEY POINTS

- Cognitive Behavioural Therapy (CBT) may be an effective treatment for depression following an ABI; however, it may not be more effective than supportive psychotherapy.
- CBT may be similarly effective when provided in groups or individually over the phone.
- CBT combined with motivational interviewing or non-directive counselling may be equally effective for the management of depression in individuals with TBI.
- CBT may improve feelings hopelessness, as well as self-esteem and subjective sexual wellbeing.

Compassion Focused Therapy

Compassion Focused Therapy (CFT) refers to a form of psychotherapy that involves a compassion model to help individuals who feel high levels of shame, self-criticism and who experience difficulties feeling safeness or warmth in their relationships with others and themselves (Gilbert, 2009). CFT highlights the

evolutionary trait of affiliation and caring, and how human cognition is adapted for social processing (Gilbert, 2014).

TABLE 5 | Compassion Focused Therapy for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Campbell et al., (2019) UK RCT PEDro=7 $N_{Initial}$=24, N_{Final}=24	**Population:** TBI=24; Mean Age=47±8.9yr; Gender: Male=20, Female=4; Mean Time Post Injury=141mo; Severity: Mild=0, Moderate=15, Severe=7. **Intervention:** Participants were randomized to receive 50min of compassion focused imagery (CFI) or relaxation imagery (RI). Outcome measures were assessed before and after a preparatory 20min instructional video and pre- and post-intervention. **Outcome Measures:** Motivation for Intervention Scale (MIS), Fears of Compassion Scale (FoC), State-Trait Anxiety Inventory (STAI), Positive and Negative Affect Schedule (PANAS), Empathy Quotient (EQ), Self Compassion Scale (SCS), Relaxation Scale (RS), Heart Rate Variability (HRV).	1. Motivation for therapy increased after participants watched the preparatory instructional video (MIS; p=.001). 2. No significant differences were observed across all outcomes between groups pre- and post-intervention (p>.05). 3. CFI did not produce changes in measures of self-compassion, empathy, relaxation or anxiety.
Ashworth et al. (2015) UK Pre-Post N=12	**Population:** TBI=7, Stroke=3, ABI=2; Mean Age=40.9yr; Gender: Male=7, Female=5. **Intervention:** Participants received two phases of compassion-focused therapy (CFT) 1 day/wk for 18wk. Group sessions focused on identifying emotions that encompass ABI and strategies to manage them. Individual sessions addressed content from mood groups and in-depth development of CFT skills. Inter-session homework was encouraged. Assessments were conducted at baseline, 18wk, and 3mo follow-up. **Outcome Measure**: Hospital Depression and Anxiety Scale (HADS), Forms of Self-Criticism/Self-Attacking and Self-Reassuring Scale (FSCRS).	1. Significant decreases in depression and anxiety on the HADS from baseline to post treatment and baseline to follow-up (p<0.05). 2. Significant increase in reassured self and reductions in hatred and inadequate self, according to FSCRS, from baseline to post-treatment and baseline to follow-up (p<0.05).

Discussion

Two studies examined the use of CFT. In an RCT, Campbell et al. (2019) compared compassion focused imagery (CFI) to relaxation imagery (RI) and found no significant differences between the groups in terms of mood, empathy, self-compassion or relaxation. Although a promising and cost-effective intervention, no significant improvements in mood were observed between groups. Future research, using a larger sample size is necessary to determine the efficacy of this intervention in the management of depression in individuals with TBI. In a pre-post study, Ashworth et al. (2015) examined a CFT intervention for individuals with ABI who presented with emotional difficulties receiving neuropsychological rehabilitation. The intervention included compassionate mind mood group sessions and one-to-one CFT

sessions. The authors found that CFT was associated with reduction in depression, as measured by the HADS (Ashworth et al., 2015).

Conclusions

There is level 1b evidence (Campbell et al., 2019) that CFI and RI may not be more effective than RI for the improvement of measures of mood, self-compassion and empathy.

There is level 4 evidence (Ashworth et al., 2015) that CFT may reduce depression post ABI.

KEY POINTS

- Compassion Focused Imagery (CFI) may not be mor effective than Relaxation Imager (RI) for mood, self-compassion and empathy.
- Compassion Focused Therapy (CFT) may decrease depression symptoms in individuals with ABI.

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT) is a form of psychotherapy that targets the process of thinking and aims to take a nuanced approach to distress by increasing the individual's ability to undertake meaningful activity when distress is present (Graham et al., 2016).

TABLE 6 | Acceptance and Commitment Therapy for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Sander et al. (2021) USA RCT PEDro=5 $N_{Initial}$=98, N_{Final}=93	**Population:** TBI; *ACT* (n=44); Mean age=37.73yr; Gender: Male=25, Female=19; Mean time post-injury=57.4mo; Severity: Mild=19, Moderate=7, Severe=19. *Usual care* (n=49); Mean age=38.27yr; Gender: Male=31, Female=18; Mean time post-injury=47.01mo; Severity: Mild=22, Moderate=9, Severe=18. **Intervention:** Participants were randomly allocated to eight 1.5h sessions of Acceptance and Commitment Therapy (ACT) or usual care. Outcome measures were assessed within 2wk of the last session and 3mo posttreatment. **Outcomes:** Brief symptom inventory 18 (BSI-18), Acceptance and action questionnaire-II (AAQ-II), Participation Assessment with Recombined Tools-Objective (PART-O).	1. When compared to the usual care group, participants in the ACT group demonstrated lower scores on the BSI-18 anxiety subscales (p=0.01). 2. No between-group difference were observed on the BSI 18 Depression subscale.
Whiting et al. (2020)	**Population:** Severe TBI=19*; ACT Therapy (n=10):* Mean Age=36.4yr; Gender: Male=8, Female=2; Mean Time	1. There was a significant group by time interaction on the DASS-depression subscale

Australia RCT PEDro=8 N=19	Post Injury=20.7mo. *Befriending Therapy (n=9):* Mean Age=37.2yr; Gender: Male=7, Female=2; Mean Time Post Injury=33.3mo. **Intervention:** Participants were randomly assigned to an Acceptance and Commitment Therapy (ACT) intervention (ACT-Adjust) or Befriending Therapy, in conjunction with a holistic rehabilitation program. The ACT-Adjust program involved mindfulness exercises, psychoeducation, and experiential exercises relevant to that session's focus. Befriending Therapy was utilized as an active control, which focused on neutral topics which are of interest to participants and unlikely to elicit a negative emotional response. Both interventions were delivered in 7 sessions, 1.5h/wk. Outcome measures were assessed post-intervention and at 1-mo follow-up. **Outcome Measure:** Acceptance and Action Questionnaire - Acquired Brain Injury (AAQ-ABI), Motivation for Traumatic Brain Injury Rehabilitation Questionnaire (MOT-Q), Survey of Life Principles Version 2.2, Depression, Anxiety and Stress Scale (DASS), Hospital Anxiety and Depression Scale (HADS), Positive and Negative Affect Scales (PANAS), General Health Questionnaire-12 (GHQ-12), Short Form-12 (SF-12), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	(p=0.03), where the scores in the ACT-Adjust had larger decreases over the course of treatment compared to scores in Befriending. 2. The ACT-Adjust group demonstrated a greater reduction in DASS-stress scores compared with the Befriending group post-intervention (p=0.03). 3. No significant differences were found for DASS depression (p=0.13) and DASS stress (p=0.12) between baseline and one month follow up, indicating the interaction effect found at post intervention were not maintained at follow up.

Discussion

In an RCT, Whiting et al. (2020) examined the effect of an Acceptance and Commitment Therapy (ACT) intervention on psychological distress post TBI. Individuals were allocated randomly into two groups, the ACT intervention or an active control that received Befriending Therapy, in conjunction with a holistic rehabilitation program. The authors found that the ACT group showed a greater reduction of depressive symptoms post intervention, as measured by the DASS, when comparted to the control group; however, the effect was not maintained at follow-up (Whiting et al., 2020). In the RCT by Sander et al. (2021), eight sessions of ACT were not effective for depression, compared to standard care.

Conclusions

There is level 1b evidence (Sander et al., 2021) that ACT may not be effective for depression when compared to standard care.

There is level 1b evidence (Whiting et al., 2020) that ACT may be effective for depression in individuals with TBI, when compared to Befriending Therapy.

KEY POINTS

- Acceptance and Commitment Therapy (ACT) may reduce depressive symptoms when compared to Befriending Therapy (BT); however, it may not be effective for depression compared to standard care in individuals with moderate to severe TBI.

Positive Psychology

Positive psychology refers to the study of positive emotions, happiness and well-being. In rehabilitation, the main focus is often on acceptance of emotional, physical and cognitive difficulties that may me permanent, while engaging in meaningful activities within the limitations imposed by such difficulties (Evans, 2011).

TABLE 7 | Positive Psychology for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Andrewes et al. (2014) UK RCT Pedro=5 $N_{Initial}$=10, N_{Final}=9	**Population:** TBI; Mean Age=42.2yr; Gender: Male=9, Female=1; Mean Time Post Injury=4.8yr. **Intervention:** In-patients being treated for substance misuse and challenging behavior were randomized to 12wk Positive Psychology group (intervention group) or control. Positive Psychology consisted of "Three Good Things" and "Signature Strengths" interventions. **Outcome Measure:** Seligman's Authentic Happiness Index (AHI), Head Injury Semantic Differential Scale (HISDS), The Hospital Anxiety and Depression Scale (HADS), Brief Strengths Test.	1. No significant differences were found between the average age, time since injury and the HADS scores. 2. After the "three good things" intervention, the intervention group scored significantly higher on the AHI measurement of happiness than the control group (p=0.02). 3. No significant between group differences for the AHI scores from pre-test compared to at the end of the 12wk program.

Discussion

In an RCT, Andrewes et al. (2014) examined the effectiveness of two positive psychology interventions on mood and self-concept in individuals with TBI. The intervention "Three positive things in life" required participants to write three positive events that occurred each day, while the "Value in Action (VIA) signature strengths" intervention required them to identify their five key strengths as well as the values that aligned with them. The authors found a significant interaction between the intervention and control groups, with the intervention group scoring significantly higher in the Seligman's Authentic Happiness Inventory, when compared to the control group.

Conclusions

There is level 2 evidence (Andrewes et al., 2014) that positive psychology may be effective for the improvement of happiness in individuals with TBI.

KEY POINTS

- Positive Psychology may improve happiness post TBI.

Neuro-Systemic Psychotherapy

The neuro-systemic approach aims to reduce emotional and behavioural disorders experienced by individuals with TBI by improving relational dysfunctions with systems such as family, conjugal, social institutional and professional; while considering the individual's specific cognitive disorders (Wiart et al., 2012).

TABLE 8 | Neuro-systemic Psychotherapy for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Wiart et al. (2012) France Case Series N= 47	**Population:** TBI; Mean Age=33.4yr; Gender: Male=35, Female=12; Mean GCS=6.4; Mean Time Post Injury=11.1yr. **Intervention:** Retrospective review of patients with mood disorders referred to a single physician for at least 1yr of neuro-systemic psychotherapy. **Outcome Measure:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Glasgow Outcome Scale.	1. A significant improvement of affective disorders was found in depression ($p<0.001$).

Discussion

In one case series study, Wiart et al. (2012) reported on the effectiveness of a neuro-systemic psychotherapy intervention for individuals with TBI who presented with affective/behaviour disorders. In this study, a retrospective analysis of an at least 1-year psychotherapy was conducted to investigate the evolution of a variety of psychological symptoms, including depressive mood. The authors found significant improvements in depression.

Conclusions

There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may improve depressive mood in individuals with TBI.

KEY POINTS

- Neuro-Systemic Psychotherapy may be effective for the treatment of depression post TBI.

Behavioural Activation

Behavioural Activation is a form of psychotherapy that aims to increase participation in meaningful activities as a means to break the negative feedback loop of decreased activity and low mood that occurs as a result of depression (Stein et al., 2021). Behavioural activation encourages individuals with depression to schedule time to reconnect with environmental positive reinforcement (Ekers et al., 2014).

In a systematic review, Uphoff et al. (2020) found that behavioural activation may be more effective than humanistic therapy, medication and conventional care. However, further research is needed on ABI populations.

TABLE 9 | Behavioural Activation for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Hart et al. (2020) USA RCT PEDro=5 $N_{Initial}$=65, N_{Final}=59	**Population:** TBI=65; *Treatment Group (Intention Condition; n=38):* Mean Age= 40.4±15.2yr; Gender: Male=30, Female=8; Mean Time Post Injury=7.4±5.5yr; Severity: Moderate-to-Severe. *Control Group (Motivation Condition; n=21):* Mean Age=38.5±15.3yr; Gender: Male=17, Female=4; Mean Time Post Injury=4.4±4.3yr; Severity: Severe. **Intervention:** Participants were randomized to receive a single session of behavioural activation followed by 8wk of daily SMS (text) messages supporting goals for increased rewarding/meaningful activities (intention condition) or a single attentional control session followed by 8wk of motivational SMS messages (motivation condition). Outcome measures were assessed at baseline, 4 and 8wk. **Outcome Measures:** Environmental Reward Observational Scale (EROS), Behavioural Activation for Depression Scale (BADS), Brief Symptom Inventory Global Severity Index (BSI GSI), Participation Assessment with Recombined Tools-Objective (PART-O).	1. No significant group differences were observed between interventions on any outcome measure at 4 or 8wk. 2. From baseline to 4 and 8 wk, participants receiving the intentional condition significantly improved on measures of Environmental reward (EROS; $p<0.05$), Behavioral activation (BADS; $p<0.05$), Emotional distress (BSIGSI; $p<0.05$), Productivity (PART-O Productivity subscale; $p<0.05$).
Bombardier et al. (2009) USA RCT PEDro=6 $N_{initial}$=171, N_{final}=126	**Population:** TBI; *Intervention* (n=64): Mean age=37.1y; Gender: Male=43, Female=21; Severity: Severe=21, Moderate=27, Mild=13; Time post-injury<24h. *Control* (n=62): Mean age=34.5y; Gender: Male=51, Female=11; Severity: Severe=19, Moderate=28, Mild=15; Time post-injury<24h. **Intervention:** Patients were randomly assigned to receive a telephone intervention or usual care. The intervention included elements of problem solving and behaviour activation therapy and using Motivational Interviewing (MI) counseling style. Outcomes were assessed at baseline and 1-yr post-discharge. **Outcome Measures:** Brief Symptom Inventory (BSI), Short-Form-36 (SF-36), Neurobehavioural Functioning Inventory (NFI) – depression subscale.	1. BSI-depression subscale scores were significantly higher in the control group after 1-year when compared with the intervention group ($p=0.003$). 2. On the BSI-D and NFI-D ($p=0.002$) subscales, mean treatment group scores were significantly lower than those of the control group.

Discussion

In an RCT, Hart et al. (2020) compared the effects of text message-enhanced behavioural activation to control group. The intervention group received a session of behavioural activation followed by daily SMS messages supporting goals for 8 weeks. The control group received one single session of attention control followed by 8 weeks of SMS messages. Although no significant between group differences were observed, the text message group significantly improved from baseline to follow-up on measures of depression and emotional distress. Future research is necessary to determine the efficacy of behavioural activation therapy for the management of depression in individuals with TBI.

In the study by Bombardier et al. (2009), participants were randomized into a telephone intervention or usual care. The intervention included elements of behavior activation and problem-solving therapy, delivered using motivational interviewing counseling style. The authors found that the treatment group had lower depression scores, as measured by the depression subscales of the Brief Symptom Inventory (BSI) and the Neurobehavioural Functioning Inventory (NFI) (Bombardier et al., 2009).

Conclusions

There is level 1b evidence (Bombardier et al., 2009) that a telephone intervention incorporating elements of behavioral activation therapy may improve depressive symptoms following a TBI.

There is level 2 evidence (Hart et al., 2020) that text message-enhanced behavioural activation therapy may not be different than attention control session combined with text messages for depressive symptoms in individuals with TBI.

KEY POINTS

- Text message-enhanced behavioural activation therapy may not be different than text message-enhanced attention control for depression post moderate to severe TBI.
- A telephone intervention combining elements of behavioral activation therapy and problem-solving therapy may improve depression post TBI.

Mindfulness-Based Interventions

Mindfulness-based interventions relate to the practice of experiencing the present moment with acceptance and full awareness, and it has been used in counseling to help individuals living with mental health conditions such as anxiety and depression (Brown et al., 2013).

TABLE 10 | Mindfulness-Based Interventions for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Combs et al. (2018) USA Pre-Post $N_{Initial}$=29, N_{Final}=19	**Population:** TBI=15, ABI=4; Mean Age=32.8yr; Gender: Male=17, Female=2; Severity of Injury: Mild=3, Severe=12, ABI patients not specified. **Intervention:** Inpatients at a Veterans Affairs Polytrauma Rehabilitation Program (PTRP) participated in a Yoga-based mindfulness-based group intervention that included yoga and mindfulness skills. The intervention utilized aspects of mindfulness-based stress reduction (MBSR). Participants' beliefs were evaluated with a questionnaire before starting and when leaving PTRP. **Outcome Measures:** Questionnaires about current pain, TBI symptoms, sleep, psychological function, and beliefs about mindfulness and yoga. Format based on Beliefs About Yoga Scale (BAYS)	1. Participants generally perceived some benefit from attending the yoga mindfulness-based group interventions. 2. The number of mindfulness-based group session showed significant positive correlations on participants self-reported mood ($p<0.001$), physical health ($p<0.05$), focus ($p<0.05$) and self-awareness ($p<0.05$). 3. Changes in participants' beliefs about relaxation skills' potential to improve psychological functioning was nonsignificant. 4. Pre- post- intervention data showed no statistically significant difference between severity ratings for depression.

Discussion

In a pre-post study, Combs et al. (2018) examined the effectiveness of a group-based intervention that incorporated aspects of MBSR and yoga, focusing on participants' self-report of perceived benefit. The authors found that participants were more likely to believe MBSR could benefit physical health, focus, self-awareness, and overall health with the more sessions they attended. However, changes in participants' beliefs about the potential of relaxation skills to improve psychological functioning were not significant (Combs et al., 2018).

Conclusions

There is level 4 evidence (Combs et al., 2018) that MBSR may be an effective at reducing symptoms of depression post TBI.

KEY POINTS

- Mindfulness-Based Stress Reduction (MBSR) may be effective at reducing depressive symptoms in individuals with TBI; however, may not impact severity.

Art Therapy

Creative art therapy is a complementary therapy facilitated by an art therapist that is used to help individuals to adapt to stressful life situations associated with illness or disability, particularly those in palliative care (Iguina & Kashan, 2019).

TABLE 11| Art Therapy for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Di Vita et al. (2022) Italy PCT $N_{Initial}$=12, N_{Final}=8	**Population:** Severe TBI; Gender=Not Reported; *Psychotherapy:* Mean Age=38.5yr, *Art Therapy:* Mean Age=30.6yr; Mean GCS=Not Reported; Mean Time Post-Injury=12mo **Intervention:** Participants were allocated to either Psychotherapy or Art Therapy and were subsequently exposed to the alternate intervention. The intervention duration was 1.5hrx4mo. Outcomes were assessed at baseline (B1), at 2-mo (B2), 4-mo after B2 (T1), 2-mo after crossover (T2), 4-mo after T2 at the completion of the 2nd phase of the intervention(T3), and at 2-mo follow-up (T4). **Outcome Measure:** Patient Competency Rating Scale (PCRS), Mayo-Portland Adaptability Inventory (MPAI-4), Quality of Life after Brain Injury (QOLIBRI), Clinical Outcomes in Routine Evaluation - Outcome Measure (CORE-OM), Brain Injury Grief Inventory (BIGI), Difficulties in Emotion Regulation Scale (DERS), Brief - Coping Orientation to Problems Experienced Inventory (Brief-COPE), Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory-X (STAI-X).	1. Subjective Well-Being subscale scores in the *PsyArt* group were significantly higher those in the *ArtPsy* group ($p<.05$). 2. Wilcoxon signed-rank test yielded higher scores for depression in the BDI-II at B2 than at T2 ($p<.05$). 3. At the end of both treatments, patients showed a reduction in depressive symptoms and in the perception of physical problems

Discussion

In a PCT study, Di Vita et al. (2022) examined the use of art therapy and psychotherapy to help individuals with severe TBI to adapt to life experiences, and to reach a higher level of self-awareness, social functioning and emotional autoregulation. Participants in both treatment groups showed a reduction in depressive symptoms.

Conclusions

There is level 2 evidence (Di Vita et al., 2022) that art therapy may reduce symptoms of depression in individuals with severe TBI.

KEY POINTS

Art Therapy may be effective for the reduction of depressive symptoms post severe TBI.

Psychoeducation

Psychoeducation interventions have been used in healthcare to help patients understand and manage their mental health condition by reinforcing their individual skills and resources to be able to better cope with their situation (Casañas et al., 2012). Psychoeducation is based on providing patients and their families with information about their illness or disorder to enable them to understand their condition better and to adhere to medical treatment; for instance, psychoeducation has been used to help individuals with bipolar disorder and their family members to identify mood episodes (Rabelo et al., 2021).

TABLE 12 | Psychoeducation for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Bell et al. (2011) USA RCT PEDro=6 $N_{Initial}$=433, N_{Final}=299	**Population:** TBI; Mean Age=39yr; Gender: Male=323, Female=110; Mean GCS=9.7 **Intervention:** Participants were randomly assigned to either scheduled telephone intervention or usual care in the community. The treatment group received telephone calls over 21mo consisting of education, problem-solving, and referrals. Outcomes were assessed at 1 and 2 yr. **Outcome Measures:** Functional Independence Measure (FIM), Disability Rating Scale (DRS), Participation Assessment with Recombined Tools-Objective (PART-O), Glasgow Outcome Scale-Extended (GOS-E), 12-Item Short Form Health Survey (SF-12), Brief Symptom Inventory-18, EuroQOL (EQ-5D), Perceived Quality of Life (PQoL).	1. No significant differences in emotional status were observed at year 1 between the groups, as measured by the Brief Symptom Inventory-18 (p=0.898) and SF-12 - mental (p=0.310). 2. No significant differences were found for emotional and mental status at year 2 in the Brief Symptom Inventory-18 (p=0.931) or the SF-12 mental score (p=0.262).
Sinnakaruppan et al. (2005) UK RCT PEDro=5 $N_{Initial}$=89, N_{Final}=83	**Population:** TBI=41, Caregivers=42; Age Range=21-63yr; Gender: Male=41, Female=42. Time Post Injury=2 to 94mo; GCS=3-12. **Intervention:** Caregivers and patients were randomly assigned to an educational training program led by a neuropsychologist (8 x 2.5hr sessions) or a waitlist control. **Outcome Measures:** Hospital Anxiety and Depression Scale (HADS), General Health Questionnaire-28 (GHQ-28), Rosenberg Self-Esteem Scale (RSE), Coping Orientation Problems Experienced Scale (COPE), Functional Independence Measure (FIM), Rivermead Behavioural Memory Test (RBMT), Behavioural Assessment of Dysexecutive Syndrome (BADS), Weschler Adult Intelligence Scale-Third Edition (WAIS-III).	1. There were improvements for both the groups; however, a comparison of means between the two samples did not show a statistically significant change (p=0.615) for HADS anxiety. 2. There was a modest reduction in the HADS Depression mean score for both the groups at follow-up; however, group differences were not significant (p=0.331).

Author Year Country Study Design Sample Size	Methods	Outcome
Neumann et al. (2017) USA Pre-Post N=17	**Population:** TBI=17; Mean Age=46.12yr; Gender: Male=13, Female=4; Mean Time Post Injury=8.73yr; Mean PTA=95.35d; Mean LOC=14.18d. **Intervention:** Lessons incorporated psycho-educational information and skill-building exercises teaching emotional vocabulary, labeling, and differentiating self-emotions; interoceptive awareness; and distinguishing emotions from thoughts, actions, and sensations. **Outcome Measures:** Toronto Alexithymia Scale (TAS-20), Levels of Emotional Awareness Scale (LEAS), State Trait Anxiety Inventory (STAI), Patient Health Questionnaire (PHQ-9) - Depression, State Trait Anger Expression Inventory (STAX-2I), Positive and Negative Affect Scale (PANAS), Difficulty with Emotion Regulation Scale (DERS), Satisfaction Questionnaires.	1. Significant improvements on the TAS-20 and LEAS scores at post-test and follow-up from baseline. 2. No significant change in PHQ-9 scores or Negative affect at post-test or follow-up.

Discussion

In an RCT, Bell et al. (2011) examined a telephone intervention in the community, compared to usual care. The intervention consisted of education, problem-solving and assistance with referrals. The authors found no significant differences in emotional status and mood, as measured by the Brief Symptom Inventory and the Short Form 12 – mental sub-scale.

In a pre-post study, Neumann et al. (2017) implemented a psychoeducational information and skill-building exercises program for post TBI individuals. The program involved teaching emotional vocabulary, labelling and differentiating emotions, as well as the distinction between actions, sensations and emotions. The authors did not find any significant improvements for depression, as measured by the PHQ-9 (Neumann et al., 2017). In the RCT by Sinnakaruppan et al. (2005), both individuals with TBI and their caregivers received an educational training program focused on cognitive abilities, with results indicating no significant improvements in depression.

Conclusions

There is level 1b evidence (Bell et al., 2011) that psychoeducation delivered on the phone may not be more effective than usual care for mood in individuals with TBI.

There is level 2 evidence (Sinnakaruppan et al., 2005) that an educational program for individuals with TBI and their caregivers focused on cognitive abilities may not decrease depression.

There is level 4 evidence (Neumann et al., 2017) that psychoeducation may not be effective for the treatment of depression in individuals with TBI.

KEY POINTS

- Psychoeducation may not be an effective treatment for depression following TBI.

Music Therapy

Music therapy is based upon the hypothesis that music encourages more harmonious cerebral activity given the involvement of both hemispheres in processing musical stimuli (Besson & Schon, 2001). As guided by a music therapist, the therapy can involve a combination of listening, singing, and playing instruments. While music therapy is often used in cognitive rehabilitation, it has also been utilized as an intervention for mood.

TABLE 13 | Music Therapy for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Siponkoski et al. (2022) RCT Crossover PEDro=5 N=38	**Population:** TBI; *AB group:* Gender: Male=10, Female=10; Mean Age=41.6yr; Mean GCS=12.3; *BA group:* Gender: Male=12, Female=6; Mean Age=41.8yr; Mean GCS=10.9; Time Post-Injury=8.8mo **Intervention:** Participants were randomly allocated to receive a neurological music therapy intervention immediately or after 3 months. After 3 months, the groups crossed over. Modules included rhythmical training, structured cognitive-motor training and assisted music playing with improvisation. The intervention lasted 20 sessions, 60min, 2x/wk. Outcomes were assessed at baseline, at 3-mo, 6-mo post-intervention crossover, and 18-mo follow up. **Outcome Measure:** Behaviour Rating Inventory of Executive Function – Adult version (BRIEF-A), Beck Depression Inventory II (BDI-II), Quality of Life after Brain Injury (QOLIBR)	1. The scores BRIEF-A showed improvement for the AB Group, when compared to the BA group at 3mo (p=0.030). 2. The BRIEF-A improved significantly in the AB group from baseline to 3mo (p=0.002) and from baseline to 6mo (0.020), but not from 3mo to 6mo. 3. The change in the BRIEF-A over the time points did not reach statistical significance in BA group (p=0.275). 4. No significant results on the other measures were observed.
Guetin et al. (2009) France Pre-Post N=13	**Population:** TBI; Mean Age=31yr; Gender: Male=3, Female=10; Mean Time Post Injury=8yr. **Treatment:** Participants received music therapy (1 hr/wk for 20wk). Each session was divided into two segments: receptive music therapy (e.g., listening) and active music therapy (e.g., playing an instrument). Assessments were conducted at baseline, 1wk, 5wk, 10wk, 15wk, and 20wk. **Outcome Measure:** Hospital Anxiety and Depression Scale (HADS).	1. Following each music therapy session, significant improvements in mood were noted on the HADS (p<0.05). 2. Anxiety scores significantly decreased from baseline to 10wk, 15wk, and 20wk (p<0.05). 3. Depression scores significantly decreased from baseline to 10wk and 15wk (p<0.05).

Author Year Country Study Design Sample Size	Methods	Outcome
Thaut et al. (2009) USA PCT N=54	**Population:** TBI=24, Stroke=5, Other=4; Mean Age=31yr; Gender: Male=3, Female=10. **Intervention:** Participants were assigned to a treatment group (n=31) or a control group (n=23). The treatment group received four different sessions of neurologic music therapy (30 min) focused on emotional adjustment, executive function, attention, and memory. The control group were sent to a quiet room to rest for 30 min over four sessions. **Outcome Measure:** Multiple Affect Adjective Checklist (MAACL), Brief Symptom Inventory 18 (BSI-18).	1. On the MAACL, Depression and Anxiety improved significantly in the treatment group ($p<0.05$) compared to the controls. 2. On the MAACL, Positive Affect significantly worsened in the control group ($p=0.04$). 3. On the MAACL, Hostility significantly improved in the control group ($p=0.02$) but not the treatment group ($p=0.06$). 4. On the BSI-18, both groups showed significant improvement (treatment group, $p<0.01$; control, $p=0.010$).

Discussion

In an RCT, Siponkoski et al., (2022) examined the efficacy of a music therapy intervention for improving mood compared to a standard care control group. Participants in this study were not diagnosed with a depressive disorder, and enhancement of mood was a secondary goal of the study. The intervention consisted of a trained music therapist leading 20, 60-minute training sessions of music production on the drums and piano, including rhythmical training, structured cognitive-motor training and assisted music playing with improvisation. The authors found that there were nonsignificant improvements in Beck Depression Inventory (BDI) scores from baseline to post-intervention (Siponkoski et al., 2022).

In a pre-post study, Guétin et al. (2009) examined the effect of both receptive (i.e., listening to music) and active (e.g., singing, writing a song, playing an instrument) music therapy. The authors found significant improvements in mood, including depression, immediately after sessions and over time (Guétin et al., 2009). In a PCT study by Thaut et al. (2009), a treatment group participated in four sessions of music therapy focusing on attention, memory, executive function, and emotional adjustment, while the control group received no treatment. The authors found that the treatment group showed significant reductions in symptoms of depression, when compared to the control group (Thaut et al., 2009).

Conclusions

There is conflicting level 2 evidence (Siponkoski et al., 2022; Thaut et al., 2009) and level 4 evidence (Guétin et al., 2009) regarding the effectiveness of music therapy for depression in individuals with ABI.

KEY POINTS

- There is conflicting evidence regarding the use of music therapy to alleviate depression following ABI.

Physical Activity

The positive impact of physical activity on mood has been well-established in the general population (Byrne & Byrne, 1993), and there is evidence that exercise is an effective therapy for depression in patients without ABI (Kvam et al., 2016; Schuch et al., 2016). A variety of physical activity interventions have been used to treat mood-related issues in individuals following ABI.

TABLE 14 | Physical Activity for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
	Aerobic Exercise	
Bellon et al. (2015) USA RCT PEDro=6 $N_{Initial}$=123, N_{Final}=69	**Population:** TBI; Mean Age=43.7yr; Gender: Male=41, Female=28; Mean Time Post Injury=100.5mo; Severity: Mild=10, Moderate=10, Severe=35. **Intervention:** Participants were randomized into a walking group (treatment) or nutrition group (control). The home-based walking group was administered a pedometer to track steps taken weekly for 12wk, with a coaching call 3 days/wk to encourage increase in weekly step count. The home-based nutrition group learned about healthy eating habits through coaching calls 3 days/wk for 12 wk. After 12wk, participants crossed over. Measures were assessed at baseline, 12wk, and 24wk. **Outcome Measure:** Centre for Epidemiological Studies-Depression (CES-D), Perceived Stress Scale (PSS).	1. There was a significant effect for Assessment Time (p=0.007) with scores decreasing (less depression) by 24 weeks. 2. Stress on the PSS decreased overall from baseline to post-treatment for all participants (p=0.006), with a greater decrease in the walking group (p=0.006).
Hassett et al. (2009) Australia RCT PEDro=8 N=62	**Population:** Severe TBI; Fitness Center Group (n=32): Mean Age=35.4yr; Gender: Male=27, Female=5; Median Time Post Injury=2.6 mo. Home-Based Group (n=30): Mean Age=33yr; Gender: Male=26, Female=4; Median Time Post Injury=2.3 mo. **Intervention:** Participants were randomly assigned to either an exercise intervention group at a fitness center or to a home-based exercise group. Fitness center participants were supervised by a personal trainer (1hr, 3x/wk, 12wk), the home-based exercise group followed an exercise plan and were monitored by a physiotherapist. Assessment at baseline, end of intervention and 3mo follow-up. **Outcome Measures:** 20m Shuttle Test, Heart Rate (HR), Body Mass Index (BMI), Waist-to-Hip-ratio (WHR), Depression Anxiety Stress Scale (DASS), Profile of Mood States (POMS), Brain Injury Community Rehabilitation Outcome (BICRO-39), Sydney Psychosocial Reintegration Scale (SPRS).	1. There were no between-group significant differences in psychological functioning, including depression (p=0.238), anxiety (p=0.132) and stress (p=0.131).

Author Year Country Study Design Sample Size	Methods	Outcome
Bateman et al. (2001) UK RCT PEDro=7 N=157	**Population:** Severe ABI; TBI=44, Stroke=70, Subarachnoid Hemorrhage=15, Other=28; Gender: Male=97, Female=60. *Training Group* (n=79): Mean Age=41.7yr; Mean Time Post Injury=22.2 wk. *Control Group* (n=79): Mean Age=44.7yr; Mean Time Post Injury=25.5wk. **Intervention:** Participants were divided to receive either an exercise intervention (cycle training) or relaxation training (control group) for 30min sessions, 3x/wk for 12wk. **Outcome Measures:** Heart Rate (HR), Body Mass Index (BMI), Modified Ashworth Scale (MAS), Berg Balance Scale (BBS), Rivermead Mobility Index (RMI), Barthel Index (BI), Functional Independence Measure (FIM), Nottingham Extended Activities of Daily Living (NEADLI), Hospital Anxiety and Depression Scale (HADS).	1. No significant group differences were reported for the HADS anxiety and depression scores.
Weinstein et al. (2017) USA Pre-Post $N_{Initial}$=12, N_{Final}=10	**Population:** TBI; Mean Age=32.9yr; Gender: Male=4, Female=6; Mean Time Post Injury=6.6yr; Severity: Mild=5, Moderate=4, Severe=1. **Intervention:** Participants completed one-on-one supervised aerobic exercise sessions (3 days/wk for 12wk) where they reached 70-80% of maximum heart rate. Assessments were conducted before and after sessions at baseline, 4wk, 8wk, and 12wk. **Outcome Measure:** Profile of Mood States - Short Form (POMS-SF).	1. Significant improvement from baseline to 12wk were found, as 80% of participants reported less mood disturbance on POMS-SF (p=0.04); there was a 9% reduction in POMS-SF scores (p=0.04). 2. There were significant short-term changes in POMS-SF scores in response to singular exercise sessions.
Chin et al. (2015) USA Pre-Post N=7	**Population:** TBI=7; Mean Age=33.3yr; Gender: Male=2, Female=5; Mean Time Post Injury=4.0yr; Severity: Mild=3, Moderate=4. **Intervention:** Supervised vigorous aerobic treadmill training for 30 min, 3 times per wk for 12 wks. **Outcome Measures:** Trail Making Test (TMT-A and B), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Pittsburgh Sleep Quality Index (PSQI), Beck's Depression Inventory (BDI).	1. No significant changes observed for PSQI or BDI scores following exercise training.
Gordon et al. (1998) USA Case Control N=240	**Population:** TBI; *Non-Exercise Group (n=176)*: Mean Age=37.1yr; Mean Time Post Injury=9.1yr. *Exercise Group (n=64)*: Mean Age=37.8yr; Mean Time Post Injury=11.2yr. **Intervention:** Retrospective comparison of exercisers and non-exercisers. **Outcome Measure:** Beck Depression Inventory (BDI), The Institute for Rehabilitation Research (TIRR) Symptom Checklist.	1. Individuals who exercised had less depressed mood (BDI) than those who did not exercise (p<0.01). 2. Individuals who exercised reported significantly fewer symptoms on the TIRR checklist compared to those who did not exercise (p<0.0004).

Author Year Country Study Design Sample Size	Methods	Outcome
Tai Chi		
Blake & Batson (2009) UK RCT PEDro=6 N=20	**Population:** TBI; Gender: Male=15, Female=5; Injury Severity: Mild=7, Moderate=8, Severe=5. *Treatment Group (n=10)*: Mean Age=44.5yr; Mean Time Post Injury=16.4 yr. *Control Group (n=10)*: Mean Age=46.2yr; Mean Time Post Injury=13.62 yr. **Intervention:** The treatment group performed tai chi (qigong) for 1 hr/wk over 8wk. The control group attended non-exercise social and leisure activities for 1 hr/wk over 8wk. Measures were assessed at baseline and 8wk. **Outcome Measure:** General Health Questionnaire-12 (GHQ-12), Physical Self-Description Questionnaire.	1. At 8wk, GHQ-12 showed a significant improvement in mood scores for those in the treatment group compared to the control group (p=0.026). 2. Physical self-esteem was found to improve significantly from baseline to 8wk for those in the treatment group (p=0.017).
Yoga		
Combs et al. (2018) USA Pre-Post $N_{Initial}$=29, N_{Final}=19	**Population:** TBI=15, ABI=4; Mean Age=32.8yr; Gender: Male=17, Female=2; Severity of Injury: Mild=3, Severe=12, ABI patients not specified. **Intervention:** Inpatients at a Veterans Affairs Polytrauma Rehabilitation Program (PTRP) participated in a Yoga-based mindfulness-based group intervention that included yoga and mindfulness skills. The intervention utilized aspects of mindfulness-based stress reduction (MBSR). Participants' beliefs were evaluated with a questionnaire before starting and when leaving PTRP. **Outcome Measures:** Questionnaires about current pain, TBI symptoms, sleep, psychological function, and beliefs about mindfulness and yoga. Format based on Beliefs About Yoga Scale (BAYS)	1. Participants generally perceived some benefit from attending the yoga mindfulness-based group interventions. 2. The number of mindfulness-based group session showed significant positive correlations on participants self-reported beliefs about the benefits of mindfulness and yoga for overall health (p<0.001), mood (p<0.001), physical health (p<0.05), focus (p<0.05) and self-awareness (p<0.05). Self-reported beliefs about sleep and cause of pain were not significantly correlated with number of sessions attended (p>0.05). 3. Changes in participants' beliefs about relaxation skills' potential to improve psychological functioning was nonsignificant. 4. Pre- post- intervention data showed no statistically significant difference between severity ratings for depression.
Dance		
Sarkamo et al. (2021) Finland RCT Crossover PEDro=7 N=11	**Population:** TBI; Gender: *AB Group:* Male=3, Female=3, *BA Group:* Male=4, Female=1; *AB group:* Mean Age=36.3yr *BA group:* Mean Age=35.0yr; *AB group:* Mean Time Post Injury=9.2yr *BA group:* Mean Time Post Injury=5.8yr **Intervention:** Participants were randomized to either the AB or BA group. The AB group received the dance intervention during the first 3-mo phase while the BA group received the intervention during the second 3-mo phase. The intervention duration was 60min/d, 2 sessions/wk, 12wk. Outcomes were assessed at	1. Scores on the depression measure (BDI-II) significantly improved as a result of the dance intervention (p=.002). 2. There was a consistent, large effect size on the BDI-II (d=1.19-1.74) indicating overall improvement of mood.

Author Year Country Study Design Sample Size	Methods	Outcome
	baseline, at 3-mo, and at 6-mo follow-up. **Outcome Measure:** Trunk Impairment Scale (TIS), Berg Balance Scale (BBS), Action Research Arm Test (ARAT), 6-meter walking test (6MWT), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Wechsler Adult Intelligence Scale IV, (WAIS-IV) Sustained Attention to Response Test (SART), Behaviour Rating Inventory of Executive Function - Adult Version (BRIEF-A), Beck Depression Inventory-II (BDI-II), Quality of Life after Brain Injury, (QOLIBRI)	

Discussion

Eight studies examined the effectiveness of aerobic exercise in improving mood and related symptoms post TBI; none of the studies explicitly included participants with a formal depression diagnosis. In the pre-post study by Weinstein et al. (2017), the authors found that a 12 weeks of high-intensity aerobic training resulted in mood improvements, as measured by the POMS (Weinstein et al., 2017). Similarly, in a case control study, Gordon et al. (1998) reported that individuals who exercised reported significantly fewer symptoms of depression when compared to individuals who did not exercise.

In an RCT, Bellon et al., (2015) compared a walking group to a nutrition group and found that depression, as measured by the CES-D, decreased significantly by 24 weeks. In the pre-post study by Chin et al. (2015), the authors reported that 12 weeks of vigorous aerobic treadmill training also did not significantly reduce symptoms of depression post-intervention (Chin et al., 2015). In a pre- post study, Combs et al. (2018) examined the effects of a yoga-based mindfulness group intervention that utilized aspects of mindfulness-based stress reduction (MBSR) and found no statistically significant differences between severity ratings for depression. In an RCT, Hassett et al. (2009) found no differences on depression and psychological functioning between a group that exercised at a fitness centre and a group that exercised at home. Bateman et al. (2001) compared cycle ergometer aerobic training and a relaxation training control and found no differences for measures of depression.

Tai Chi and Dance rehabilitation interventions were also examined. In an RCT, Blake and Batson (2009) investigated the benefits of the Chinese exercise Tai Chi in individuals with TBI, using Tai Chi Qigong. The authors found significant improvement in mood compared to the control group. An RCT Crossover by Sarkamo et al. (2021) examined the effectiveness of a dance paired with specialized rehabilitation for the treatment of depression. The authors found that the treatment had medium-to-large effect sizes on self-reported depression scores compared to the no-treatment control condition. Overall, physical activity may reduce symptoms of depression. Perry et al. (2018) reported in a meta-analysis that exercise

for the treatment of depression in patients with TBI had a small to moderate positive effect; however, it should be noted that this meta-analysis included mild TBI. Further research may be needed to determine which types of exercise may be more effective following a moderate to severe TBI.

Conclusions

There is level 1a evidence (Sarkamo et al., 2021) that dance therapy might reduce symptoms of depression post ABI.

There is level 1b evidence (Bellon et al., 2015) that walking may be effective for improvement of depression.

There is level 1b evidence (Blake & Batson, 2009) that Tai Chi may improve mood compared to wait-list controls following TBI.

There is level 1b evidence (Hassett et al., 2009) that exercising at a fitness center is no more effective than exercising at home for depression and psychological function post severe TBI.

There is level 1b evidence (Bateman et al., 2001) that cycle ergometer aerobic training may not be effective for depression post severe ABI, compared to relaxation training.

There is level 3 evidence (Gordon et al., 1998), and level 4 evidence (Weinstein et al., 2017) that aerobic exercise may be effective for mood in individuals with TBI.

There is level 4 evidence (Chin et al., 2015) that aerobic exercise using an elliptical machine, or a treadmill may not improve depression in individuals with TBI.

There is level 4 evidence (Combs et al., 2018) that a yoga-based mindfulness group intervention may not be effective for the management of depression post TBI.

KEY POINTS

- Aerobic exercise may be effective for depression post ABI.
- Exercise using an elliptical machine, or a treadmill might not be effective for depression.
- Exercise at a fitness center may not be different than exercising at home for depression in individuals with severe TBI.
- Tai Chi, and Dance therapy may improve symptoms of depression in individuals with ABI.
- A yoga-based mindfulness group intervention may not be effective for depression post TBI.
- Cycle ergometer aerobic training may not be more effective than relaxation training for depression in those with severe ABI.

Rehabilitation Programs

Rehabilitation programs that address multiple components besides mood, can potentially improve depression in those with moderate to severe ABI. Following a brain injury, individuals may benefit from a holistic approach to rehabilitation delivered by an interprofessional team, ensuring coordination of care to address all aspects of the individual's life (Lizzo et al., 2021).

TABLE 15 | Rehabilitation Programs for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Multidisciplinary Rehabilitation		
Mendes et al. (2021) Portugal RCT PEDro=6 N=27	**Population:** TBI; *Experimental group* (EG) (n=8); Mean Age=37yr; Gender: Male=8, Female=0; Mean GCS= 6, Time Post Injury Mean=5.09 mo. *Control Group I* (CGI) (n=10); Mean Age=37.2yr; Gender: Male=8, Female=2; Mean GCS=9, Time Post Injury Mean=53 mo. *Control Group II (CGII)* (n=9); Mean Age: 39.4yr; Gender: Male=6, Female=3; Mean GCS= 7; Time Post Injury= 1.66mo. **Intervention:** Participants received a remote holistic neuropsychological intervention program supported by a VR platform 40-60min 5x/ wk for 16 wk (cognitive training 3x/ wk and psychosocial 2x/wk). Control Group I received conventional holistic neuropsychological intervention program for 22hr/ wk x22 wk. Control Group II did not receive any intervention. **Outcome Measures:** Montreal Cognitive Assessment (MoCA), Hospital Anxiety and Depression Scale (HADS), Quality of Life after Brain Injury (QOLIBRI); Token Test (TT), Wisconsin Card Sorting Test (WCST), Trail Making Test A, Trail Making Test B, Hopkins Verbal Learning Test (HVLT), Weschler Memory Scale-III (WMS-III), Stroop Test.	1. There were no significant differences found between the groups in depression and anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS) Portuguese Version.
Powell et al. (2002) USA RCT PEDro=4 $N_{initial}$=110, N_{final}=94	**Population:** Severe TBI; Gender: Male=71, Female=23. *Outreach Group* (n=48): Mean Age=34yr; Mean Time Post Injury=4 yr. *Information Group* (n=46): Mean Age=35yr; Mean Time Post Injury=2.7 yr. **Intervention:** Participants were randomly allocated to either an outreach treatment group provided by a multidisciplinary team (2-6hr/wk, 6-12wk) or an information treatment group which involved a therapist providing a booklet of resources at a single home visit. **Outcome Measures:** Barthel Index (BI), Brain Injury Community Rehabilitation Outcome-39 Scales (BICRO-39), Functional Independence Measure (FIM), Functional Assessment Measure (FAM), Hospital Anxiety and Depression Scale (HADS).	1. The outreach group had greater change scores on the psychological wellbeing ($p<0.025$) subscale of the BICRO-39 than the information group. 2. The two groups did not differ in the extent of change from intake to follow up for either anxiety or depression, as measured by the HADS.

Author Year Country Study Design Sample Size	Methods	Outcome
Wade et al. (1998) UK RCT PEDro=6 $N_{Initial}$=314, N_{Final}=218	**Population:** *Follow-up Services by Specialist Team* (n=184): Mean age=33.53yr; Gender: Male=130, Female=54; Mean Time post-injury=Not Reported; Severity: Mild=48, Moderate=39. Severe=31, Not Reported=14. *Standard Care* (n=130): Mean age=32.45yr; Gender: Male=102, Female=28; Mean Time post-injury=Not Reported; Severity: Mild=31, Moderate=23, Severe=24, Not Reported=8. **Intervention:** Patients were randomized to receive standard hospital care or additional services by a specialist team following discharge as needed. Outcomes were assessed at baseline and at 6mo. **Outcomes:** Rivermead head injury follow-up questionnaire (RHFUQ), Rivermead post-traumatic amnesia protocol (RPP), Rivermead post-concussion symptom questionnaire (RPQ), Hospital Anxiety and Depression (HADS), Short orientation memory and concentration test (SOMC).	1. No significant differences were found in depression.
Feiger et al. (2023) USA Case Series N=174	**Population:** TBI; Gender: Male=137, Female=37; Mean Age=40.38yr; Mean Time Post-Injury= 212.67d **Intervention:** A residential post-acute rehabilitation program that provided personalized services based on individual needs of survivors of moderate/severe TBI. Services included physical therapy, occupational therapy, speech language therapy, cognitive rehabilitation, adaptive sports, life planning, and individual and/or family psychological counseling. The mean length of the rehabilitation program was 88.76d. Outcomes were assessed at admission and discharge from the program**.** **Outcome Measure:** Controlled Oral Word Association Test (COWAT), Trail Making Test-B (TMT-B), Hopkins Verbal Learning Test-Revised (HVLT-R), Wechsler Adult Intelligence Scale 4th Edition, Beck's Depression Inventory-II (BDI), Mayo-Portland Adaptability Inventory Adjustment Index (MPAI-4).	1. Psychosocial adjustment impairment significantly reduced from admission to discharge (p<.001). 2. Admission psychosocial adjustment impairment had a positive significant association with depression when controlling for cognitive functioning (p=.02), however depression did not in turn predict psychosocial adjustment impairments at discharge.
Schonberger et al. (2014) Australia Pre-Post N=42	**Population:** TBI; Mean Age=32yr; Gender: Male=37, Female=5; Mean Time Post Injury=81d. **Intervention:** Community Based Rehabilitation Program with a multi-disciplinary team (3-4×/wk). **Outcome Measure:** Hospital Anxiety and Depression Scale (HADS), Self-Awareness of Deficits Interview (SADI), Sydney Psychosocial Reintegration Scale-2 (SPRS) and Reactions to Impairment and Disability Inventory (RIDI).	1. There was a significant association between positive RIDI and low levels of self-reported depression on the HADS (p<0.001). 2. No significant effect of time was found for the HADS.
Self-Awareness Rehabilitation		
Schmidt et al. (2013) Australia	**Population:** *Video Feedback* (n=18): Mean age=42.7yr; Gender: Male=14, Female=4; Mean time post injury=1.5yr; Mean GCS=8.1. *Verbal Feedback* (n=18):	1. There were no significant differences between groups in depression, anxiety and stress scores, as measured by the DASS-21.

Author Year Country Study Design Sample Size	Methods	Outcome
RCT PEDro=8 N=54	Mean age=41.6yr; Gender: Male=14, Female=4; Mean time post injury=4.7yr; Mean GCS=7.1. *Experimental Feedback* (n=18): Mean age=37.5yr; Gender: Male=18; Mean time post injury=5.8yr; Mean GCS=7.0. **Intervention:** Participants received instructions for meal preparation on 4 occasions in one of three formats. The video feedback group watched their recorded meal preparation sessions, the verbal feedback group received feedback on task completion without the video, and the experimental group received no therapist feedback on task completion. **Outcome Measures:** Awareness Questionnaire (AQ), Self-perceptions in Rehabilitation Questionnaire (SPIRQ), Depression Anxiety Stress Scale (DASS), Behavioural Assessment of the Dysexecutive Syndrome, Wisconsin Card Sorting Test (WCST), Wechsler Memory Scale Third Edition (WMS-III).	
Goal-based Rehabilitation		
Hart & Vaccaro (2017) USA RCT PEDro=6 N=8	**Population:** Severe TBI. *GI* (n=4): Mean age=23.8yr; Gender: Male=1, Female=3; Mean time post-injury=2.5yr; *GR* (n=4): Mean age=34.3yr; Gender: Male=3, Female=1; Mean time post-injury=2.7yr. **Intervention:** Participants were randomized to receive text messages for goal-related implementation intentions (GI) for 8wk to improve socialization and emotional function, or to an educational review regarding goals with no follow-up messages (GR). Outcomes were assessed at baseline and post-intervention. **Outcomes:** Brief Symptom Inventory-18 (BSI-18), Participation Assessment with Recombined Tools Objective (PART-O), Goal Attainment Scale (GAS).	1. There were no significant differences between treatment groups for BSI-18 depression and anxiety, (p>0.05).

Discussion

Multidisciplinary rehabilitation was examined in three studies. In an RCT, Mendes et al. (2021) compared holistic neuropsychological rehabilitation delivered via virtual reality to conventional neuropsychological rehabilitation and a control group that received no intervention. The authors found no differences in depression, as measured by the HADS, Portuguese version (Mendes et al., 2021). In a pre-post study, Schonberger et al. (2014) found that a community-based rehabilitation program led by a multidisciplinary team resulted in no significant psychological changes; with good psychological adjustment more closely related to good functional status. In a retrospective case series, Feigner et al. (2023) examined a group of individuals who have received post-acute multidisciplinary rehabilitation to determine if neuropsychological functioning was a predictor of psychosocial adjustment difficulties at discharge. The authors found that depression was not a mediator for the relationship between cognitive

functioning and psychosocial adjustment outcomes. In the study by Powell et al. (2002), an outreach intervention with a multidisciplinary group in the community was no different than an information booklet of resources for measures of depression. Similarly, additional follow-up services by a specialist team was no different than standard care for depression in the RCT by Wade et al. (1998).

In an RCT, Schmidt et al. (2013) examined the effect of feedback for the rehabilitation of self-awareness. Participants performed a task that involve meal preparation and randomly received 1 or 3 feedback types: video plus verbal feedback, verbal feedback or experiential feedback. The authors found no significant group differences in depression (Schmidt et al., 2013). In an RCT, Hart and Vaccaro (2017) examined the implementation of intentions on goal-relevant outcomes, with or without SMS reminders. Goals were related to emotional function and socialization in individuals who had difficulties with self-regulation. The authors found no differences between the groups for depression, as measured by the depression sub-scale of the Brief Symptom Inventory-18 (BSI-18).

Conclusions

There is 1b evidence (Mendes et al., 2021) that holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for depression than conventional neuropsychological rehabilitation.

There is level 1b evidence (Schmidt et al., 2013) that video feedback for self-awareness rehabilitation may not be different than verbal or experiential feedback for depression post TBI.

There is level 1b evidence (Hart & Vaccaro, 2017) that a goal intention intervention with reminders via text messages may not improve depression post severe TBI.

There is level 1b (Wade et al., 1998), level 2 evidence (Powell et al., 2002) and level 4 evidence (Feigner et al., 2023; Schonberger et al., 2014) that community-based rehabilitation programs alone and specialist follow-up may not improve depression post TBI, and that depression may not mediate cognitive functioning and psychosocial outcomes following post-acute rehabilitation.

KEY POINTS

- Community-based rehabilitation may not improve depression post TBI.
- Depression may not mediate cognitive functioning and psychosocial outcomes following post-acute multidisciplinary rehabilitation.
- Holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for depression than conventional neuropsychological rehabilitation.
- Self-awareness training and goal-based rehabilitation may not be effective for depression post TBI.

Cognitive Rehabilitation

Cognitive rehabilitation aims to help individual with ABI to regain cognitive function or to compensate for cognitive deficits, and it can be implemented using technologies such as computer-based cognitive tools and virtual reality (De Luca et al., 2018).

TABLE 16 | Cognitive Rehabilitation for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
De Luca et al. (2023) Italy RCT PEDro=6 N=20	**Population:** TBI; *Experimental group*(n=10): Gender: Male=5, Female=5; Mean Age=46.2yr; *Control Group* (n=10): Gender: Male=6, Female=4; Mean Age=43.1yr; Time Post-Injury=>6-mo **Intervention:** Participants were randomized to either the experimental group or the control group. The experimental group received innovative virtual reality training (VR-CT) whereas the control group received conventional cognitive treatment (C-CT). All participants received 24 sessions of the same standard cognitive rehabilitation 3x/wk for 8wk. All outcomes were assessed before and after the intervention. **Outcome Measure:** Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT), Frontal Assessment Battery (FAB), Hamilton Rating Scale for Depression (HRS-D), Psychological General Well Being Index (PGWBI) Coping Orientation to the Problems Experiences-new Italian version (COPE-NIV).	1. The virtual reality (VR-CT) group showed significant differences in depressive symptoms HRS-D (p<.008) and positive well-being (p<.005), as well as in coping strategies, including social support (p<.01), avoidance strategies (p<.005) and positive attitude (p<.007). 2. Between-group post-treatment analysis revealed statistically significant differences in the COPE sub-items, including positive attitude (p<.02).
Corallo et al. (2022) Italy RCT PEDro=7 N=12	**Population:** Severe ABI, TBI=7, Vascular=5**;** Mean Age=46.9yr; *Intervention Group* (n=6): Gender: Male=3, Female=3; *Control Group* (n=6): Gender: Male=4, Female=2; Time Post-Injury=Not Reported. **Intervention:** Participants were randomly allocated to either an intervention group receiving cognitive rehabilitation and feedback from a humanoid robot or a control group receiving traditional cognitive rehabilitation 3x/wk for 8wk. Both groups received conventional physiotherapy and speech therapy in addition to cognitive rehabilitation. Outcomes were assessed at admission (T0), after 1 month (T1), and after an additional 2 months (T2). **Outcome Measure:** Level of Cognitive Functioning Scale (LCF) Mini Mental State Examination (MMSE) Severe Impairment Battery (SIB) Beck Depression Inventory (BDI-II) Hamilton Rating Scale for anxiety (HAM-A) Functional Independence Measure scale (FIM) EuroQol-5D (EQ-5D).	1. The experimental treatment significantly improved symptoms of anxiety (p<.001) and depression (p<.001) as measured by the HAM-A and BDI-II respectively.

Author Year Country Study Design Sample Size	Methods	Outcome
Ownsworth et al. (2017) Australia RCT PEDro=7 $N_{initial}$=54, N_{final}=50	**Population:** Severe TBI. *EBL* (n=27): Male=20, Female=7; Mean age=37.37yr; Mean time post-injury=36.44mo. *ELL* (n=27): Male=23, Female=4; Mean age=37.86yr; Mean time post- injury=40.81mo. **Intervention:** Participants were randomly allocated to the errorless learning (ELL) or error-based learning (EBL) groups and received eight 1.5h therapy sessions over 8wk. Outcomes were measured at baseline, and at 1wk, and 6mo. **Outcome Measures:** Chevignard's Cooking Task, Behavioural Assessment of Dysexecutive Syndrome (BADS), The Awareness Questionnaire (AQ), Patient Competency Rating Scale (PCRS), Sydney Psychosocial Reintegration Scale (SPRS), Care and Needs Scale (CANS), Depression Anxiety and Stress Scales-21 (DASS-21).	1. EBL participants demonstrated better self-awareness than ELL participants ($p<0.05$). 2. Behavioral competency on the PCRS was significantly better in the EBL group than in the ELL group ($p<0.05$). 3. There were no significant between-group differences observed in the Zoo Map task of BADS, or in anxiety and depression, as measured by the DASS-21 ($p>0.05$).
Chiaravalloti et al. (2016) USA RCT PEDro=9 $N_{Initial}$=69, N_{Final}=53	**Population:** TBI. *Treatment Group* (n=35): Mean Age=37.17yr; Gender: Male=27, Female=8; Mean Time Post Injury=120mo; Mean GCS=4.83. *Control Group* (n=34): Mean Age=40.68yr; Gender: Male=24, Female=10; Mean Time Post Injury=102mo; Mean GCS=5.0. **Intervention:** Participants were randomized to receive the modified Short Memory Technique (TG) to improve learning, or conventional therapy (CG) in 10 sessions x5 wk. Participants in the TG were randomized to receive 5 monthly booster sessions (BS) or control sessions (CS) after treatment. Outcomes were assessed before and after treatment, and at 6mo follow-up. **Outcome Measures:** California Verbal Learning Test (CVLT), Memory Assessment Scales (MAS), Rivermead Behavioural Memory Test (RBMT), Frontal System Behaviour Scale (FrSBe), State Trait Anxiety Inventory (STAI), Chicago Multidimensional Depression Inventory (CMDI).	1. There were no significant differences between the groups for depression [F (1, 61) = 0.024; CI = −12.62 to 14.72] or anxiety [F (1, 57) = .075; CI = −4.63 to 4.86] from before to after treatment
Dundon et al. (2015) Ireland RCT PEDro=3 N=26	**Population:** TBI; Mean Age=38.96yr; Gender: Male=19, Female=7, Length of PTA= >7d. **Intervention:** Participants were assessed during a dichotic listening task (DLT) (Study 1) presented at 6 levels of distraction difficulty, and randomly received either adaptive training (AT, n=9), non-adaptive training (NAT, n=8), or no training (NT, n=9) between sessions (Study 2). The cognitive training procedure was based on attention process training (APT). Outcomes were assessed before and after training. **Outcome Measures:** Perceived Stress Questionnaire (PSQ), Calgary Symptoms of Somatic Stress (C-SOSI),	1. The main effect of Time was significant for the C-SOSI ($p=0.066$). 2. The interaction between Group and Time was not significant ($p=0.114$).

Author Year Country Study Design Sample Size	Methods	Outcome
	Test of Everyday Attention (TEA), Rivermead Behavioural Memory Test (RBMT), Wechsler Test of Adult Reading (WTAR), Speed and Capacity of Language Processing Test (SCOLP), Wechsler Memory Scale (WMS), Hayling Sentence Completion Test, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI).	
Cantor et al. (2014) USA RCT PEDro=6 N=98	**Population:** TBI; Mean Age=45.3yr; Gender: Male=37, Female=61; Mean Time Post Injury=12.6yr; Severity: Mild=49, Moderate=19, Severe=30. **Intervention:** Participants were randomly assigned to either the Short-Term Executive Plus (STEP) cognitive rehabilitation program or to a waitlist control. Participants received group sessions of emotional regulation (2 sessions, 45min) and an individual problem-solving session of attention training (1 session, 60min) per day (3d/wk for 12wk). Group sizes were generally 4-6 participants. **Outcome Measures:** Problem Solving Inventory (PSI), Frontal System Behavioural Scale (FrSBe), Behavioural Assessment of the Dysexecutive Syndrome (BADS), Self-awareness of Deficits Interview (SADI), Attention Rating and Monitoring Scale (ARMS), Difficulties in Emotion Regulation Scale (DERS), Stroop Color and Word Test (SCWT), Controlled Oral Word Association Test (COWAT), Animal Naming Test, Wechsler Adult Intelligence Scale (WAIS-III), Short Category Test (SCT), Trail Making Test B, Symbol Digit Modalities Test (SDMT), Auditory Consonant Trigrams (ACT), Test of Reading Speed, Woodcock Johnson III Tests of Cognitive Ability auditory attention scale (WJ-III-COG), Beck Depression Inventory-Second Edition (BDI-II), State-Trait Anxiety Inventory (STAI), Hopkins Verbal Learning Test-Revised (HVLT-R), Participation Objective Participation Subjective (POPS), Life-3 Scale, Self-Efficacy Questionnaire (GSE).	1. There were no group differences for emotion regulation (Difficulties in Emotion Regulation Scale). 2. No change in treatment effects were found for depression.
Bergquist et al. (2009) USA RCT Crossover PEDro=6 N=14	**Population:** Severe TBI; Mean Age=48yr; Gender: Male=7, Female=7. **Intervention:** Individuals were allocated to either an active calendar acquisition intervention group or the control diary group. Participants had 30 therapist mediated sessions, which were completed via Instant Messaging (IM). At the end of the 30 sessions, they crossed over to the other group. During the calendar condition, participants were encouraged to use the online calendar to plan and remember events. IM sessions were used to review tasks completed.	1. No significant differences in depression scores between groups were observed, as measured by the depression scale of the NFI.

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Neurobehavioural Functioning Inventory (NFI) – depression scale, Community Integration Questionnaire (CIQ), Compensation Techniques Questionnaire (CTQ).	
Vanderploeg et al. (2008) USA RCT PEDro=7 N=360	**Population:** TBI; Mean Age=32.4yr; Gender: Male=335, Female=25; GCS <12. **Intervention:** Patients were randomly assigned to specific cognitive-didactic therapy (n=180) or functional-experiential rehabilitation therapy (n=180) for 1.5-2.5hr/d over 20-60d. **Outcome Measure:** Functional Independence Measure (FIM), Disability Rating Scale (DRS), Present State Examination (PSE), Apathy Evaluation Scale, Neurobehavioral Rating Scale, Rancho Los Amigos Scale (RLAS).	1. No significant differences were found in depressed mood, as measured by the Present State Examination (p=0.50). 2. No differences in irritable behaviour (p=0.53) and angry behaviour were found (p=0.31).
Rath et al. (2003) USA RCT PEDro=2 N=46	**Population:** TBI: Mean Age=43.6yr; Gender: Male=23, Female=37; Mean Time Post Injury=48.2 mo, Severity: Mild=27, Moderate-Severe=30, Unknown=3. **Intervention:** Participants were randomized into the innovative (n=32) or conventional (n=28) treatment groups for the remediation of problem-solving deficits. The innovative group received focused on emotional self-regulation and clear thinking. The conventional group received 24 sessions (2-3hr) focusing on cognitive remediation and psychosocial groups. **Outcome Measure:** Weinberg Visual Cancellation Test, Stroop Test, Controlled Oral Word Association Test (COWAT), Will temperament scale, Wechsler Memory Scale-III (WMS-III), Watson Glaser Critical Thinking Appraisal, Wechsler Adult Intelligence Scale Third Edition (WAIS-III), Sickness Impact Profile (SIP), Community Integration Questionnaire (CIQ), Problem Checklist (PCL), Brief Symptom Inventory (BSI), Rosenberg Self-Esteem Scale (RSES), Wisconsin Card Sorting Test (WCST), Problem Solving Inventory (PSI).	1. Significant improvements for the innovative group in emotional self-regulation and self-esteem. 2. On the PCL, the conventional group endorsed significantly less severe somatic symptoms after treatment (p<0.005). 3. On the RSES, the innovative group reported improved self-esteem after treatment, (p<0.05). Improvement approached significance in the conventional group (p< 0.08). 4. Following treatment, the innovative group showed significant treatment gains in PSQ, emotional self-regulation sub-scores (p=0.01 and p<0.01 respectively).
McMillan et al. (2002) UK RCT PEDro=5 N=130	**Population:** TBI; *Mindfulness Training Attentional Control Training (ACT)* (n=44): Mean Age=34.6yr; Gender: Male=35, Female=9; Median GCS=9. *Physical Exercise (PE)* (n=38): Mean Age=31.4yr; Gender: Male=30, Female=8; Median GCS=10. *Control Group* (n=48): Mean Age=36.2yr; Gender: Male=36, Female=12; Median GCS=9. **Intervention:** The ACT group received supervised practice (5 sessions of 45min over 4wk) and were given an ACT audiotape to practice daily with. The PE group	1. No significant differences in anxiety or depression, as measured by the Hospital Anxiety and Depression Scale (HADS).

Author Year Country Study Design Sample Size	Methods	Outcome
	had the same amount of therapist contact, but the audiotape was based on physical training. The control group had no therapist contact. Outcomes were assessed post-training, at 6mo and 12mo. **Outcome Measures:** Test of Everyday Attention (TEA), Paced Auditory Serial Addition Test (PASAT), Adult Memory and Information Processing Battery (AMIPB), Trail Making Test A, Trail Making Test B, Sunderland Everyday Memory Questionnaire (EMQ), Cognitive Failures Questionnaire (CFQ), Hospital Anxiety and Depression (HADS), General Health Questionnaire (GHQ-28), Rivermead Post-Concussion Questionnaire (RPQ).	
Fasotti et al. (2000) Netherlands RCT PEDro=5 N=22	**Population:** TBI; *Experimental Group* (n=12): Mean Age=26.1yr; Gender: Male=8, Female=4, Mean length of PTA=64.3d, Mean Time Post Injury=9.8mo; *Control group* (n=10): Mean Age=30.1yr, Gender: Male=7, Female=3, Mean length of PTA=64.2d, Mean Time Post Injury=8.3mo. **Intervention:** Participants in the experimental group received Time Pressure Management (TPM) training (1hr, 2-3x/wk, 2-3wk) using videotaped short stories to increase awareness of errors and deficits. The control group received concentration training (30min, 2-5hr/wk, 3-4hr). Outcomes were assessed 2wk prior to training, post-training, and at 6mo. **Outcome Measures:** Rey Auditory Verbal Learning Test (RAVLT), Rivermead Behavioural Memory Test (RBMT), The Auditory Concentration Test (TACT), Paced Auditory Serial Addition Test (PASAT), Visual Choice Reaction Test, Scale for Subjective Well-being for the Elderly (SSWO), Trauma Complaints List.	1. There were no significant effects or group interactions for psychosocial well-being, as measured by the Scale for Subjective Well-being for the Elderly (SSWO).
Salazar et al. (2000) USA RCT PEDro=6 $N_{initial}$=120, N_{final}=107	**Population:** TBI; *Hospital rehabilitation* (n=67): Mean age=25yr; Gender: Male=62, Female=5; Mean Time post-injury=38d; Mean GCS=9.4; *Home rehabilitation* (n=53): Mean age=26yr; Gender: Male=51, Female=2; Mean Time post-injury=39d. Mean GCS=9.5. **Intervention:** Patients were randomly assigned to either an intensive, standardized, 8wk, in-hospital cognitive rehabilitation program or a limited home rehabilitation program with weekly telephone support from a psychiatric nurse. Outcomes were assessed at baseline and at the 1yr follow-up. **Outcomes:** Katz Adjustment scale (KAS), Halstead-Reitan Neuropsychological Battery, Buschke Selective Reminding Test (SRT), Continuous Visual Memory Test (CVMT), Paced Auditory Serial Addition Test (PASAT), Wisconsin Card Sorting Test (WCST), Wechsler Memory	1. There were no significant differences between treatment groups reported at 1 year in measures of belligerence (p=0.19), social irresponsibility (p=0.99), antisocial behaviour (p=0.24), social withdrawal (p=0.40), and apathy (p=0.21). 2. At 1 year after randomization, no significant differences were found for verbal or physical aggression (p=0.82). 3. No significant differences were found at 1 year for major depression (p=0.26) and generalized anxiety (p=0.33), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Author Year Country Study Design Sample Size	Methods	Outcome
	Scale Revised (WMS-R), Auditory Consonant Trigrams (ACT).	
Ruff et al. (1994) USA RCT PEDro=3 N=15	**Population:** Severe head injury; Mean Age=26.9yr; Time Post Injury≥6mo. **Intervention:** Participants were randomized to one of two treatment conditions: attention training followed by memory training (Group A; n=7) or vice versa (Group B; n=8). Training was provided using THINKable, a computer-based multi-media program. Participants were assessed before, during and after training. **Outcome Measures:** 2 + 7 Selective Attention Test, WAIS-R Digit Symbol, Continuous Performance Test (CPT); Rey Auditory Verbal Learning Test (RAVLT), Corsi Block Learning Test, Beck Depression Inventory (BDI).	1. No significant differences were observed in depression scores, as measured by the Beck Depression Inventory (BDI).
Ruff & Niemann (1990) USA RCT PEDro=7 N=24	**Population:** TBI; Gender: Male=17, Female=7. Group 1 (n=12): Mean Age=28.3yr; Mean Time Post Injury=44.3mo. Group 2 (n=12): Mean Age=31.1yr; Mean Time Post Injury=52.2 mo. **Intervention:** Group 1 participated in an intensive cognitive retraining program, which was comprised of 4 modules and ran for 12 wk. The control group participated in a day treatment rehabilitation program focused on psychosocial functioning and activities of daily living. **Outcome Measures:** Katz Adjustment Scale (KAS).	1. Individuals in both groups experienced a decrease in depressed mood, as measured by the KAS

Discussion

De Luca et al. (2023) compared a non-immersive virtual reality intervention that included problem-solving and planning retraining, to standard cognitive rehabilitation. The authors found significant differences in depressive symptoms and positive well-being, as well as in coping strategies and positive attitude in favor of the virtual reality group (De Luca et al., 2023). Similarly, Corallo et al. (2022) found that cognitive rehabilitation with the assistance of a humanoid robot, compared to conventional therapy, resulted in significant improvements in symptoms of depression. In an RCT, Ruff and Niemann (1990) compared participants in an eight-week cognitive remediation program with those attending a functional rehabilitation program. As measured by the Katz Adjustment Scale, both groups experienced significant decreases in depressed mood after treatment (Ruff & Niemann, 1990). In the RCT by Rath et al. (2003), a training program aimed at improving problem-solving deficits via emotional regulation had a positive effect on participants' self-esteem and emotional regulation.

In a RCT crossover, Bergquist et al. (2009) used instant messaging to assist the delivery of cognitive rehabilitation and found no group differences in depression, as measured by the depression scale of the NFI. Cognitive training (Short-Term Executive Plus; STEP) was also examined by Cantor et al. (2014), who found no significant group differences for emotion regulation or depression. Similarly, no effect on well-being or mood post TBI was reported in three RCTs that examined time pressure management (Fasotti et al. 2000), attention control training (McMillan et al., 2002), attention process training (Dundon et al., 2015), and modified short memory technique for learning deficits (Chiaravalloti et al., 2016). When comparing cognitive-didactic and functional experiential treatment in an RCT, Vanderploeg et al. (2008) found no differences in depressed mood. In the study by Ownsworth et al. (2017), no differences were reported for mood between an errorless learning and an error-based learning groups. In the RCT by Salazar et al. (2000), the authors found no differences in major depression when comparing in-hospital cognitive rehabilitation and a home program with telephone support from a psychiatric nurse.

Conclusion

There is level 1b evidence (Corallo et al., 2022; De Luca et al., 2023) that cognitive rehabilitation with the assistance of a humanoid robot or non-immersive virtual reality may improve depression, coping and well-being in individuals with ABI.

There is level 1b evidence (Bergquist et al., 2009) that cognitive rehabilitation delivered with the assistance of instant messaging may not improve depression post severe TBI.

There is level 1b evidence (Cantor et al., 2014) that a Short-Term Executive Plus (STEP) cognitive Rehabilitation Program may not improve emotion regulation or depression post TBI.

There is level 1b evidence (Ruff & Niemann, 1990) that a cognitive remediation program and a functional rehabilitation program focusing on psychosocial functioning may be equally effective for improving depression in individuals with TBI.

There is level 1b evidence (Chiaravalloti et al., 2016) and level 2 evidence (Dundon et al., 2015; Fasotti et al. 2000; McMillan et al., 2002) that time pressure management training, attentional training and modified short memory technique may not be effective for mood and well-being post TBI.

There is level 1b evidence (Ownsworth et al., 2017; Vanderploeg et al., 2008) that cognitive-didactic training and errorless learning may not improve depression post TBI, compared to functional-experiential training and error-based training respectively.

There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for depression post moderate to severe TBI.

There is level 2 evidence (Ruff et al., 1994) that attention and memory training may not be different for the improvement depression post TBI.

There is level 2 evidence (Rath et al., 2003) that problem-solving training and attention process training may improve self-esteem and mood post TBI.

KEY POINTS

- Cognitive rehabilitation with the assistance of technology may reduce depressive symptoms in individuals with moderate to severe TBI; however, instant messaging or cognitive training alone may not improve depression in individuals with severe TBI.
- Intensive cognitive retraining and psychosocial functioning rehabilitation may be equally effective for the reduction of depressed mood post TBI; however, attention training may not be more effective than memory training for depression post TBI.
- While Time Management Training, Attentional Training and Modified Short Memory Technique may not improve mood and well-being, problem-solving training seem to have a positive effect.
- Cognitive didactic-training may not improve depressed mood, compared to functional-experiential treatment. Similarly, errorless learning may not improve mood, compared to error-based learning.
- In-hospital cognitive rehabilitation may not be different than home rehabilitation with telephone support for depression post TBI.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (rTMS) has shown promising results in populations without TBI; however, the effectiveness might not be entirely clear (Brunoni et al., 2017). There is limited literature evaluating its role for the management of depression in individuals with ABI.

TABLE 17 | Transcranial Magnetic Stimulation for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Rodrigues et al. (2020) Brazil RCT PEDro=8 $N_{Initial}$=36, N_{Final}=27 Post-Hoc Analysis of Neville et al. (2019)	**Population:** TBI*; Active rTMS (n=16)* Mean Age=32.8yr; Gender: Male=14, Female=2; Mean Time Post Injury=17.8mo; Mean GCS=4.0. *Sham rTMS (n=11):* Mean Age=31.6yr; Gender: Male=10, Female=1; Mean Time Post Injury=17.6mo; Mean GCS=3.0. **Intervention:** In a Post-hoc Analysis RCT, participants were randomly assigned to an active or sham Repetitive Transcranial Magnetic Stimulation (rTMS) condition. The active rTMS group received 10-Hz rTMS stimulation over the left dorsolateral prefrontal cortex, whereas the control group received stimulation with the sham coil over the same region of the brain. rTMS procedures	1. In both groups, there was a significant main effect of time on depressive scores on the BDI-II (p=0.002) after the third assessment. 2. There were no significant adverse effects reported between the groups after the first (p=0.23) and the second week of stimulation (p=0.29). 3. While high frequency rTMS had significant improvements were reported for depressive symptoms in both groups, differences were not significant.

Author Year Country Study Design Sample Size	Methods	Outcome
	were applied with the MagPro X100 magnetic stimulator connected to a figure-of-eight coil, for 20 min each session, for a total of 10 sessions. Outcome measures were assessed immediately after the last rTMS session and 90 days post-intervention. **Outcome Measure:** Spielberger State-Trait Anxiety Inventory (STAI), Beck Depression Scale- 2nd Edition (BDI-II), Executive Function Index (EF Index).	

Discussion

In a post-hoc analysis of an existing RCT (Neville et al., 2019), Rodrigues et al. (2020) evaluated the effects of repetitive transcranial magnetic stimulation (rTMS) on depression in individuals with TBI. The authors found no significant differences were between groups.

Conclusions

There is level 1b evidence (Rodrigues et al., 2020) that repetitive transcranial magnetic stimulation (rTMS) may not be effective for the management of depression post TBI.

KEY POINTS

- Transcranial magnetic stimulation (rTMS) may not be effective for the improvement of symptoms of depression in individuals with moderate to severe TBI.

Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) has been used for treating numerous conditions such as depression, schizophrenia and substance use disorders, as well as for the improvement of cognitive functions in healthy individuals and in those living with Alzheimer's disease (Lefaucheur et al., 2017).

TABLE 18 | Transcranial Magnetic Stimulation for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Rushby et al. (2021) Australia	**Population:** TBI; Mean Age=50.0yr; Gender: Male=21, Female=7; Mean Time Post Injury=13.9yr; Mean PTA length=37.47d.	1. There were no significant differences between active and sham sessions for depression and anxiety, as measured by the

Author Year Country Study Design Sample Size	Methods	Outcome
RCT crossover PEDro=6 N=30	**Intervention:** Participants received a single session anodal (non-invasive transcranial direct current stimulation (tDCS) applied to the left parietal lobe or sham stimulation. Outcomes were assessed before and after sessions. **Outcome Measures:** N-Back Task, Hospital Anxiety and Depression Scale (HADS), Profile of Mood States (POMS), Alertness and Fatigue Scale, Skin Conductance.	HADS and the depression subscale of the POMS (p>0.05).
Sacco et al. (2016) Italy RCT PEDro=4 N=32	**Population:** Severe TBI. Mean Time Post Injury=8.73yr. *Treatment Group* (n=16): Mean Age=37.7yr, Gender: Male=12, Female=4; *Control Group* (n=16): Mean Age=35.2yr, Gender: Male=14, Female=2. **Intervention:** Participants were randomized to receive transcranial direct current stimulation or sham with computer-assisted training exercises (2/d, 5d). Outcomes were assessed at baseline (T0), before treatment (T1), after treatment (T2), and 1mo follow-up (T3). **Outcome Measures:** Repeatable Battery for the Assessment of Neurological Status (RBANS), Beck Depression Inventory (BDI), Test for the Examination of Attention.	1. No significant differences were found in depression scores, as measured by the Beck Depression Inventory (BDI) (p=0.305).

Discussion

Two RCTs (Rushby et al., 2021; Sacco et al., 2016) examined the use of transcranial direct current stimulation (tDCS) compared to sham. No significant differences were found for depression, as measured by the Hospital Anxiety and Depression Scale (HADS), the depression subscale of the Profile of Mood States (POMS), and the Beck Depression Inventory (BDI).

Conclusions

There is level 1a evidence (Rushby et al., 2021) and level 2 evidence (Sacco et al., 2016) that transcranial direct current stimulation (tDCS) may not improve depression post TBI.

KEY POINTS

- Transcranial direct current stimulation (tDCS) may not improve depressive symptoms in individuals with moderate to severe TBI.

Peer Support

There is limited literature on peer support interventions in the TBI population. In a systematic review, Hughes et al. (2020) found that peer support groups for individuals with ABI result in several benefits such as feeling connected and interacting with others, as well as providing and receiving support.

TABLE 19 | Peer Support for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Levy et al. (2021) Canada RCT PEDro=7 N=13	**Population:** TBI=13; Severity: Moderate=3, Severe=9, Other=1; *Experimental Group (n=6):* Mean Age=50.8yr; Gender: Male=4, Female=2. *Control Group (n=7):* Mean Age=35.6yr; Gender: Male=5, Female=2. **Intervention:** Participants were randomized into a weekly intervention or waitlist control group. Participants received a Peer Support Program (OBIA) as soon as they were able to match with a mentor. The waitlist control group participated in the OBIA Peer Support Program after completing their time in the study. Outcome measures were assessed at 2mo and at 4mo. **Outcome Measure:** Community Integration Questionnaire (CIQ), Patient Health Questionnaire (PHQ)-9, Short Form-20 (SF-20), TBI Self-efficacy Questionnaire (TBI-SE).	1. The intervention group experienced an initial worsening of mood at the two-month time point followed by an improvement at the four-month time point (p=0.447) as measured by the PHQ-9. 2. The intervention group had a significantly lower mean SF-20 score than the control group at two months (p=0.021), however, this was not maintained at four months. 3. No significant main effects for time or group were observed in mood.
Hanks et al. (2012) USA RCT PEDro=5 N=96	**Population:** TBI=96; Gender: Male=74, Female=22; Caregivers=62; Peer Mentored Group: Mean Age=38.46yr; Mean GCS=9.39. TBI Control Group: Mean Age=40.90yr; Mean GCS=9.8. Caregiver Mentored Group: Mean Age=51.87 yr. Caregiver Control Group: Mean Age=50.18yr. **Intervention:** Participants and caregivers were randomly assigned to either a peer mentoring program or to a control group. Discussions in mentoring sessions included emotional well-being, post-TBI quality of life, and community integration. **Outcome Measures:** Peer Mentoring Questionnaire, Family Assessment Device (FAD), Coping Inventory for Stressful Situations (CISS-21), 12-Item Short-Form Health Survey (SF-12), Brief Symptom Inventory-18 (BSI-18), Community Integration Measure (CIM), Short Michigan Alcoholism Screening Test (SMAST).	1. There was no difference between groups in anxiety (p=0.31) and depression symptoms (p=07). 2. The mentored group had decreased somatic symptoms of emotional distress, less emotion-focused (p=0.04) and avoidance coping (p=0.03), as well as lower alcohol use (p=0.01) and fewer somatic symptoms of emotional distress. 3. Individuals who received mentoring had significantly better behavioral control and less chaos in the living environment (p=0.04).
Struchen et al. (2011) USA RCT PEDro=5	**Population:** TBI; Mean Age=31.7yr; Gender: Male=24, Female=6; Mean Time Post Injury=3.5mo; Mean GCS=6.3. **Intervention:** Participants were randomly assigned to either receive a social peer mentor (treatment group)	1. There was an unexpected increase in depressive symptoms, as measured by self-report on the CES-D after the conclusion of the 3-month peer mentoring period.

Author Year Country Study Design Sample Size	Methods	Outcome
N=28	or to a waitlist (control group). **Outcome Measures:** Craig Handicap Evaluation and Reporting Technique-Short Form (CHART-SF), Social Activity Interview (SAI), Centre for Epidemiological Studies Depression Scale (CES-D), UCLA Loneliness Scale-Version 3, 6-Item Interpersonal Support Evaluation List (6-ISEL), Satisfaction with Life Scale (SWLS).	

Discussion

In an RCT, Levy et al. (2021) examined the efficacy of a peer support program for individuals with TBI. Participants were randomized to either the Ontario Brain Injury Association (OBIA) Peer Support Program or a waitlist control condition and outcomes were recorded at 2- and 4-months. The authors found that the intervention group experienced an initial worsening of mood at the two-month time point followed by an improvement at the four-month time point; however, differences were not significant. Similarly, in the RCT by Struchen et al. (2011), there was an unexpected increase in depressive symptoms after the conclusion of the 3-month peer mentoring period. Similarly, no differences in depression were reported by Hanks et al. (2012) in an RCT that enrolled both participants with TBI and their caregivers.

Conclusions

There is level 1b evidence (Levy et al., 2021) and level 2 evidence (Hanks et al., 2012; Struchen et al., 2011) that peer support may not improve depression in individuals with TBI.

KEY POINTS

- Peer support may not be effective for the management of depression post moderate to severe TBI.

Social Skills Training

Initially developed for individuals with autism, social skills training is an intervention often delivered in groups that involves goal setting, role modeling, behavioral rehearsal and other behavioral strategies to help individuals improve social function (Dubreucq et al., 2022). There is limited evidence on the effectiveness of social skills training for mood disorders.

TABLE 20| Social Skills Training for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
McDonald et al. (2008) Australia RCT PEDro=6 N=39	**Population:** TBI; Gender: Male=28, Female=11. *Treatment Group (n=13)*: Mean Age=35.5yr; Mean Time Post Injury=4.0yr. *Social Group (n=13)*: Mean Age=34.3yr; Mean Time Post Injury=4.3yr. *Waitlist Group (n=13)*: Mean Age=35.3yr; Mean Time Post Injury=3.5yr. **Intervention:** Participants were randomly allocated to waitlist (deferred treatment group; n=13), control (non-therapeutic social group; n=13), or the social skills group (treatment group; n=13). Participants in the skills training group attended 12wk program of group and individual sessions totaling 4 hr/wk. Control group received 4 hr/wk of social activities only for 12wk. **Outcome Measure:** Behaviorally Referenced Rating System of Intermediary Social Skills Revised (BRISS-R), The Awareness of Social Inference Test (TASIT), Depression Anxiety Stress Scale (DASS), Katz Adjustment Scale (KAS-R1), Social Performance Survey Schedule (SPSS), La Trobe Communication Questionnaire (LCQ), SPRS, Katz adjustment scale-R1 (KAS), the Social Performance Survey Schedule (SPSS), La Trobe Communication Questionnaire (LTCQ), Sydney Psychosocial Reintegration Scale (SPRS).	1. No overall treatment effect was found for anxiety and depression, as measured by the Depression Anxiety Stress Scale (DASS).

Discussion

In a multicenter RCT, McDonald et al. (2008) compared social skills training, social activity, and a waitlist control group. The authors reported no overall treatment effect for anxiety and depression, as measured by the Depression Anxiety Stress Scale (DASS).

Conclusions

There is level 1b evidence (McDonald et al., 2008) that a social skills training programs may not improve depression post TBI.

KEY POINTS

- Social skills training may not be effective in improving depression in individuals with TBI.

Light Therapy

Light therapy or phototherapy is a non-pharmacological intervention that involves exposing the individual to daily bright light to manage symptoms associated with sleep-wake disorders and seasonal depression (Tao et al., 2020).

TABLE 21 | Light Therapy for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Connolly et al. (2021) Australia RCT Crossover PEDro=8 $N_{Initial}$=28, N_{Final}=24	**Population:** ABI, TBI=19, Stroke=5; *Treatment-placebo* (n=16): Gender: Male=9, Female=7; Mean Age=43.13yr; *Placebo-treatment* (n=8): Gender: Male=5, Female=3; Mean Age=46.75yr; *Overall*: Severity: Mild=17%. Moderate=26%. Severe=53% Mean Time Post Injury=10.23yr **Intervention:** Participants received daytime short wavelength enriched high-intensity white light intervention (correlated color temperature >5000K) and blue depleted light (<3000K) 3h prior to sleep for 2mo at home. The placebo involved receiving usual light (correlated color temperature ~3000-4000 K) for 2mo at home. The participants crossed over at 2mo. The intervention itself lasted 2mo. Outcomes were measured for 2wk pre-intervention, 1/mo during the protocol (mid-and end of treatment/control condition), and at 1-mo follow up. **Outcome Measure:** Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Psychomotor Vigilance Task (PVT), Hospital Anxiety and Depression Scale (HADS), Participation Objective Participation Subjective (POPS), Activity diary, Side Effects Questionnaire, End of Light Therapy Questionnaire, Actigraphy and sleep diary	1. No significant differences in depressive symptoms (HADS) in treatment relative to placebo.
Bell et al. (2021) USA RCT PEDro=7 $N_{Initial}$=131, N_{Final}=116	**Population:** Severe TBI; White Light Group (n=65): Gender: Male=45, Female=20; Mean Age=39.7yr; Red Light Group (n=66): Gender: Male=44, Female=22; Mean Age=42.1yr. Mean Time Post Injury=33.2d. **Intervention:** Participants were randomized to either the Bright White Light (BWL; 440-480nm) intervention group or the Red Light (RL) group. Sessions were 30min/d, for a maximum of 10d or until discharge. Outcomes were assessed before and after the intervention. **Outcome Measure:** Positive and Negative Affect Scale (PANAS), Karolinska Sleepiness Scale (KSS), Barrow Neurological Institute Fatigue Scale (BNI-FS), Visual Analog Scale for cooperation (VAS), Symbol Digit Modalities Test (SDMT), Actigraphy	1. There were no significant differences between groups for any outcome measure post intervention.

Author Year Country Study Design Sample Size	Methods	Outcome
Quera Salva et al. (2020) France RCT PEDro=7 N=20	**Population:** TBI=20; *Intervention Group* (Blue-enriched white light therapy, BWL; n=10): Mean Age=34.2yr; Gender: Male=7, Female=3; Mean Time Post Injury=7.9yr; Initial GCS=5.88. *Control Group* (No light therapy, N-BWL; n=10): Mean Age=39yr; Gender: Male=4, Female=6; Mean Time Post Injury=10yr; Initial GCS=6.00. **Intervention:** Participants were randomly allocated to receive blue-enriched white light therapy (BWL) 30min upon waking every day for 4wk or no light therapy. Outcome measures were assessed at baseline, 2wk, 4wk and 6wk. **Outcome Measures:** Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh sleep quality index (PSQI), 17-item Hamilton Depression Scale (HAD-17), 12-item Short Form Health Survey (SF-12).	1. Individuals in the Blue-enriched white light therapy (BWL) showed significantly improved measures of depression from baseline to 4 weeks as measured by the HAD-17 (p=0.04), with improvements being maintained at 6 weeks.
Sinclair et al. (2014) Australia RCT PEDro=6 N=30	**Population:** TBI; Mean Age= 42yr; Male=24, Female=6; Mean Time Post Injury=1106d; Severity: Mild=7, Moderate=8, Severe=15. **Intervention:** Participants were randomized to one of three home-based treatment groups: blue light therapy (n=10), yellow light therapy (n=10) or the no treatment control group (n=10). Participants were instructed to use the device for 45min each morning, within 2hr of waking up, for 4wk. Outcomes were assessed at baseline, at 4wk and 8wk. **Outcome Measures:** Fatigue Severity Scale (FSS), Psychomotor Vigilance Task (PVT), Beck Depression Inventory (BDI-II), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS).	1. There were no significant differences in symptom severity across time for any treatment condition for depression (p>0.05), as measured by the BDI-II.

Discussion

Four RCTs examined light therapy interventions. Bell et al. (2011) and Connolly et al. (2021) compared bright white light exposure to a placebo such as blue light or red light. No significant differences were observed between groups for depression. Similarly, Sinclair et al. (2014) found no significant differences in depressive symptoms severity across time when comparing blue light therapy, yellow light therapy and a no treatment control group.

Only in one RCT (Quera-Salva et al. 2020), blue-enriched white light therapy, compared to no light therapy, resulted in improved measures of depression from baseline to follow-up that were maintained at 6 weeks post intervention.

Conclusion

There is level 1a (Connolly et al., 2021) and level 1b evidence (Bell et al., 2021) that exposure to bright white light may not be effective for the management of depression post TBI.

There is level 1b evidence (Sinclair et al., 2014) that blue light may not be different than yellow light for depression following a TBI.

There is level 1b evidence (Quera-Salva et al., 2020) that blue enriched white light may improve depression post TBI, compared to no light therapy.

KEY POINTS

- Light therapy using bright white light, blue light or yellow light may not be effective for depression in individuals with moderate to severe TBI.
- Blue-enriched white light, compared to no light therapy, may improve depressive symptoms with sustained effects at 6 weeks in individuals with moderate to severe TBI.

Biofeedback Training

Biofeedback training is a promising intervention for the management of anxiety and stress. In a meta-analysis, Goessl et al. (2017) found that heart rate variability biofeedback was associated with a reduction in stress and anxiety in both clinical settings and in the community. Neurofeedback is a type of biofeedback that has been used for the treatment of depression and anxiety in non-TBI populations (Hammond, 2005).

TABLE 22 | Biofeedback Training for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Wearne et al. (2021) Australia RCT PEDro=8 N=50	**Population:** TBI*; Biofeedback group*(n=25): Gender: Male=17, Female=8; Mean Age=50.02yr; Mean GCS=6.82; Mean Time Post-Injury=14.36yr; *Waitlist Group* (n=25): Gender: Male=19, Female=6; Mean Age=43.12yr; Mean GCS=5.80; Mean Time Post-Injury=12.70yr **Intervention:** Participants were randomly allocated to either a heart rate variability biofeedback training group or a waitlist group receiving usual care. Intervention consisted of 6 training sessions with the therapist and self-practice sessions at home. There were 6 sessions, 1hr/d with a therapist and 8 sessions, 20-40min/d at home for 2wk. Outcomes were assessed before and after the intervention.	1. Participants in the biofeedback group endorsed significantly fewer symptoms on the depression subscale of the DASS-21 ($p<.05$), and greater resting state-positive mood on the SAM-Mood subscale ($p<.005$) at the post-intervention compared to those in the waitlist group. 2. No significant differences were seen between the biofeedback group and the control group in all the other outcomes ($p>0.05$) at post-intervention

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: Paced Auditory serial Addition Task (PASAT), Heart Rate (HR), Respiration rate, Skin Conductance (SCL).	
Neurofeedback		
Elbogen et al. (2021) USA Pre-Post $N_{Initial}$=41, N_{Final}=36	**Population:** TBI; Gender: Male=35, Female=6; Mean Age=38.57yr; Mean GCS=Not Reported; Time Post-Injury=13.11yr; PTA >1hr=64%. **Intervention:** Participants were instructed to perform "mobile neurofeedback" using a portable EEG headset linked to an application on a mobile device. The duration was 10min sessions, 4x/wk, for 3mo. Outcomes were assessed at baseline and at 3-mo. **Outcome Measure:** Regional Pain Scale, Patient-Reported Outcomes Measurement Information System (PROMIS), PTSD Checklist for DSM-5 (PCL-5), Patient Health Questionnaire (PHQ-9).	1. At follow-up individuals reported significantly reduced depression (p=.001). 2. Analysis of the number of phone calls/ home visits revealed a significant correlation with number of staff and reduced depressive symptoms (p=.03).

Discussion

Two studies (Elbogen et al., 2021; Wearne et al., 2021) examined the use of biofeedback. In an RCT, Wearne et al. (2021) found that participants who received biofeedback training had significantly fewer depressive symptoms and greater positive mood when compared to a waitlist control group that received standard care. In a pre-post study by Elbogen et al. (2021), participants used a portable EEG neurofeedback headset linked to an application on a mobile device. The authors found that, at follow-up, participants reported significantly reduced depression (Elbogen et al., 2021).

Conclusion

There is level 1b evidence (Wearne et al., 2021) that biofeedback may improve depressive symptoms post TBI.

There is level 4 evidence (Elbogen et al., 2021) that a mobile neurofeedback device may reduce depressive symptoms in individuals with TBI.

KEY POINTS

- Biofeedback training may improve depressive symptoms in individuals with moderate to severe TBI.

Therapeutic Writing

Writing has been used as a therapeutic approach to help individuals process negative emotions associated with stressful or traumatic experiences (Smyth & Helm, 2003). Writing has been used to address persona trauma, mood disorders, bulimia symptoms, and chronic pain; writing therapy includes journaling, story writing, poetry, personal narratives, letter writing, and the use of online platforms (e.g., blogs) (Haertl & Ero-Phillips, 2019).

TABLE 23 | Therapeutic Writing for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Bugg et al. (2009) UK RCT PEDro=6 $N_{initial}$=148, N_{final}=67	**Population:** *Information group* (n=31); Gender: Male=3, Female=28; Mean age=36.65yr; Time post-injury<1mo; TBI severity: Not serious=1, Mild=9, Moderate=9, Very serious=9, Extremely serious=3. *Control group* (n=36); Gender: Male=16, Female=20; Mean age=38.14yr; Time post-injury<1mo; TBI severity: Not serious=3, Mild=7, Moderate=16, Very serious=8, Extremely serious=2; **Intervention:** Patients were randomized to a writing and information group or an information control group. Both groups received an information booklet 1mo post-injury, and participants in the writing group wrote about emotional aspects of their trauma over three 20min sessions 5-6wk post-injury. Outcomes were assessed at baseline, and at 3, and 6mo post-injury. **Outcome Measures:** Hospital Anxiety and Depression Scale (HADS), World Health Organization Quality of Life Measure (WHOQoL), Post-traumatic Diagnostic Scale (PDS).	1. There were no significant between group differences for the PDS scores. 2. There were no statistically significant differences between treatment groups for anxiety or depression, as measured by the HADS.

Discussion

In an RCT study, Bugg et al. (2009) examined the effect of writing as a self-help intervention on the severity of psychological symptoms in individuals who had a TBI and were at risk of developing PTSD symptoms. Both the intervention and the control group were given a self-help information booklet with a questionnaire, those in the intervention condition had sessions with a researcher and engaged in a writing activity that involved writing about emotions and feelings related to their injury. The authors found no group differences in depressive symptoms, as measured by the Hospital Anxiety and Depression Scale HADS (Bugg et al., 2009).

Conclusion

There is level 1b evidence (Bugg et al., 2009) that writing as a self-help intervention may not improve depression following a TBI.

KEY POINTS

- A writing intervention may not improve depressive symptoms in individuals with moderate to severe TBI.

Pharmacological Interventions

Depression following ABI can be treated with pharmacological interventions. Among these interventions are various antidepressants: selective serotonin reuptake inhibitors such as paroxetine, fluoxetine, sertraline, or citalopram; serotonin norepinephrine reuptake inhibitors such as duloxetine, milnacipran, and venlafaxine; and tricyclic antidepressants such as amitriptyline and nortriptyline. Anticonvulsants such as carbamazepine have also been used to treat depression post ABI.

Sertraline

Sertraline is a selective serotonin reuptake inhibitor that has been used to treat chronic depression, with sustained efficacy as a treatment to prevent emergence of depression in high-risk patients (Keller et al., 1998). The use of Sertraline for depression post-TBI is often reported to be the first-line treatment option, which may be due to their favourable side-effects and positive impact on cognition (Fann et al., 2009; Warden et al., 2006). It has also been used to treat obsessive-compulsive disorder, post-traumatic stress disorder panic disorder, premenstrual dysphoric disorder in women, and social anxiety disorder (Singh & Saadabadi, 2019).

TABLE 24 | Sertraline for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Fann et al. (2017) USA RCT PEDro=9 N=62	**Population:** *Sertraline* (n=31); Gender: Male=23, Female=8; Mean age=38yr; Mean time post-injury=4.3mo; Severity: Mild=16, Moderate=6, Severe=9. *Placebo* (n=31); Gender: Male=24, Female=7; Mean age=36.9yr; Mean time post-injury=4.9mo. TBI severity: Mild=13, Moderate=7; Severe=11. **Intervention:** Patients were randomized to receive either sertraline or placebo daily for 12wk. Outcomes were assessed at baseline, 1, 3, 6, 8, 10, and 12wk. **Outcome Measures:** Hamilton Anxiety and Depression Scale (HAM-D)-17 Item, Symptom Checklist-20, Clinician-rated Clinical Global Impression scale (CGI), Short Form 36 (SF-36), Sheehan Disability Scale, Trail	1. Depression significantly improved from baseline to 12 weeks in both treatment groups ($p<0.001$). 2. There were no statistically significant differences between treatment groups for depression (HAM-D), anxiety (HAM-A) or anger and aggression (BAAQ).

Author Year Country Study Design Sample Size	Methods	Outcome
	Making Test B, Head Injury Symptom Checklist, Brief Anger and Aggression Questionnaire (BAAQ), Brief Pain Inventory, Hamilton Anxiety Rating Scale (HAM-A).	
Novack et al. (2009) USA RCT PEDro=8 N=99	**Population:** *Treatment* (n=49): Mean age=35.3yr; Gender: Not Reported; Mean GCS=5.8; Mean time post-injury=21.5d. *Control* (n=50); Mean age=34.5yr; Gender: Not Reported; Mean GCS=5.8; Mean time post-injury=19.2d. **Intervention:** Patients were randomized to receive either 50mg Sertraline or placebo daily for 3mo. Outcomes were assessed weekly while in hospital, every other week for the first 3mo after discharge, and 3, 6, and 12mo after discharge. **Outcomes:** Hamilton Depression Rating Scale (HRDS-6), Neurobehavioural Functioning Inventory (NFI) – Depression Subscale, Structured Clinical Interview for DSM Disorders (SCID-I)	1. There were no significant differences in the subscale at 6 and 12-month follow-up.
Ashman et al. (2009) USA RCT PEDro=10 N=41	**Population:** TBI; Mean Age=49.1yr; Gender: Male=24, Female=17; Mean Time Post Injury=17.7mo; Injury Severity: Mild=15, Moderate=16, Severe=10. **Intervention:** Patients were diagnosed with major depression. The treatment group (n=22) received sertraline (25mg adjusted every 2wk, up to 100 mg) and the control (n=19) received a placebo, both for 10wk. **Outcome Measures:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Hamilton Rating Scale for Depression (HAM-D), Beck Anxiety Inventory (BAI), Life-3 Scale.	1. Treatment responders, based on HAM-D (score <10 or decreased by 50%), were 59% in the treatment group and 32% in the control (p=0.08). 2. Changes in scores on the depression as measured by the HAM-D showed improvement (p<0.001) but no group effects were found.
Kant et al. (1998) USA Pre-Post N=13	**Population:** TBI; Mean Age=37.6yr; Gender: Male=10, Female=3; Injury Severity: Mild=5, Moderate=6, Severe=6; Mean Time Post Injury=2yr. **Intervention:** Participants with aggression received sertraline (50-200 mg/day) for 8 wk. Assessments were conducted at 4wk and 8wk. **Outcome Measure:** Overt Aggression Scale-Modified (OAS-M), Anger Irritability Assault Questionnaire (AIAQ), Beck Depression Inventory (BDI).	1. Significant improvement on OAS-M (p<0.001) and AIAQ (p<0.01) found at 4wk and 8wk. 2. Significant improvement on BDI found at 4wk (p=0.04) but not 8wk (p=0.14).

Discussion

In the RCT by Ashman et al. (2009) participants with major depression were randomized to receive sertraline or placebo. The authors found improvements in depression over time for both groups; however, no statistically significant differences were found between the two groups. Similarly, in an RCT by Fann et al. (2017), the authors failed to demonstrate any significant advantage of sertraline over placebo in managing major depression. In contrast, Novack et al. (2009) reported initial promising results in their RCT, wherein the sertraline group exhibited lower depression scores compared to the placebo

group at the first follow-up at 3 months. However, this disparity did not persist in subsequent follow-ups at 6 and 12 months, suggesting a transient effect of sertraline on depression symptoms. A pre-post study by Kant et al. (1998) highlighted short-term improvements in depression scores at the 4-week follow-up, as measured by the BDI. However, these gains were not sustained at the 8-week mark, underscoring the challenges of maintaining treatment efficacy over time.

Sertraline for depression post-TBI has conflicting evidence. All RCTs had fluctuating dosage of sertraline (starting at 25mg and moving to 200mg over time) except for Novak et al. (2009), which has a fixed amount of 50mg. This brings up the topic of optimal dosing of sertraline for depression in people with TBI. Studies conducted on the general population found that a starting dose of 50 mg/day is the usually effective therapeutic and optimal dose when considering both efficacy and tolerability for most patients (Preskorn & Lane, 1995). While a more recent review found that dosage from 50mg to 200mg are affective, studies looking at flexible dosage of Sertraline were more likely to have patients who dropped out or were missing due to intolerance or poor outcomes (Luo et al., 2023). It should be noted that the reviews by Luo et al. (2023) and Preskorn & Lane et al. (1995) are conducted on the general population; thus, its implication of people with TBI is uncertain.

Conclusions

There is level 1b evidence (Ashman et al., 2009; Fann et al., 2017) that sertraline may not be more effective than placebo for managing major depression post TBI.

There is level 1b (Novack et al., 2009) and level 4 evidence (Kant et al., 1998) that sertraline may improve depression symptoms in the first four weeks to 3 months; however, effects may not be maintained after six months to a year.

KEY POINTS

- Sertraline may not be effective to treat major depression in individuals with moderate to severe TBI.
- Sertraline may improve depressive symptoms in the first three months compared to placebo; however, effects may not be sustained after six months.

Amantadine

Amantadine is a antiviral agent originally used to treat influenza; however, it is now used mostly to treat Parkinson disease, particularly for the management of tremors, rigidity and bradykinesia (Chang & Ramphul, 2018). Amantadine has been used as a wakefulness-promoting agent with a positive effect on cognition (Plantier & Luaute, 2016). While Amantadine has been commonly prescribed for Parkinson's

disease, and for cognitive recovery post ABI (Loggini et al., 2020); there is limited research on the use of amantadine for anxiety management in this population.

TABLE 25 | Amantadine for the Management of Depression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Hammond et al. (2014) USA RCT PEDro=9 $N_{Initial}$=76, N_{Final}=72	**Population:** TBI; *Amantadine Group (n=38)*: Mean Age=34.7yr; Gender: Male=25, Female=13; Mean Time Post Injury=5.3yr; Mean GCS=9.5. *Placebo Group (n=38)*: Mean Age=42.1yr; Gender: Male=22, Female=16; Mean Time Post Injury=4.7yr; Mean GCS=7.5. **Intervention:** Participants were randomized to receive placebo or 100 mg of amantadine 2x/day for 28 days. Assessments were conducted at baseline and 28 days. **Outcome Measure:** Neuropsychiatric Inventory (NPI) Irritability (NPI-I), NPI Agitation/ Aggression (NPI-A), NPI Distress (NPI-D), Beck Depression Inventory-II (BDI-II), Brief Symptom Inventory (BSI), Global Mental Health Scale (GMHS).	1. Eighty-one percent of the amantadine group had improved irritability by at least 3 points on NPI-I, compared to 44% of placebo (p=0.0016). 2. Significant difference in frequency and severity of irritability on NPI-I between amantadine and placebo groups (p=.0085). 3. No significant differences between amantadine and placebo groups on NPI-D, BDI-II, BSI-Anxiety, or GMHS. 4. Only individuals with moderate to severe aggression at baseline on NPI-A had significant reduction in aggression after amantadine treatment compared to placebo (p=0.046).

Discussion

In an RCT, Hammond et al. (2014) found no significant differences between individuals who received amantadine and those who received placebo in depression, as measured by the Beck Depression Inventory-II (BDI-II) (Hammond et al., 2014).

Conclusion

There is level 1b (Hammond et al., 2014) that amantadine may not be effective for the management of depression post TBI.

KEY POINTS

- Amantadine may not be effective for depression in individuals with moderate to severe TBI.

Desipramine

Desipramine is a tricyclic antidepressant that has been used in the treatment of resistant depression, particularly in individuals who did not respond to other antidepressants (Souery et al., 2011).

TABLE 26 | Desipramine for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Wroblewski et al. (1996) USA RCT Crossover PEDro=4 N=10	**Population:** Severe TBI; Mean Age=32.2yr; Gender: Male=7, Female=3; Mean Time Post Injury=1.5yr. **Intervention:** Patients were diagnosed with major depression. The treatment group (n=6) received desipramine (150 mg/d for 30day, 150-300 mg/day after) and the control group (n=4) received a placebo. The control group crossed over and received desipramine after day 30. **Outcome Measures:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Affect/Mood Scale (AMS).	1. Three individuals from each group had nearly complete resolution of depression (DSM) on desipramine. 2. Seventy percent of individuals showed improvement over time on the AMS. 3. There were different rates of improvement over time in those started on the desipramine rather than placebo, with the treatment group making more rapid and greater improvements (p=0.001).

Discussion

In a single, small crossover RCT, Wroblewski et al. (1996) found that desipramine was effective in treating major depression. However, given that recent evidence on this medication for the TBI population is scarce, additional studies are necessary before conclusions can be made regarding its effectiveness. Additionally, a review by Tani et al. (2022) supported the use of desipramine to improve depression in severe TBI but distinguishes that TCAs, such as desipramine, are probably less effective than SSRIs, such as Sertraline, in the treatment of post-TBI depression and are associated with more complications such as seizures (Wroblewski et al., 1990).

Conclusions

There is level 2 evidence (Wroblewski et al., 1996) that desipramine may improve major depression in moderate to severe TBI compared to placebo. However, more research is needed to determine its effectiveness.

KEY POINTS

- Desipramine may be an effective treatment for major depression post TBI; however, further research is required.

Huperzine A

Huperzine A is an acetylcholinesterase (AChE) inhibitor that has been used to treat cognitive impairment and major depressive disorder (Zheng et al., 2016).

TABLE 27 | Huperzine A for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Zafonte et al., (2020) USA RCT PEDro=9 $N_{Initial}$=14, N_{Final}=12	**Population:** Moderate to Severe TBI=14; *Treatment Group (Huperzine; n=7):* Mean Age= 37±16.21yr; Gender: Male=5, Female=2; Mean Time Post Injury=155.4±130.27d; *Control Group (Placebo; n=7):* Mean Age=39±12yr; Gender: Male=5, Female=2; Mean Time Post Injury=226.86±120.30d. **Intervention:** Participants were randomized to receive Huperzine A starting at a dose of 100µg/d, increasing to a therapeutic dose (600µg/d) or placebo for 12wk. Outcome measures were assessed at baseline, 6, 12, 12, 24 and 52wk. **Outcome Measures:** California Verbal Learning Test-2nd Edition (CVLT-II), Beck Depression Index (BDI), British Columbia Post-concussion Symptom Inventory (BC-PSI), Galveston Orientation Amnesia Test (GOAT), Trail Making Test Part B (TMT-B). Traumatic Brain Injury Quality of Life Scale (TBI-QOL), Ruff Neurobehavioral Inventory (RNBI).	1. No significant differences were observed between groups (p>.05) on any outcome measure.

Discussion

In an RCT, Zafonte et al. (2020) compared the effects of Huperzine A to placebo. The authors found that there were no significant differences between groups on measures of depression. More research is needed to determine its efficacy in individuals with moderate to severe TBI.

Conclusions

There is level 1b evidence (Zafonte et al., 2020) that Huperzine A may not improve depression in individuals with TBI.

KEY POINTS

- Huperzine A may not be an effective treatment for depression in individuals with TBI.

Risperidone

Risperidone is an antipsychotic used for the management of psychosis-induced aggression or agitation (Ostinelli et al., 2018). It should be noted that, due to lack of evidence for antipsychotic effectiveness, prolonged post-traumatic amnesia and decreased cognitive function (Bogner et al., 2015; McKay et al.,

2018; Mysiw et al., 2006), current recommendations and reviews advise against the use of antipsychotics to manage behaviour (Plantier & Luaute, 2016; Ponsford et al., 2014; Williamson et al., 2018). There is limited research on the use of risperidone for agitation, anger and aggression in individuals with ABI.

TABLE 28 | Risperidone for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Deb et al. (2020) UK RCT PEDro=6 N=14	**Population:** TBI=14, Severity: Mild=3, Moderate=4, Severe=5*; Risperidone Group (n=6)* Mean Age=39.3yr; Gender: Male=5, Female=1. *Placebo Group (n=8):* Mean Age=43.1yr; Gender: Male=5, Female=3. **Intervention:** Participants were randomly allocated into two groups: Risperidone or Placebo. Those in the experimental group received 1mg once daily dose of Risperidone up to a dose of 4mg/day, if necessary. Those in the placebo group received an equivalent amount of placebo capsules. Follow-ups were done by telephone every week and at 1wk post-treatment to assess improvement. **Outcome Measure:** Modified Overt Aggression Scale (MOAS), Glasgow Outcome Scale - Extended (GOS-E), Irritability Questionnaire (IRQ), Hospital Anxiety and Depression Scale (HADS), Clinical Global Impression (CGI), Udvalg for Kliniske Undersogelser Scale (UKU), EQ- 5D, Short Form 12 (SF-12).	1. The score changes in the HADS- Anxiety were slightly greater in the risperidone group whereas HADS- Depression score change was slightly greater in the placebo group; however, significance was not reached.

Discussion

In a small RCT by Deb et al. (2020), participants were randomized to receive either risperidone or a placebo in a dose of 1-4mg daily as necessary for 12 weeks. The authors found that the score changes in the HADS for Depression score were slightly greater in the placebo group; however, significance was not reached (Deb et al., 2020). Given that some studies have suggested that frequent use of risperidone may reduce cognitive and functional recovery in individuals with TBI (Williamson et al., 2019), caution is recommended.

Conclusions

There is level 1b evidence (Deb et al., 2020) that risperidone may not be effective for the management of depression in individuals with TBI.

KEY POINTS

- Risperidone may not be effective in reducing depressive symptoms post TBI.

Methylphenidate

Methylphenidate is a stimulant that has been used for the treatment of behavioural disorders associated with attention deficit hyperactivity disorder (ADHD) (Britton, 2012). There is limited research on the use of methylphenidate for depression and mood post TBI.

TABLE 29 | Methylphenidate for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Jenkins et al. (2019) UK RCT Crossover PEDro=9 $N_{Initial}$=46, N_{Final}=40	**Population:** TBI=40; *Methylphenidate first* (n=20): Mean Age= 40yr; Gender: Male=18, Female=2; Mean Time Post Injury=67mo; Mean GCS=8.3. *Placebo First* (n=20): Mean Age=39yr; Gender: Male=16, Female=4; Mean Time Post Injury=67mo; Severity: Mean GCS=8.3. **Intervention:** Participants were randomized to receive 0.3mg/kg of methylphenidate (treatment group) 2x/d for 2wk with crossover to placebo (control group) 2x/d for 2wk and vice versa. Outcome measures were assessed at baseline, at 2 wk, and at 4wk. **Outcome Measures:** Choice Reaction Time (CRT) Task, Single-Photon Emission Computed Tomography (SPECT), Trail Making Test (TMT), Delis-Kaplan Executive Function System (D-KEFS), Stroop Color Word Test, Wechsler Memory Scale - People Test, Wechsler Abbreviated Scale for Intelligence (WASI), Lille Apathy Rating Scale (LARS), Visual Analogue Scale for Fatigue (VAS-F), Glasgow Outcome Scale-Extended (GOSE), Hospital Anxiety and Depression Scale (HADS), Frontal Systems Behaviour Scale (FrSBe), Cognitive Failures Questionnaire (CFQ), Rating Scale of Attentional Behaviour (RSAB).	1. Individuals with low caudate Dopamine Transporter (DaT) showed significant improvements in self-reported apathy (p=0.03). 2. No significant difference in behaviour, as measured by the Frontal Systems Behaviour Scale (FrSBe). 3. No significant difference were found in anxiety or depression, as measured by the HADS.
Gualtieri & Evans (1988) United States RCT Crossover PEDro=7 N=15	**Population:** TBI, Mean age=24.1yr; Gender: Male=10, Female=5; GCS < 8; Mean time post-injury=46.8mo. **Intervention:** Participants were assigned to receive three conditions in randomized order. 1) Placebo; 2) Methylphenidate (0.15mg/kg twice daily; 3) Methylphenidate (0.30mg/kg twice daily. Intervention was 12d, with 2d washout between conditions. **Outcome Measures:** Adult Activity Scale (AAS), Examiners Rating Scale (EXRS) – mood and cooperation, Self-rating scale - Analogue Mood Scale (SRS) – mood scale, Ruff 2 & 7 Selective Attention Test, Verbal Fluency Test (VFT), Non-Verbal Fluency Test (NVF), Selective Reminding Test (SRT), Trail Making Test-A, Trail Making Test-B, Continuous Performance Test (CPT), Digit Symbol Substitution Test, Benton Visual Retention test (BVRT)	1. Participants reported improvement in mood post intervention; however, results need to be interpreted with caution given the small number of participants.

Discussion

In an RCT crossover, Jenkins et al. (2019) compared methylphenidate to placebo and found no significant group differences in depression, as measured by the Hospital Anxiety and Depression Scale (HADS). In another RCT with crossover design, Gualtieri and Evans (1988) examined the effectiveness of methylphenidate to treat the sequelae of TBI. The authors found an improvement in mood post intervention, as measured by the Examiners Rating Scale (EXRS) – mood and cooperation, and the Analogue Mood Scale (SRS). However, given the small sample, results should be interpreted with caution.

Conclusions

There is conflicting evidence (Gualtieri & Evans, 1988; Jenkins et al., 2019) that methylphenidate may improve mood in individuals with severe TBI; however, more research is needed.

KEY POINTS

- Further research is needed to determine whether or not methylphenidate may improve mood in individuals with moderate to severe TBI.

Cerebrolysin

Cerebrolysin is a neuropeptide preparation used to enhance neuroplasticity and neuroprotection in conditions such as TBI, stroke, subarachnoid hemorrhage, Parkinson's disease, Alzheimer disease, and multiple sclerosis (Jarosz et al., 2023).

TABLE 30 | Cerebrolysin for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Muresanu et al. (2020) Romania RCT PEDro=10 $N_{Initial}$=142, N_{Final}=139	**Population:** TBI; *Cerebrolysin* (n=80): Mean age=46.4yr; Gender: Male=72, Female=8; Time post-injury<4h; Mean GCS=10.2; *Control* (n=59): Mean age=48.8yr; Gender: Male=51, Female=8; Time Post-injury<4h. Mean GCS=10.6. **Intervention:** Participants were randomly allocated to receive either 50mL of Cerebrolysin or physiological saline solution per day for 10d, followed by an additional two 10d treatment cycles with 10mL. Outcomes were assessed at 10d, 30d and 90d post-TBI. **Outcomes:** Glasgow Outcome Scale Extended (GOS-E), Barthel Index, Mini-Mental State Examination (MMSE),	1. Only the HADS depression sub-scale showed a medium to large size effect at 30-day (p=0.0263) and at 90-day (p=0.0026), while HADS-anxiety did not show significance at 30 days (p=0.3453) and 90 days (p=0.4860).

Author Year Country Study Design Sample Size	Methods	Outcome
	Wechsler adult intelligence scale (WAIS), Stroop Color-Word Test—Victoria Version (VST), Color Trails Test (CTT), Hospital Anxiety and Depression Scale (HADS).	
Poon et al. (2020) Italy RCT PEDro=9 N=40	**Population:** TBI; Mean Age=38.1yr; Gender: Male=32, Female=8; Mean Time Post Injury <6hr; Mean GCS=9.9. **Intervention:** Participants were randomized to receive either Cerebrolysin (50mL) or placebo for 10d, followed by two additional treatment cycles (10mL dailyx10d). Outcomes were assessed at baseline, 10d, 30d, and 90d. **Outcome Measures:** Glasgow Outcome Scale Extended (GOS-E), Barthel Index (BI), Mini-Mental State Examination (MMSE), Wechsler adult intelligence scale - III (WAIS-III), Stroop Color-Word Test—Victoria version (VST), Finger Tapping Test (FTT), Color Trails Test (CTT), Hospital Anxiety and Depression Scale (HADS).	1. For the HADS Anxiety Scale, a stand-alone statistically significant superiority of Cerebrolysin was found with an effect size close to be considered "large" (p = 0.0378). 2. For the HADS depression subscale, a "large" treatment effect was shown at the final endpoint after 180 days (p=0.0204).

Discussion

In an RCT, Muresanu et al. (2020) found that cerebrolysin had significant effects on depression compared to placebo, with the HADS depression sub-scale showing a medium to large size effect at 30 and 90 days. Similarly, Poon et al. (2020) found that cerebrolysin had a large treatment effect on depression at 180 days.

Conclusion

There is level 1b evidence (Muresanu et al., 2020; Poon et al., 2020) that cerebrolysin may improve depression post TBI.

KEY POINTS

- Cerebrolysin may be effective for depression in individuals with a moderate to severe TBI.

Rivastigmine

Rivastigmine is an acetylcholine inhibitor that increases the levels of a brain chemical called acetylcholine which allows communication of the nerve cells(Birks & Evans, 2015). Rivastigmine has been used to treat cognitive and behavioral symptoms in Alzheimer disease and diffuse Lewy body

disease, as well as other conditions such as in vascular dementia and Parkinson's disease (Farlow, 2003).

TABLE 31| Rivastigmine for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Tenovuo et al. (2009) Finland RCT Crossover PEDro=9 N=102	**Population:** TBI; Mean age=45.5yr; Gender: Males=61, Female=39; Mean time post-injury=8yr; Mean GCS=11. **Intervention:** Individuals were randomized to receive one of two dosing rivastigmine schedules (placebo then rivastigmine or rivastigmine then placebo). Treatment lasted 8wk once a max dose of 12mg/d was reached. **Outcome Measures**: Symptom Checklist-90, Satisfaction with Life Scale (SWLS), Finnish Traumatic Brain Injury Questionnaire (FITBIQ), Simple Reaction Time Test, Ten-choice reaction time (10CRT), The Subtraction Test, Vigilance Test.	1. No significant difference (Symptom Checklist 90; SCL-90). 2. More participants in the intervention group reported depressed mood as an adverse event.
Silver et al. (2009) USA RCT PEDro=9 N=127	**Population:** TBI, GCS<9 =80%. *Rivastigmine* (n=65): Mean Age=36.9yr, Gender: Male=43, Female=22, Time Post Injury=73.5mo; *Placebo* (n=62): Mean Age=38yr, Gender: Male=42, Female=20, Time Post Injury=100.1mo. **Intervention:** Participants were randomized to receive rivastigmine (1.5 mg 2x/d to a max of 12 mg/d) or placebo. **Outcome Measures:** Cambridge Neuropsychological Test Automated Battery (CANTAB), Hopkins Verbal Learning Test (HVLT), Wechsler Adult Intelligence Scale (WAIS), Trail Making Test A, Trail Making Test B, Controlled Oral Word Association Test (COWAT), Clinician's Global Impression of Chage (CGIC), Satisfaction with Life Scale (SWLS), Beck Depression Inventory II (BDI-II).	1. Significant decrease in depression ($p<0.001$) in favor of the treatment group as measured by the Beck Depression Inventory-II (BDI-II).
Silver et al. (2006) USA RCT PEDro=9 N=123	**Population:** TBI; Mean GCS=6.5. *Rivastigmine* (n=80): Mean Age=37yr, Gender: Male=53, Female=27, Mean Loss of Consciousness=23.3d; *Placebo* (n=77): Mean Age=37.1yr, Gender: Male=53, Female=24, Mean loss of Consciousness=22.5d. **Intervention:** Participants were randomized to receive either rivastigmine (3-6 mg/d) or placebo. At the end of the first 4 wk, rivastigmine doses were increased to 3.0 mg, 2x/d. If necessary, doses were decreased to 1.5 mg or 4.5 mg 2x/d. **Outcome Measures:** Trail Making Test A, Trail Making Test B, Hopkins verbal learning test (HVLT), Cambridge Neuropsychological Test Automated Battery (CANTAB), Wechsler Adult Intelligence Scale-III (WAIS-III),	1. No significant differences were observed in the Beck Depression Inventory-II (BDI-II).

Author Year Country Study Design Sample Size	Methods	Outcome
	Neurobehavioral Functioning Inventory (NFI), Beck Depression Inventory II (BDI-II), Satisfaction with Life Scale (SWLS), Clinical Global Impression of Change.	

Discussion

The effectiveness of rivastigmine compared to placebo was examined in three RCTs (Silver et al., 2006; 2009; Tenovuo et al., 2009). While Silver et al. (2006) reported no significant differences in depression, as measured by the Beck Depression Inventory-II (BDI-II), a subsequent RCT (Silver et al. 2009) reported a significant decrease in depression with treatment, as measured by the BDI-II. In another RCT, Tenovuo et al. (2009) reported no significant differences in mood, as measured by the Checklist-90.

Conclusion

There is conflicting level 1a evidence (Tenovuo et al., 2009) and level 1b evidence (Silver et al., 2006; 2009) regarding the efficacy of rivastigmine for the treatment of depression post TBI. Further research is required.

KEY POINTS

- There is conflicting evidence regarding the effectiveness of rivastigmine for depression following a moderate to severe TBI. Further research is needed.

Dextroamphetamine

Amphetamine is a stimulant drug used to mange narcolepsy and attention deficit hyperactivity disorder (ADHD) (Martin & Le, 2020). There is very limited research on the use of dextroamphetamine for the management of mood post ABI.

TABLE 32 | Dextroamphetamine for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Hart et al. (2018) USA RCT PEDro=10	**Population:** TBI=32; *DEX group (n=17)* Mean Age=39.6yr; Gender: Male=11, Female=6; Mean Time Post Injury=53.6d; Mean GCS=8.2. *Placebo group (n=15)* Mean Age=38.7yr; Gender: Male=15, Female=0; Mean Time Post Injury=60.2d; Mean GCS=7.5.	1. No differences were reported for mood (p=0.33), as measured by the Profile of Mood States (POMS). 2. There was slightly more emotional distress in the dextroamphetamine group.

Author Year Country Study Design Sample Size	Methods	Outcome
N=32	**Intervention:** Participants were randomly allocated to either be administered 10mg of dextroamphetamine (DEX), or an identical placebo daily for 3 weeks. Outcome measures were completed at weekly intervals. **Outcome Measures:** Moss Attention Rating Scale (MARS), Hopkins Rehabilitation Rating Scale (HRER), Cognitive Failures Questionnaire (CFQ), Rating Scale of Attentional Behavior (RSAB), Finger Tapping Test (FT), Symbol Digit Modalities Test (SDMT), Functional Independence Measure (FIM), Disability Rating Scale (DRS), Agitated Behavior Scale (ABS), Profile of Mood States (POMS).	

Discussion

In an RCT, Hart et al. (2018) compared the effects of 10mg of dextroamphetamine (DEX) to an identical placebo. Each intervention condition was implemented for 3 weeks with outcome measures taken each week. The authors found no significant differences for mood, as measured by the Profile of Mood States (POMS), and there was slightly more emotional distress in the dextroamphetamine group.

Conclusions

There is level 1b evidence (Hart et al., 2018) that dextroamphetamine may not be effective for depression in individuals with TBI.

KEY POINTS

- Dextroamphetamine may not reduce depressive symptoms post moderate to severe TBI.

Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor that is indicated to treat attention deficit hyperactivity disorder (ADHD) in children and adults; additionally, atomoxetine is sometimes used off-label to treat individuals with depression (Fedder et al., 2023).

TABLE 33| Atomoxetine for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Ripley et al. (2014) USA RCT Crossover PEDro=7 $N_{initial}$=55, N_{final}=49	**Population:** Mean age=40.6yr; Gender: Male=41, Female=14; Mean Time post-injury=7.8yr; Mean GCS=6.8. **Intervention:** Patients were randomized to receive either 40mg Atomoxetine 2x/d for 2 wk or placebo, with a 2-wk wash out placebo period between treatments. **Outcomes:** Cognitive Drug Research (CDR) Computerized Cognitive Assessment System, Stroop Color and Word Test, Adult ADHD Self-Report Scale (ASRS), Neurobehavioral Functioning Inventory (NFI) – Depression Scale.	1. There were no significant differences observed in primary or secondary outcomes between treatment groups ($p<0.15$).

Discussion

In an RCT crossover, Ripley et al. (2014) examined the effects of atomoxetine on measures of attention and depression following TBI. The authors found no significant differences the depression scale of the Neurobehavioral Functioning Inventory (NFI) between groups.

Conclusions

There is level 1a evidence (Ripley et al., 2014) that atomoxetine may not improve depression, compared to placebo post moderate to severe TBI.

KEY POINTS

- Atomoxetine may not improve depression, compared to placebo, in individuals with moderate to severe TBI.

Recombinant Human Growth Hormone

Growth Hormone is a pituitary peptide hormone that plays a major role in metabolism and growing in humans (Ranke & Wit, 2018).

TABLE 34| Recombinant Human Growth Hormone for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Dubiel et al. (2018) United States RCT PEDro=7 N=40	**Population:** TBI; Mean age=31.1yr; Gender: Male=34, Female=6; Mean Time Post injury=64.1d. GCS: Mild=4, Moderate=3, Severe=32, Unknown=1. **Intervention:** Individuals were randomized to receive either recombinant human growth hormone (rhGH) or placebo. Follow-up was at 1-mo, 3-mo, 6-mo and 12-mo. 1-mo and 3-mo follow-up was only taken for IGF-1 concentrations. **Outcome Measures:** Functional Independence Measure (FIM), Disability Rating Scale (DRS), Glasgow Outcome Scale-Extended (GOSE), Galveston Orientation and Amnesia Test (GOAT), Wechsler Adult Intelligence Scale-III (WAIS-III), Delis Kaplan Executive Function System (DKEFS), Trail Making Test A, Trail Making Test B, California Verbal Learning Test-2 (CVLT-2), Controlled Oral Word Association Test (COWAT), Brief Symptom Inventory (BSI), Fatigue Severity Scale (FSS), Rivermead post-concussion questionnaire (RPQ) , Satisfaction with Life Scale (SWLS), Short Form 36 (SF-36).	1. There were no significant differences in mood, as measured by the BSI (p=0.89) and the SF 36-mental health (p=0.10).
High Jr et al. (2010) USA RCT PEDro=8 N=23	**Population:** TBI; *Active rhGH* (n=12): Mean Age=36.1yr, Time Post Injury=11yr, Mean GCS=5.8; *Placebo* (n=11): Mean Age=39.1yr, Time Post Injury=5.1yr, Mean GCS=6.6. **Intervention:** Participants were randomized to either a growth hormone replacement (rhGH) group or a placebo. Initially the drug was administered at 200 ug, followed by a 200 ug increase every month until the dosage reached 600 ug. Both groups received these injections for one year. **Outcome Measures:** Controlled Oral Word Association Test (COWAT), Wechsler Adult Intelligence Scale-III (WAIS-III), Finger Tapping Test (FTT), Digit Span Test, California Verbal Learning Test - II (CVLT-II), Trail Making Test A, Trail Making Test B, Delis–Kaplan Executive Function System (DKEFS), Beck Depression Inventory-II (BDI-II), Disability Rating Scale (DRS), Community Integration Questionnaire (CIQ).	1. No significant differences between groups were found in depression scores, as measured by the Beck Depression Inventory-II (BD-II).

Discussion

In two RCTs, Dubiel et al. (2018) and High et al. (2010) examined the effects of recombinant human growth hormone (rhGH) post TBI. No significant effects on depression were found, compared to placebo, as measured by the Beck Depression Inventory-II (BDI-II), the Short Form 36 (SF-36) and the Brief Symptom Inventory (BSI).

Conclusions

There is level 1b evidence (Dubiel et al., 2018; High et al., 2010) that recombinant human growth hormone (rhGH) may not be effective for depression post TBI, compared to placebo.

KEY POINTS

- Recombinant human growth hormone (rhGH) may not improve depression, when compared to placebo, in individuals with moderate to severe TBI.

Melatonin

Melatonin is a hormone involved in the regulation of the sleep-wake cycle that has been often used as a supplement to improve conditions such as insomnia and other sleep disorders (Xie et al., 2017).

TABLE 35| Melatonin for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Grima et al. (2018) Australia RCT Crossover PEDro=9 N=33	**Population:** TBI; *Melatonin-placebo group* (n=18): Mean Age=35yr; Gender: Male=61%, Female=39%; Median Time Post Injury=61mo; Severity: Median GCS= 5. *Placebo-melatonin group* (n=15): Mean Age=38yr; Gender: Male=73%, Female=27%; Median Time Post Injury= 25mo; Severity: Median GCS=8. **Intervention:** Participants with chronic insomnia were randomly allocated to a 4wk melatonin or placebo treatment before crossover. The melatonin formula was a prolonged release formula (2mg). Outcome were measured at baseline and at the end of each treatment phase. **Outcome Measures:** Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS), Hospital Anxiety Depression Scale (HADS), Short-Form Health Survey (SF-36).	1. Melatonin was also associated with a significant but small decrease in self-reported anxiety symptomatology, with no differences in depression. 2. The HADS anxiety scores were significantly lower in the melatonin arm compared to the placebo arm (p=0.0006). 3. HADS depression scores were not significantly different between treatments (p=0.68).
Kemp et al. (2004) UK RCT Crossover PEDro=5 N=7	**Population:** TBI; Mean age=39.6yr; Gender: Male=7; Mean time post-injury=36.3mo; Severity: Mild=2, Moderate=3, Severe=2. **Intervention:** Patients were randomized to receive either 5mg Melatonin or 25mg Amitriptyline daily for 1mo, with a 2wk washout period between treatments. Outcomes were assessed at baseline and after each treatment cycle.	1. There were no significant treatment effects on anxiety (p=0.66) or depression (p=0.97), as measured by the HADS.

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcomes: Speed and Capacity of Language-Processing Test (SCOLP), Adult Memory and Processing Batter (AMIPB), Hospital Anxiety and Depression Scale (HADS).	

Discussion

In an RCT crossover, Grima et al. (2018) examined the effect of melatonin on sleep disturbances in individuals who had sustained a TBI. Participants were given prolonged-release melatonin formulation of 2mg, and placebo capsules for 4 weeks separated by a 48-hour washout period. The authors found no significant differences in depression, as measured by the Hospital Anxiety Depression Scale (HADS). Similarly, Kemp et al. (2004) compared melatonin and amitriptyline in the management of sleep disorders post TBI. The authors found no significant differences for depression.

Conclusions

There is level 1a evidence (Grima et al., 2018) that melatonin may not improve depression post TBI, compared to placebo.

There is level 2 evidence (Kemp et al., 2004) that melatonin may not be more effective than amitriptyline for depression post TBI.

KEY POINTS

- Melatonin may not be effective for depression following a moderate to severe TBI, compared to placebo or to amitriptyline.

Modafinil

Modafinil is a stimulant used to treat excessive daytime sleepiness, daytime fatigue associated with narcolepsy, obstructive sleep apnea and sleep work shift disorder; off-label uses include ADHD, bipolar depressive episodes, drug dependence and cancer-related fatigue (Greenblatt & Adams, 2018).

TABLE 36| Modafinil for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Jha et al. (2008) USA RCT PEDro=8 $N_{Initial}$=51, N_{Final}=46	**Population:** TBI=51; Mean Age=38.3yr; Gender: Male=35 (69%), Female=16; Mean Time Post Injury=5.8yr; Severity: Mild=25.5%, Moderate=23.5%, Severe=51%. **Intervention:** The treatment group (n=27) received modafinil (100 mg/d for 3d, then 200 mg/d for 11d, then a maintenance dose of 400 mg/d for 8wk). The control group (n=24) received a placebo. At the end of phase 1 (8wk) both groups crossed-over. **Outcome Measures:** Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Epworth Sleepiness Scale (ESS), Short Form 12 (SF-12), ImPACT, CPT-II, Beck Depression Inventory - II (BDI-II).	1. No significant differences were observed between the two groups in depression as measured by the BDI-II.

Discussion

In an RCT, Jha et al. (2008) examined the effect of modafinil, compared to placebo for the treatment of fatigue and daytime sleepiness post TBI. The authors found no significant differences between the modafinil and placebo groups in depression, as measured by the Beck Depression Inventory-II (BDI-II). The research on using modafinil is sparse; however, a case report by Tcheremissine and Rachal Tcheremissine and Rachal (2017), found that a 58-year-old patient with TBI experienced benefit from using modafinil (100mg/day titrated to 300mg/day) as evidenced by significant improvements in depressive symptoms and greater ability to participate in all activities of daily living. This case report did not state the severity of TBI; thus, the results should be proceeded with caution.

Conclusions

There is level 1b evidence (Jha et al., 2008) that modafinil may not improve depression post TBI, compared to placebo.

KEY POINTS

- Modafinil may not improve depression in individuals with a moderate to severe TBI.

Phenytoin

Phenytoin is a first-generation anticonvulsant medication that is commonly used in the management and treatment of epilepsy, generalized tonic-clonic seizures, complex partial seizures, and status epilepticus (Gupta & Tripp, 2019).

TABLE 37| Phenytoin for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Dikmen et al. (1991) USA RCT PEDro=6 $N_{Initial}$=244, N_{Final}=124	**Population:** TBI; Phenytoin Group (n=104): Mean Age=30.9yr; Gender: Male=82, Female=22; Median GCS=11. Placebo Group (n=101): Mean Age=32.9yr; Gender: Male=70, Female=31; Median GCS=9. **Intervention:** Patients were randomized to receive phenytoin or a placebo for 1yr post injury. Patients were then observed for another 1yr while unmedicated. **Outcome Measure:** Halstead-Reitan Neuropsychological Test Battery (HRNB), Wechsler Memory Scale (WMS), Trail Making A, Trail Making Test B, Stroop Test, Katz Adjustment Scale (KAS), Sickness Impact Profile (SIP).	1. No significant difference Sickness Impact Profile (SIP) psychosocial subscale (p=0.29), including emotions and feelings.

Discussion

In an RCT, Dikmen et al. (1991) examined the effects of phenytoin, compared to placebo, on neuropsychological, cognitive and psychosocial measures post moderate to severe TBI. The authors found no significant differences in mood or psychosocial functioning.

Conclusions

There is level 1b evidence (Dikmen et al., 1991) that phenytoin may not improve mood and psychosocial functioning post TBI compared to placebo.

KEY POINTS

- Phenytoin may not be effective for mood and psychosocial functioning, compared to placebo, in individuals with a moderate to severe TBI. Further research is needed.

Bradycor

Bradycor is a bradykinin receptor antagonist used in the treatment of inflammation (Marmarou et al., 1999). There is limited evidence on the use of bradycor post moderate to severe TBI.

TABLE 38| Bradycor for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Marmarou et al. (1999) USA RCT PEDro=8 N=136	**Population:** Severe TBI; Bradycor (n=66): Mean Age=30yr; Gender: Male=47, Female=19; Mean Time Post Injury=10hr; Mean GCS=6.0. Placebo (n=67): Mean Age=34yr; Gender: Male=55, Female=12; Mean Time Post Injury=10hr; Mean GCS=6.1. **Intervention:** Participants were randomized to receive continuous intravenous infusion of either Bradycor (3.0 µg/kg/min) or placebo for 5d. Outcomes were assessed at 3mo and 6mo. **Outcome Measures:** Intracranial Pressure (ICP), modified Therapy Intensity Level scale (TIL), Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Rey Complex Figure, Controlled Oral Word Association (COWAT), Symbol Digit, Nine-hole peg test Neurobehavioural Functional Inventory (NFI) - depression.	1. An increase in depressive symptoms associated with the Bradycor group (p=0.01) were found from 3- to 6-month, as reported by family members.

Discussion

In an RCT, Marmarou et al. (1999) examined the efficacy of Bradycor, a bradykinin antagonist, within twelve hours of severe TBI. While participants who received bradycor showed an improvement in outcomes at 3 months and 6 months, there was an increase in depressive symptoms associated with the Bradycor group, as reported by their family members. No significant differences were found In depression as reported by participants themselves.

Conclusions

There is level 1b evidence (Marmarou et al., 1999) that bradycor may not improve depression post severe TBI and it may be associated with an increase in depressive symptoms.

KEY POINTS

- Bradycor may be ineffective for the management of depression post severe TBI, and it may cause an increase in depressive symptoms. Further research is needed to examine the efficacy and safety of this medication.

Combination Therapy

Some individuals who live with depression do not respond to therapy with just one medication, often the use of one antidepressant only; therefore, a combination of medication may be needed (Lam et al., 2002).

TABLE 39| Combination Therapy for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Perino et al. (2001) Italy Pre-Post N=20	**Population:** TBI; Gender: Male=11, Female=9. *Group A (n=11)*: Mean Age=26.9yr; Mean GCS Score=5.5; Mean Time Post Injury=4.7 mo. *Group B (n=9)*: Mean Age=31.3yr; Mean GCS Score=6.1; Mean Time Post Injury=34.6 mo. **Intervention:** Patients diagnosed with major depression received citalopram (20 mg/d) and carbamazepine (600 mg/d) and were divided into subgroups based on time post injury (Group A, <6mo; Group B, 24-36mo). **Outcome Measures:** Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI).	1. Total sample significantly improved from baseline to 12wk on the BPRS (62.3±17.6 versus 51.7±12.8, p≤0.05) and CGI (4.4±1.1 versus 3.4±0.8, p≤0.005). 2. When comparing groups, Group B had higher global scores on the BPRS at baseline and 12wk than Group A.

Discussion

A pre-post study by Perino et al. (2001) examined the effects of combining citalopram and carbamazepine on major depression post TBI. The authors found that a combination of citalopram and carbamazepine significantly reduced depressive symptoms in patients diagnosed with major depression after 12 weeks (Perino et al., 2001).

Conclusions

There is level 4 evidence (Perino et al., 2001) that a combination of citalopram and carbamazepine may be an effective treatment for major depression post TBI.

KEY POINTS

- Citalopram combined with carbamazepine may improve major depression in individuals with moderate to severe TBI.

Fish Oil Supplementation

Omega-3 fatty acids found in fish such as salmon, tuna and sardines, are considered beneficial dietary sources for the prevention of conditions such as coronary disease (Harris, 2004).

TABLE 40| Fish Oil Supplementation for the Management of Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Kagan et al. (2021) Israel RCT PEDro=6 $N_{Initial}$=150, N_{Final}=51	**Population:** Severe TBI; *Intervention* (n=25); Mean age=41.8y; Gender: Not Reported; Mean time post-injury=Not Reported; Mean ISS=34.5. *Control* (n=26); Mean age=45.6y; Gender: Not Reported; Mean time post-injury=Not Reported; Mean ISS=34.6. **Intervention:** Patients were randomized into groups that received enteral feeding with fish oil (treatment) or without (control) fish oil. Outcomes were assessed at baseline and 6mo after discharge. **Outcomes:** Fatty acids, Brief Illness Perceptions Questionnaire (IPQ), Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Post-traumatic Checklist Scale (PCL), Hospital Anxiety and Depression Scale (HADS), Rivermead Head Injury Follow-up Questionnaire (RHI).	1. Treatment groups did not significantly differ in presentation of anxiety and depression at 6 months. 2. No group differences in PTSD symptoms, as measured by the PCL scale were observed at 6 months.

Discussion

In an RCT by Kagan et al. (2021) examined the effects of enteral nutrition enriched with fish oil supplementation on the onset and development of PTSD. Patients with polytrauma who were admitted to the intensive care unit (ICU) received enteral feeding with fish oil or without. The authors found no differences in depression between groups at six months follow-up.

Conclusions

There is level 1b evidence (Kagan et al., 2021) that enteral nutrition with fish oil supplementation may not prevent depression after ICU discharge in individuals with severe TBI.

KEY POINTS

- Enteral nutrition enriched with fish oil supplementation may not prevent the development of depression post ICU discharge in individuals with polytrauma and severe TBI.

Lisdexamfetamine Dimesylate

Lisdexamfetamine is an amphetamine drug used for the treatment of attention-deficit hyperactivity disorder (ADHD) in children (Blick & Keating, 2007). There is limited research on Lisdexamfetamine Dimesylate in individuals with moderate to severe TBI.

TABLE 41 | Lisdexamfetamine Dimesylate for Depression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Tramontana et al. (2014) USA RCT Crossover PEDro=7 $N_{Initial}$=22, N_{Final}=13	**Population:** Mean age=28.85y; Gender: Male=9, Female=4; Mean Time post-injury=15.58mo. Severity: Moderate=9, Severe=4. **Intervention:** Patients were randomly assigned to Lisdexamfetamine Dimesylate (LDX) (dosage as needed) or placebo for 6wk each, 12wk of treatment in total. Outcomes were assessed at baseline and at 6wk and 12wk. **Outcomes:** Wechsler Abbreviated Scale of Intelligence (WASI), Frontal Systems Behavioural Evaluation (FrSBE), Wisconsin Card Sorting Test (WCST), Finger Oscillation (Tapping test), Trail Making Test A, Trail Making Test B, Continuous Performance Test (CPT), Digit Span, Stroop Color Word Test, Digit Symbol Test, Paced Auditory Serial Addition Test (PASAT), Benton Visual Retentions Test, Conners Adult ADHD Rating Scale (CAARS), Behaviour Rating Inventory of Executive Function Adult Version (BRIEF-A), Quality of Life Inventory (QOLI), Beck Depression Inventory-II (BDI-II) - Beck Anxiety Inventory (BAI).	1. Cases with lower self-ratings of depression on the BDI-II pre-treatment tended to do better on LDX in planning and organization (p=0.03). 2. In the BRIEF-A, scores on the Inhibit scale predicted treatment outcomes on measures such as self-ratings of depression on the BDI-II (p=0.031).

Discussion

In an RCT, Tramontana et al. (2014) examined the effects of Lisdexamfetamine Dimesylate (LDX) compared to placebo on cognitive and neurobehavioural measures in individuals with TBI. While the authors found that lower pre-treatment depression was associated with better planning and organization performance in the treatment group, no further interactions or effects were reported.

Conclusions

There is level 1a evidence (Tramontana et al., 2014) that Lisdexamfetamine Dimesylate may not have an effect on depression post TBI; however, further research is needed.

KEY POINTS

- Further research is needed to determine the effects of Lisdexamfetamine Dimesylate on depression post moderate to severe TBI.

Anxiety

Anxiety emerges as a complex emotional state intertwined with feelings of apprehension triggered by cognitive assessments of real or perceived threats, predisposing individuals to a spectrum of disorders including phobias, panic disorder, generalized anxiety disorder, social anxiety and agoraphobia (Chand, Marwaha, et al., 2021). The etiology of anxiety encompasses an interaction of stressful life events, childhood adversity, genetic factors, and exposure to trauma; in addition, there is a high comorbidity between depression and anxiety, resulting in additional complexities for the management of both conditions (Thibaut, 2017). Anxiety is commonly reported following brain injuries and it can significantly affect the daily functioning of an individual (Bertisch et al., 2013).

Incidence and Prevalence of Anxiety

Following an ABI, anxiety has been reported to occur in 4% to 34% of individuals (Alway et al., 2016; Alway et al., 2012; Anke et al., 2015; Deb et al., 1999; Fann et al., 1995; Gould et al., 2014; Hart et al., 2016; O'Donnell et al., 2008; Osborn et al., 2016; van Reekum et al., 1996). In a meta-analysis of 32 studies, self-reported rates of anxiety in the TBI population were approximately 37% (Osborn et al., 2016). Post-ABI anxiety has demonstrated a positive correlation with depression (Sigurdardottir et al., 2013), as well as non-productive coping strategies (Spitz et al., 2013). Moreover, individuals with anxiety disorders post-ABI have reported lower life satisfaction and functional recovery one year post-injury (Anke et al., 2015).

Non-Pharmacological Interventions

Psychotherapy

Cognitive Behavioural Therapy

Cognitive behavioral therapy (CBT) is a type of psychotherapy that focuses on the relationship between emotion, cognition and behaviour, and targets automatic thoughts and underlying beliefs that impact the individual's response to events (Chand et al., 2022). In a review and a systematic review by Waldron et al. (2013) and Verberne et al. (2019) respectively, CBT has been reported to have promising benefits for reducing anxiety symptoms in individuals with ABI.

TABLE 42 | Cognitive Behavioural Therapy for the Management of Anxiety Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Ponsford et al. (2016) Australia RCT PEDro=7 $N_{Initial}$=75, N_{Final}=51	**Population:** TBI; *CBT+MI Group (n=26):* Mean Age=46.69yr; Gender: Male=18, Female=8; Mean Time Post Injury=4.88yr; Mean GCS=10.43. *CBT+NDC Group (n=26):* Mean Age=39.88yr; Gender: Male=20, Female=6; Mean Time Post Injury=3.58yr; Mean GCS=10.48. *WC Group (n=23):* Mean Age=39.87yr; Gender: Male=17, Female=6; Mean Time Post Injury=2.61yr; Mean GCS=8.23. **Intervention:** Participants diagnosed with depression and/or anxiety were allocated to receive cognitive behavioural therapy (CBT) with either motivational interviewing (CBT+MI) or non-directive counseling (CBT+NDC), or to a waitlist control (WC). MI and NDC were each delivered for 3wk, followed by 9wk of CBT, with three CBT booster sessions 21-30wk from baseline. Assessments were conducted at baseline, 3wk, 12wk, 21wk, and 30wk. **Outcome Measure:** Depression, Anxiety & Stress Scale (DASS), Hospital & Anxiety Depression Scale (HADS), Sydney Psychosocial Reintegration Scale 2 (SPRS-2).	1. All groups demonstrated significant improvements in the HADS-Anxiety. 2. On the HADS-Anxiety, there was a significantly greater reduction in score over time in CBT+NDC versus WC ($p<0.05$) but not CBT+MI versus WC; there was no significant difference between CBT+MI and CBT+NDC. 3. Higher baseline DASS-Depression and HADS-Anxiety scores were significantly associated with greater response to treatment ($r=0.34$, $p<0.05$ and $r=0.37$, $p<0.05$, respectively). 4. When combining CBT+MI and CBT+NDC groups, there were significantly greater improvements on HADS-Anxiety ($p<0.05$) in the combined group versus WC.
Hsieh et al. (2012) Australia RCT PEDro=6 $N_{Initial}$=27, N_{Final}=17	**Population:** TBI; Mean Age=38yr; Gender: Male=13, Female=4; Mean Time Post Injury=37.9 mo; Mean PTA duration=23.8d. **Intervention:** Participants diagnosed with anxiety received motivational interviewing followed by cognitive behavioural therapy (CBT+MI; n=9), non-directive counselling followed by CBT (CBT+NDC; n=10), or standard care (control; n=8) for 12 wk. Assessments were conducted at baseline, 3wk,12 wk, and 21wk. **Outcome Measure:** Hospital Anxiety and Depression Scale (HADS), Depression Anxiety Stress Scale (DASS), Coping Style for Adults (CSA), Sydney Psychosocial Reintegration Scale (SPRS-2), Anxiety Change Expectancy Scale (ACES), Working Alliance Inventory–Short Form Revised (WAI-SR).	1. CBT+MI and CBT+NDC had significantly greater reductions on HADS-Anxiety than control (both $p=0.03$). 2. CBT+NDC had significantly greater reduction on DASS-Stress than control ($p=0.03$), but CBT-MI did not. 3. CBT+MI had significantly greater reduction on CSA-Non-productive than control ($p=0.001$), but CBT+NDC did not. 4. CBT+MI showed significantly greater reductions on HADS-Anxiety ($p=0.001$), DASS-Anxiety ($p=0.026$), and DASS-Stress ($p=0.005$) than CBT+NDC.
Hsieh et al. (2012) Australia RCT PEDro=6 N=27	**Population:** TBI; Mean Age=38yr; Gender: Male=21, Female=6; Mean Time Post Injury=37.9 mo; Mean PTA duration=23.1d. **Intervention:** Participants diagnosed with anxiety received motivational interviewing followed by cognitive behavioural therapy (CBT+MI; n=9), non-directive counselling followed by CBT (CBT+NDC; n=10), or standard care (control; n=8) for 12 wk. Assessments were conducted at baseline, 3wk,12 wk, and 21wk. **Outcome Measure:** Anxiety Change Expectancy Scale (ACES), The Anxiety scale of the Hospital Anxiety and Depression Scale (HADS), Depression, Anxiety and Stress	1. CBT+MI showed a significantly greater increase in ACES than CBT+NDC after CBT ($p=0.04$) and at 9wk follow-up ($p=0.015$), but not immediately after MI ($p=0.22$). 2. There was a moderate, non-significant correlation between posttraumatic amnesia and ACES ($r=0.485$, $p=0.067$), suggesting that greater reduction in anxiety is associated with less severe injury. 3. Participants receiving MI showed greater response to CBT, in terms of reduction in anxiety, stress and non-productive coping, compared to participants who received NDC.

Author Year Country Study Design Sample Size	Methods	Outcome
	Scales (DASS), Coping Scale for Adults (CSA), Sydney Psychosocial Reintegration Scale - Version 2 (SPRS-2).	
Anson & Ponsford (2006) Australia RCT PEDro=5 N=31	**Population:** TBI; Gender: Male=26, Female=5. *Group A (n=15)*: Mean Age=38.9yr; Mean Time Post Injury=755.8d. *Group B (n=16)*: Mean Age=37.8yr; Mean Time Post Injury=340.8d. **Intervention:** Participants were randomized to receive a CBT-based Coping Skills Group (CSG) in two groups with different duration. For Group A (n=15), baseline phase was 5wk, followed by 5wk of intervention, and a 5wk follow-up phase. For Group B (n=16), baseline was 10wk, followed by 5wk of intervention and a 10wk follow-up phase. The CSG consisted of 10 group sessions and ran for 900min 2×/wk. **Outcome Measure:** Coping Scale for Adults, Hospital Anxiety and Depression Scale, Rosenberg Self Esteem scale.	1. No significant changes in anxiety or self-esteem scores were noted following the CSG ($p>0.05$). 2. Although levels of depression and psychosocial dysfunction were significantly different between the two groups ($p<0.05$) participation in the CSG did not have an effect on their scores. 3. Both groups significantly increased their adaptive coping skills following the CSG ($p<0.01$).
Arundine et al. (2012) Canada PCT $N_{Initial}=20$, $N_{Final}=17$ Follow up to Bradbury et al. (2008)	**Population:** TBI=10, ABI=10, Severity: Moderate-Severe. *CBT Group (n=10):* Mean age=39.8yr; Gender: Male=5, Female=5; Mean Time Post Injury=7.00yr. *EC Group (n=10):* Mean age=42.5yr; Gender: Male=5, Female=5; Mean Time Post Injury=11.4yr. **Intervention:** Participants with psychological distress were randomized to receive cognitive behavioural therapy (CBT) or education control (EC). CBT involved one individual introductory session, and then 10 sessions either in a group (CBT-G) or individually by telephone (CBT-T). EC group received CBT after initial group. Assessments were conducted at baseline, post treatment, 1mo follow-up, and 6mo follow-up. **Outcome Measure:** Depression Anxiety Stress Scales 21 (DASS-21), Symptom Checklist 90 Revised (SCL-90-R).	1. At 6mo follow-up, all participants showed significant improvements from baseline on DASS-21 ($p<0.01$) and SCL-90-R ($p<0.01$); CBT-G and CBT-T were comparable.
Bradbury et al. (2008) Canada PCT N=20	**Population:** TBI=10, ABI=10, Severity: Moderate-Severe. *CBT Group (n=10):* Mean age=39.8yr; Gender: Male=5, Female=5; Mean Time Post Injury=7.00yr. *EC Group (n=10):* Mean age=42.5yr; Gender: Male=5, Female=5; Mean Time Post Injury=11.4yr. **Intervention:** Participants with psychological distress received cognitive behavioural therapy (CBT) or education control (EC). CBT involved one individual introductory session, and then 10 sessions either in a group (CBT-G) or individually by telephone (CBT-T). Assessments were conducted at baseline, post treatment, and 1mo follow-up. **Outcome Measure:** Depression Anxiety Stress Scales 21 (DASS-21), Symptom Checklist 90 Revised (SCL-90-R).	1. At post treatment and 1mo follow-up, combined CBT showed significantly greater improvement from baseline than EC on DASS-21 ($p<0.001$) and SCL-90-R ($p<0.01$). 2. On DASS-21 and SCL-90-R, there were significant improvements from baseline to post treatment and to 1mo follow-up for CBT-G ($p<0.01$) and CBT-T ($p<0.05$), but there were no significant improvements from post treatment to 1mo follow-up ($p>0.05$). 3. There were no significant differences between CBT-G and CBT-T at any time point on DASS-21 or SCL-90-R ($p>0.05$).

Author Year Country Study Design Sample Size	Methods	Outcome

Discussion

Three studies examined CBT for the management of anxiety post-ABI in combination with motivational interviewing (MI) and non-directive counseling (NDC). In an RCT, Ponsford et al. (2016) examined CBT combined with MI and NDC, compared to a waitlist control. The authors found that, while all groups showed improvements in anxiety over time, a significantly greater reduction in anxiety was observed in the CBT+NDC group versus the wait list control. When the combined groups were combined, for analysis, they showed a greater reduction of anxiety when compared to the waitlist control (Ponsford et al., 2016). Similarly, in two studies by Hsieh et al. (2012a; 2012b), both combined CBT+MI had significantly greater reductions in anxiety when compared to controls, with the CBT+MI group showing a greater response to CBT, compared to NDC (Hsieh et al., 2012a; Hsieh et al., 2012b). In an RCT of similar quality, Anson and Ponsford (2006) investigated two groups that received a CBT-based coping skills intervention of different durations. The authors found that, while both groups showed an increase in coping skills, there were no significant differences in anxiety (Anson & Ponsford, 2006).

In two PCT studies, the authors reported that CBT significantly reduced symptoms of anxiety for up to six months, whether delivered in a group or individually over the phone (Arundine et al., 2012; Bradbury et al., 2008). In a meta-analysis, Barua et al. (2024), reported CBT to have small effect sizes in reducing anxiety post-intervention, suggesting that although CBT is effective in reducing symptoms of anxiety, but when compared with other forms of active psychotherapy (i.e., supportive psychotherapy) control groups, the effect is not significantly larger.

Conclusions

There is level 1a evidence (Ponsford et al., 2006) that CBT combined with MI and NDC may be an effective treatment for anxiety post TBI, compared to waitlist controls.

There is level 1b evidence (Hsieh et al., 2012a; 2012b) that CBT combined with MI may be more effective for the management of anxiety and coping skills post TBI.

There is level 2 evidence (Anson & Ponsford, 2016) that delivering a CBT-based coping skills intervention for 10 weeks may not be more effective for anxiety than a 5 week intervention.

There is level 2 evidence (Arundine et al., 2012; Bradbury et al.,2008) that CBT delivered in a group and individually via telephone may be similarly effective in reducing anxiety following ABI.

KEY POINTS

- Cognitive behavioural therapy (CBT) combined with Motivational Interviewing (MI) and Non-Directive Counselling (NDC) may improve anxiety post TBI, compared to a waitlist control.
- Cognitive behavioural therapy (CBT) combined with Motivational Interviewing (MI) may be more effective for anxiety and coping skills.
- A 10-week CBT-based coping skills intervention may not be more effective for anxiety than a 5-week intervention.
- Cognitive behavioural therapy (CBT) delivered in a group or individually over the telephone, may be equally effective for the management of anxiety post ABI.

Neuro-Systemic Psychotherapy

The neuro-systemic approach aims to reduce emotional and behavioural disorders experienced by individuals with TBI by improving relational dysfunctions within various systems such as family, conjugal, social institutional and professional; while considering the individual's specific cognitive disorders (Wiart et al., 2012).

TABLE 43 | Neuro-systemic Psychotherapy for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Wiart et al. (2012) France Case Series N= 47	**Population:** TBI; Mean Age=33.4yr; Gender: Male=35, Female=12; Mean GCS=6.4; Mean Time Post Injury=11.1yr **Intervention:** Retrospective review of patients with mood disorders referred to a single physician for at least 1yr of neuro-systemic psychotherapy. **Outcome Measure:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Glasgow Outcome Scale.	1. A significant improvement of affective disorders was found in anxiety ($p<0.001$).

Discussion

In one case series study, Wiart et al. (2012) reported on the effectiveness of a neuro-systemic psychotherapy intervention for individuals with TBI who presented with affective/behaviour disorders. The authors found significant improvements for anxiety post TBI.

Conclusions

There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may improve anxiety in individuals with TBI.

KEY POINTS

- Neuro-systemic psychotherapy may be effective for the treatment of anxiety post TBI.

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT) is a form of psychotherapy designed to address cognitive processes, with a focus on navigating distress through fostering the individual's capacity for engaging in meaningful activities (Graham et al., 2016).

TABLE 44 | Acceptance and Commitment Therapy for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Sander et al. (2021) USA RCT PEDro=5 $N_{initial}$=98, N_{final}=93	**Population:** TBI; *ACT* (n=44); Mean age=37.73yr; Gender: Male=25, Female=19; Mean time post-injury=57.4mo; Severity: Mild=19, Moderate=7, Severe=19. *Usual care* (n=49); Mean age=38.27yr; Gender: Male=31, Female=18; Mean time post-injury=47.01mo; Severity: Mild=22, Moderate=9, Severe=18. **Intervention:** Participants were randomly allocated to eight 1.5h sessions of Acceptance and Commitment Therapy (ACT) or usual care. Outcome measures were assessed within 2wk of the last session and 3mo posttreatment. **Outcomes:** Brief symptom inventory 18 (BSI-18), Acceptance and action questionnaire-II (AAQ-II), Participation Assessment with Recombined Tools-Objective (PART-O).	1. When compared to the usual care group, participants in the ACT group demonstrated lower scores on the BSI-18 anxiety subscales (p=0.01). 2. No between-group difference were observed on the BSI 18 Depression subscale.

Discussion

In an RCT, Sander et al. (2021) examined the effectiveness of ACT on psychological distress in individuals who had sustained a TBI for ≥6 months. The authors found significant reductions in psychological distress and anxiety after eight sessions of ACT, compared to standard care.

Conclusions

There is level 1b evidence (Sander et al., 2021) that ACT may be effective for anxiety and psychological distress when compared to standard care.

KEY POINTS

- Acceptance and Commitment Therapy (ACT) may reduce anxiety and psychological distress, compared to standard care.

Psychoeducation

Psychoeducation interventions have been used in healthcare to help patients understand and manage their mental health condition by reinforcing their individual skills and resources to be able to better cope with their situation (Casañas et al., 2012).

TABLE 45 | Psychoeducation for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Sinnakaruppan et al. (2005) UK RCT PEDro=5 $N_{Initial}$=89, N_{Final}=83	**Population:** TBI=41, Caregivers=42; Age Range=21-63yr; Gender: Male=41, Female=42. Time Post Injury=2 to 94mo; GCS=3-12. **Intervention:** Caregivers and patients were randomly assigned to an educational training program led by a neuropsychologist (8 x 2.5hr sessions) or a waitlist control. **Outcome Measures:** Hospital Anxiety and Depression Scale (HADS), General Health Questionnaire-28 (GHQ-28), Rosenberg Self-Esteem Scale (RSE), Coping Orientation Problems Experienced Scale (COPE), Functional Independence Measure (FIM), Rivermead Behavioural Memory Test (RBMT), Behavioural Assessment of Dysexecutive Syndrome (BADS), Weschler Adult Intelligence Scale-Third Edition (WAIS-III).	1. There were improvements for both the groups; however, a comparison of means between the two samples did not show a statistically significant change (p=0.615) for HADS anxiety. 2. There was a modest reduction in the HADS Depression mean score for both the groups at follow-up; however, group differences were not significant (p=0.331).
Neumann et al. (2017) USA Pre-Post N=17	**Population:** TBI=17; Mean Age=46.12yr; Gender: Male=13, Female=4; Mean Time Post Injury=8.73yr; Mean PTA=95.35d; Mean LOC=14.18d. **Intervention:** Eight lessons incorporated psycho-educational information and skill-building exercises teaching emotional vocabulary, labeling, and differentiating self-emotions; interoceptive awareness; and distinguishing emotions from thoughts, actions, and sensations. **Outcome Measures:** Toronto Alexithymia Scale (TAS-20), Levels of Emotional Awareness Scale (LEAS), State	1. There were significant improvement on anxiety as measured by the STAI and positive affect scores at 2-month follow up.

Author Year Country Study Design Sample Size	Methods	Outcome
	Trait Anxiety Inventory (STAI), Patient Health Questionnaire (PHQ-9) - Depression, State Trait Anger Expression Inventory (STAX-2I), Positive and Negative Affect Scale (PANAS), Difficulty with Emotion Regulation Scale (DERS), Satisfaction Questionnaires.	

Discussion

In the RCT by Sinnakaruppan et al. (2005), both individuals with TBI and their caregivers received an educational training program, with results indicating no statistically significant improvements in anxiety. In a pre-post study, Neumann et al. (2017) examined the effectiveness of a psychoeducational information and skill-building exercises program for individuals with moderate to severe TBI. The program involved teaching emotional vocabulary, labelling, differentiating emotions, and distinguishing between actions, sensations and emotions. The authors found significant improvements in anxiety, as measured by the State-Trait Anxiety (STAI) (Neumann et al., 2017).

Conclusions

There is level 2 evidence (Sinnakaruppan et al., 2005) that an educational program for individuals with TBI and their caregivers focused on cognitive abilities may not decrease anxiety.

There is level 4 evidence (Neumann et al., 2017) that psychoeducation that involves emotion recognition and self-awareness may be effective for anxiety in individuals with moderate to severe TBI.

KEY POINTS

- Psychoeducation focused on cognitive abilities may not improve anxiety symptoms post moderate to severe TBI.
- Psychoeducation involving emotion recognition and self-awareness training may improve anxiety symptoms following a moderate to severe TBI.

Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive neurostimulation technique, has shown promising results in populations without TBI; however, the effectiveness might not be entirely clear (Brunoni et al., 2017). There is limited literature evaluating its role for the management of anxiety in individuals with ABI.

TABLE 46 | Transcranial Magnetic Stimulation for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Rodrigues et al. (2020) Brazil RCT PEDro=8 $N_{Initial}$=36, N_{Final}=27 Post-Hoc Analysis of Neville et al. (2019)	**Population:** TBI*; Active rTMS (n=16)* Mean Age=32.8yr; Gender: Male=14, Female=2; Mean Time Post Injury=17.8mo; Mean GCS=4.0. *Sham rTMS (n=11):* Mean Age=31.6yr; Gender: Male=10, Female=1; Mean Time Post Injury=17.6mo; Mean GCS=3.0. **Intervention:** In a Post-hoc Analysis RCT, participants were randomly assigned to an active or sham Repetitive Transcranial Magnetic Stimulation (rTMS) condition. The active rTMS group received 10-Hz rTMS stimulation over the left dorsolateral prefrontal cortex, whereas the control group received stimulation with the sham coil over the same region of the brain. rTMS procedures were applied with the MagPro X100 magnetic stimulator connected to a figure-of-eight coil, for 20 min each session, for a total of 10 sessions. Outcome measures were assessed immediately after the last rTMS session and 90 days post-intervention. **Outcome Measure:** Spielberger State-Trait Anxiety Inventory (STAI), Beck Depression Scale- 2nd Edition (BDI-II), Executive Function Index (EF Index).	1. There were no statistically significant changes in anxiety as measured by the STAI within each group over time (p>0.06), nor there were any significant changes between the groups (p>0.14). 2. There were no significant adverse effects reported between the groups after the first (p=0.23) and the second week of stimulation (p=0.29). 3. High frequency rTMS had no significant effect on improving anxiety symptoms.

Discussion

In a post-hoc analysis of a previous RCTs (Neville et al., 2019), Rodrigues et al. (2020) evaluated the effects of repetitive transcranial magnetic stimulation (rTMS) on anxiety in individuals with moderate to severe TBI and found no significant differences between groups for anxiety scores. Although non-invasive neurostimulation techniques, such as rTMS, remain promising for treating neuropsychiatric conditions, recent reviews suggest that more extensive RCT studies with longer follow-ups, optimized stimulation parameters and standardized methodology are required to establish their efficacy in addressing TBI sequelae (Galimberti et al., 2023).

Conclusions

There is level 1b evidence (Rodrigues et al., 2020) that repetitive transcranial magnetic stimulation (rTMS) may not be effective for the management of anxiety post TBI.

KEY POINTS

- Transcranial magnetic stimulation (rTMS) may not be effective for the improvement of anxiety in individuals with moderate to severe TBI.

Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) has been used for treating numerous conditions such as depression, schizophrenia and substance use disorders, as well as for the improvement of cognitive functions in healthy individuals and in those living with Alzheimer's disease (Lefaucheur et al., 2017).

TABLE 47 | Transcranial Magnetic Stimulation for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Rushby et al. (2021) Australia RCT crossover PEDro=6 N=30	**Population:** TBI; Mean Age=50.0yr; Gender: Male=21, Female=7; Mean Time Post Injury=13.9yr; Mean PTA length=37.47d. **Intervention:** Participants received a single session anodal (non-invasive transcranial direct current stimulation (tDCS) applied to the left parietal lobe or sham stimulation. Outcomes were assessed before and after sessions. **Outcome Measures:** N-Back Task, Hospital Anxiety and Depression Scale (HADS), Profile of Mood States (POMS), Alertness and Fatigue Scale, Skin Conductance.	1. There were no significant differences between active and sham sessions for depression and anxiety, as measured by the HADS and the depression subscale of the POMS ($p>0.05$).

Discussion

In an RCT, Rushby et al. (2021) examined the use of transcranial direct current stimulation (tDCS) compared to sham. Ther authors reported no significant differences between active and sham stimulation for anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS).

Conclusions

There is level 1a evidence (Rushby et al., 2021) that transcranial direct current stimulation (tDCS) may not improve anxiety post TBI.

KEY POINTS

- Transcranial direct current stimulation (tDCS) may not improve anxiety in individuals with moderate to severe TBI.

Biofeedback Training

Biofeedback training is a promising intervention for the management of anxiety and stress. In a meta-analysis, Goessl et al. (2017) found that heart rate variability biofeedback was associated with reduced stress and anxiety in both clinical settings and in the community.

TABLE 48 | Biofeedback Training for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Wearne et al. (2021) Australia RCT PEDro=8 N=50	**Population:** TBI*; Biofeedback group*(n=25); Gender: Male=17, Female=8; Mean Age=50.02yr; Mean GCS=6.82; Mean Time Post-Injury=14.36yr; *Waitlist Group* (n=25); Gender: Male=19, Female=6; Mean Age=43.12yr; Mean GCS=5.80; Mean Time Post-Injury=12.70yr **Intervention:** Participants were randomly allocated to either a heart rate variability biofeedback training group or a waitlist group receiving usual care. Intervention consisted of 6 training sessions with the therapist and self-practice sessions at home. There were 6 sessions, 1hr/d with a therapist and 8 sessions, 20-40min/d at home for 2wk. Outcomes were assessed before and after the intervention. **Outcome Measure:** Paced Auditory serial Addition Task (PASAT), Heart Rate (HR), Respiration rate, Skin Conductance (SCL).	1. Participants in the biofeedback group endorsed significantly fewer symptoms on the depression subscale of the DASS-21 ($p<.05$), and greater resting state-positive mood on the SAM-Mood subscale ($p<.005$) at the post-intervention compared to those in the waitlist group. 2. No significant differences were seen between the biofeedback group and the control group in all the other outcomes ($p>0.05$) at post-intervention

Discussion

In an RCT, Wearne et al. (2021) examined the effects of a heart rate variability biofeedback training intervention compared to a waitlist control in individuals with severe TBI. The intervention included six sessions of biofeedback training in which participants practiced diaphragmatic breathing by use of a visual stimulus for pacing. There were no differences in reported anxiety and stress.

Conclusions

There is level 1b evidence (Wearne et al., 2021) that Biofeedback training may not improve symptoms of anxiety in individuals with severe TBI.

KEY POINTS

- Biofeedback training may not improve anxiety post severe TBI.

Physical Activity

Engaging patients in physical activity after their injury can increase functional gains, decrease length of stay in inpatient rehabilitation and accelerate recover; particularly, high-intensity physical activity (Ramsey et al., 2018).

TABLE 49 |Physical Activity for the Management of Anxiety Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Krese et al. (2020) USA RCT Crossover PEDro=6 N=13	**Population:** TBI=13; Mean Age=45.31yr; Gender: Male=8, Female=5; Mean Time Post Injury=15d; Mean GCS=10.43. **Intervention:** Individuals participated in each of the three intervention conditions in a. randomized order: group yoga-based physical therapy (YPT), conventional physical therapy (CPT), and group seated rest (SR). Each condition lasted one hour for a total of three hours. Outcome measures were assessed immediately post-intervention. **Outcome Measure:** Wake after sleep onset (WASO), Heart Rate Variability (HRV), Spielberger State-Trait Anxiety Inventory (STAI), Electrocardiography (ECG).	1. Changes in WASO from pre- to post-treatment differed between treatments, as the overall interaction effect was significant (p=0.0203). 2. For the SR treatment, WASO rate was reduced from 14.99 to 10.60 (IRR=0.71; p=0.006) but increased slightly following CPT (IRR=1.03; p=0.802) and YPT (IRR=1.09; p=0.427) treatments. 3. The IRR for the SR condition was 0.69 lower compared to physical therapy (p=0.0218) and 0.65 times lower compared to yoga treatment (p=0.0089). IRRs did not significantly differ between yoga and physical therapy treatments (p=0.6873). 4. No statistically significant differences were found between treatment groups for STAI.
Hassett et al. (2009) Australia RCT PEDro=8 N=62	**Population:** Severe TBI; Fitness Center Group (n=32): Mean Age=35.4yr; Gender: Male=27, Female=5; Median Time Post Injury=2.6 mo. Home-Based Group (n=30): Mean Age=33yr; Gender: Male=26, Female=4; Median Time Post Injury=2.3 mo. **Intervention:** Participants were randomly assigned to either an exercise intervention group at a fitness center or to a home-based exercise group. Fitness center participants were supervised by a personal trainer (1hr, 3x/wk, 12wk), the home-based exercise group followed an exercise plan and were monitored by a physiotherapist. Assessment at baseline, end of intervention and 3mo follow-up. **Outcome Measures:** 20m Shuttle Test, Heart Rate (HR), Body Mass Index (BMI), Waist-to-Hip-ratio (WHR), Depression Anxiety Stress Scale (DASS), Profile of Mood States (POMS), Brain Injury Community Rehabilitation Outcome (BICRO-39), Sydney Psychosocial Reintegration Scale (SPRS).	1. There were no between-group significant differences in psychological functioning, including depression (p=0.238), anxiety (p=0.132) and stress (p=0.131).
Bateman et al. (2001) UK RCT	**Population:** Severe ABI; TBI=44, Stroke=70, Subarachnoid Hemorrhage=15, Other=28; Gender: Male=97, Female=60. Training Group (n=79): Mean Age=41.7yr; Mean Time Post Injury=22.2 wk. Control	1. No significant group differences were reported for the HADS anxiety and depression scores.

Author Year Country Study Design Sample Size	Methods	Outcome
PEDro=7 N=157	Group (n=79): Mean Age=44.7yr; Mean Time Post Injury=25.5wk. **Intervention:** Participants were divided to receive either an exercise intervention (cycle training) or relaxation training (control group) for 30min sessions, 3x/wk for 12wk. **Outcome Measures:** Heart Rate (HR), Body Mass Index (BMI), Modified Ashworth Scale (MAS), Berg Balance Scale (BBS), Rivermead Mobility Index (RMI), Barthel Index (BI), Functional Independence Measure (FIM), Nottingham Extended Activities of Daily Living (NEADLI), Hospital Anxiety and Depression Scale (HADS).	

Discussion

In an RCT crossover, Krese et al. (2020) randomly allocated participants into a yoga-based therapy group (YPT), a conventional physical therapy group (CPT), or a seated great group (SR). While a small decrease in anxiety, as measured by the Spielberger State-Trait Anxiety Inventory (STAI), was observed, there were no statistically significant differences between treatment groups. In an RCT, Hassett et al. (2009) found no differences on measures of anxiety between a group that exercised at a fitness centre and a group that exercised at home. In another RCT study, Bateman et al. (2001) compared cycle ergometer aerobic training and a relaxation training control and found no differences for measures of anxiety in individuals with severe ABI.

Conclusions

There is level 1a evidence (Krese et al., 2020) that yoga-based therapy may not improve anxiety post TBI when compared to conventional physical therapy or seated physical activity.

There is level 1b evidence (Hassett et al., 2009) that exercising at a fitness center is no more effective than exercising at home for anxiety post severe TBI.

There is level 1b evidence (Bateman et al., 2001) that cycle ergometer aerobic training may not be effective for anxiety post severe ABI, compared to relaxation training.

KEY POINTS

- Yoga-based therapy may not improve anxiety in individuals with moderate to severe TBI.
- Exercise at a fitness center may not be more effective for anxiety following severe TBI than exercising at home.
- Cycle ergometer aerobic training may not be more effective than relaxation training for anxiety in those with severe ABI.

Social Skills Training

Initially developed for individuals with autism, social skills training is an intervention often delivered in groups that involves goal setting, role modeling, behavioral rehearsal and other behavioral strategies to help individuals improve social function (Dubreucq et al., 2022). There is limited evidence on the effectiveness of social skills training for anxiety.

TABLE 50| Social Skills Training for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
McDonald et al. (2008) Australia RCT PEDro=6 N=39	**Population:** TBI; Gender: Male=28, Female=11. *Treatment Group (n=13)*: Mean Age=35.5yr; Mean Time Post Injury=4.0yr. *Social Group (n=13)*: Mean Age=34.3yr; Mean Time Post Injury=4.3yr. *Waitlist Group (n=13)*: Mean Age=35.3yr; Mean Time Post Injury=3.5yr. **Intervention:** Participants were randomly allocated to waitlist (n=13), control social group (non-therapeutic social group; n=13), or the social skills group (treatment group; n=13). Participants in the skills training group attended 12wk program of group and individual sessions totaling 4 hr/wk. Control group received 4 hr/wk of social activities only for 12wk. **Outcome Measure:** Behaviorally Referenced Rating System of Intermediary Social Skills Revised (BRISS-R), The Awareness of Social Inference Test (TASIT), Depression Anxiety Stress Scale (DASS), Katz Adjustment Scale (KAS-R1), Social Performance Survey Schedule (SPSS), La Trobe Communication Questionnaire (LCQ), SPRS, Katz adjustment scale-R1 (KAS), the Social Performance Survey Schedule (SPSS), La Trobe Communication Questionnaire (LTCQ), Sydney Psychosocial Reintegration Scale (SPRS).	1. No overall treatment effect was found for anxiety and depression, as measured by the Depression Anxiety Stress Scale (DASS).

Discussion

In a multicenter RCT, McDonald et al. (2008) compared social skills training, social activity, and a waitlist control group. The authors reported no overall treatment effect for anxiety and depression, as measured by the Depression Anxiety Stress Scale (DASS).

Conclusions

There is level 1b evidence (McDonald et al., 2008) that a social skills training programs may not improve anxiety post TBI.

KEY POINTS

- Social skills training may not be effective in improving anxiety in individuals with TBI.

Rehabilitation Programs

Anxiety is highly prevalent in individuals with brain injuries, and it has a negative impact on their rehabilitation outcomes (Alway et al., 2012). Rehabilitation programs post-TBI aim to restore function and participation to preinjury levels, and involve the coordination of a multidisciplinary team of clinicians such as physiatrists, neurologists, psychologists, speech and language therapists, occupational therapists, physical therapists, nurses and recreational therapists and social workers (Brasure et al., 2013).

TABLE 51| Rehabilitation Programs for the Management of Anxiety Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Goal-based Rehabilitation		
Borgen et al. (2023) Norway RCT PEDro=7 N=120	**Population:** Severe TBI**;** *Intervention Group* (n=60): Gender: Male=44, Female=16; Median Age=45.5yr (IQR 29.5-54); Median GCS=8(IQR 4-14); Median Time Post Injury=52mo (IQR 44-83); *Control Group* (n=60): Gender: Male=41, Female=19; Mean Age=Median Age=49yr (IQR 33-60.5); Median GCS=10(IQR 6-14); Median Time Post Injury= 53.5mo (IQR 44-88). **Intervention:** Participants were randomly allocated to either an individually tailored, goal-based, home intervention or a control group receiving usual care. The intervention consisted of a home-based goal-oriented rehabilitation program delivered via videoconference or phone calls to set SMART goals, lasting 8 sessions for 4mo. Outcomes were assessed at baseline, post intervention (4mo) and follow up (12mo). **Outcome Measure:** Quality of Life After Brain Injury (QOLIBRI), Participation and Recombined Tools–Objective (PART-O), EuroQol 5-dimension 5-level (EQ-5D-5L), Rivermead Post Concussion Symptoms Questionnaire (RPQ), Patient Health Questionnaire-9 item scale (PHQ-9), Generalized Anxiety Disorder 7-item scale (GAD-7), Patient Competency Rating Scale (PCRS).	1. There were no significant differences between groups for health-related quality of life or social participation. 2. At 12-mo, participants in the intervention group had significantly better scores for generic health related quality of life (p=.04), lower TBI symptoms (p=.04), and anxiety symptoms (p=.02). 3. The control group had displayed a significant decrease in social participation (p=.002).
Hart & Vaccaro (2017) USA	**Population:** Severe TBI. *GI* (n=4): Mean age=23.8yr; Gender: Male=1, Female=3; Mean time post-	1. There were no significant differences between treatment groups for BSI-18 depression and anxiety, (p>0.05).

Author Year Country Study Design Sample Size	Methods	Outcome
RCT PEDro=6 N=8	injury=2.5yr; *GR* (n=4): Mean age=34.3yr; Gender: Male=3, Female=1; Mean time post-injury=2.7yr. **Intervention:** Participants were randomized to receive text messages for goal-related implementation intentions (GI) for 8wk to improve socialization and emotional function, or to an educational review regarding goals with no follow-up messages (GR). Outcomes were assessed at baseline and post-intervention. **Outcomes:** Brief Symptom Inventory-18 (BSI-18), Participation Assessment with Recombined Tools Objective (PART-O), Goal Attainment Scale (GAS).	
Self-Awareness Rehabilitation		
Schmidt et al. (2013) Australia RCT PEDro=8 N=54	**Population:** Video Feedback (n=18): Mean age=42.7yr; Gender: Male=14, Female=4; Mean time post injury=1.5yr; Mean GCS=8.1. Verbal Feedback (n=18): Mean age=41.6yr; Gender: Male=14, Female=4; Mean time post injury=4.7yr; Mean GCS=7.1. Experimental Feedback (N=18): Mean age=37.5yr; Gender: Male=18; Mean time post injury=5.8yr; Mean GCS=7.0. **Intervention:** Participants received instructions for meal preparation on 4 occasions in one of three formats. The video feedback group watched their recorded meal preparation sessions, the verbal feedback group received feedback on task completion without the video, and the experimental group received no therapist feedback on task completion. **Outcome Measures:** Awareness Questionnaire (AQ), Self-perceptions in Rehabilitation Questionnaire (SPIRQ), Depression Anxiety Stress Scale (DASS), Behavioural Assessment of the Dysexecutive Syndrome, Wisconsin Card Sorting Test (WCST), Wechsler Memory Scale Third Edition (WMS-III).	1. There were no significant differences between groups in depression, anxiety and stress scores, as measured by the DASS-21.
Physical and Occupational Rehabilitation		
Yeh et al. (2020) China Cohort N=231,894	**Population:** TBI=231,894; Mean Age=44.16yr; Gender: Male=62.85%, Female=37.15%; Time Post Injury < 90d. **Intervention:** Participants were collected through the National Health Insurance Research Database and were divided into two groups based on if they received rehabilitation therapy or not. Rehabilitation therapy including physiotherapy and occupational therapy were recorded according to procedure codes. The intensity of the rehabilitation therapy ranged from low (1-3 courses) to high (≥15 courses). Measurements were assessed at the 15-year follow-up. **Outcome Measure:** Kaplan-Meier model for the risk of psychiatric disorders, Charlson Comorbidity Index (CCI), Hazard ratio (HR).	1. The Kaplan-Meier analysis for the cumulative risk of psychiatric disorders in the TBI-cohort and control groups showed a significant difference over the 15-year follow-up period ($p<0.001$). 2. A twofold risk of developing psychiatric disorders was reported in those with TBI when compared to the control group ($p<0.001$). 3. The patients that were associated with a higher risk of psychiatric disorders were men, the elderly, and those with all the brain surgical procedures, complications, and higher CCI ($p<0.001$). 4. There was a significant difference in the risk of psychiatric disorders between the TBI

Author Year Country Study Design Sample Size	Methods	Outcome
		cohort who did and did not receive rehabilitation therapies over the 15-year follow-up period (p<0.001). 5. Overall, the PT or OT group was associated with a lower risk of psychiatric disorders, as per the adjusted HR of 0.691 (p<0.001).
Inpatient Rehabilitation		
Neumann et al. (2022) United States Cohort $N_{Initial}$=2836, N_{Final}=1369	**Population:** Moderate to Severe TBI; Gender: Male=2077, Female=758; Mean Age=41.4yr Mean GCS= Not Reported; Mean Time Post-Injury= Not Reported **Intervention:** Prospective longitudinal cohort of individuals enrolled in the TBI Model Systems National Database with anxiety. All participants received inpatient rehabilitation. Outcomes were assessed at 1yr, 2yr, 5yr and 10yr after TBI. **Outcome Measure:** Generalized Anxiety Disorder-7 (GAD-7)	1. A significant interaction between follow-up year and age was revealed, indicating that younger participants were more likely to have increases in anxiety over time. 2. Mean GAD-7 scores for the high-increasing group started at 7.02 (SD=4.23) at year 1 and increased to 15.15 (SD=3.29) at year 10, and the mean GAD-7 scores for the high-decreasing group started at 14.61 (SD=4.18) at year 1 and decreased to 5.94 (SD=4.00) at year 10 3. Higher GAD-7 baseline scores were significantly associated with individuals who identified as Black than those who identified as White (p<.001), with having had a violent TBI (p<.001), and with having premorbid mental health problems (p<.001)
Multidisciplinary Rehabilitation		
Mendes et al. (2021) Portugal RCT PEDro=6 N=27	**Population:** TBI; *Experimental group* (EG) (n=8); Mean Age=37yr; Gender: Male=8, Female=0; Mean GCS= 6, Time Post Injury Mean=5.09 mo. *Control Group I* (CGI) (n=10); Mean Age=37.2yr; Gender: Male=8, Female=2; Mean GCS=9, Time Post Injury Mean=53 mo. *Control Group II (CGII)* (n=9); Mean Age: 39.4yr; Gender: Male=6, Female=3; Mean GCS= 7; Time Post Injury= 1.66mo. **Intervention:** Participants received a remote holistic neuropsychological intervention program supported by a VR platform 40-60min 5x/ wk for 16 wk (cognitive training 3x/ wk and psychosocial 2x/wk). Control Group I received conventional holistic neuropsychological intervention program for 22hr/ wk x22 wk. Control Group II did not receive any intervention. **Outcome Measures:** Montreal Cognitive Assessment (MoCA), Hospital Anxiety and Depression Scale (HADS), Quality of Life after Brain Injury (QOLIBRI); Token Test (TT), Wisconsin Card Sorting Test (WCST), Trail Making Test A, Trail Making Test B, Hopkins Verbal Learning Test (HVLT), Weschler Memory Scale-III (WMS-III), Stroop Test.	1. There were no significant differences found between the groups in depression and anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS) Portuguese Version.
	Population: Severe TBI; Gender: Male=71, Female=23. *Outreach Group* (n=48): Mean Age=34yr; Mean Time	1. The outreach group had greater change scores on the psychological wellbeing

Author Year Country Study Design Sample Size	Methods	Outcome
Powell et al. (2002) USA RCT PEDro=4 $N_{Initial}$=110, N_{Final}=94	Post Injury=4yr. *Information Group* (n=46): Mean Age=35yr; Mean Time Post Injury=2.7yr. **Intervention:** Participants were randomly allocated to either an outreach treatment group provided by a multidisciplinary team (2-6hr/wk, 6-12wk) or an information treatment group which involved a therapist providing a booklet of resources at a single home visit. **Outcome Measures:** Barthel Index (BI), Brain Injury Community Rehabilitation Outcome-39 Scales (BICRO-39), Functional Independence Measure (FIM), Functional Assessment Measure (FAM), Hospital Anxiety and Depression Scale (HADS).	(p<0.025) subscale of the BICRO-39 than the information group. 2. The two groups did not differ in the extent of change from intake to follow up for either anxiety or depression, as measured by the HADS.

Discussion

In the study by Borgen et al. (2023), individuals with severe TBI were randomly allocated to either an individually tailored, goal-based, home intervention or a control group that received conventional care. The intervention involved a home-based goal-oriented rehabilitation program that was delivered via videoconference or phone calls to set goals. The authors found that, at 12 months, participants who received the intervention had significantly improved anxiety (Borgen et al., 2023). In an RCT, Hart and Vaccaro (2017) examined the implementation of intentions on goal-relevant outcomes, with or without SMS reminders. Goals were related to emotional function and socialization in individuals who had difficulties with self-regulation. The authors found no differences between the groups for anxiety, as measured by the Brief Symptom Inventory-18 (BSI-18). In an RCT, Schmidt et al. (2013) examined the effect of feedback on rehabilitating self-awareness. Participants performed a task that involve meal preparation and randomly received 1 or 3 feedback types: video plus verbal feedback, verbal feedback or experiential feedback. The authors found no significant group differences in anxiety and stress (Schmidt et al., 2013).

In a cohort study, Yeh et al. (2020) explored the risk of psychiatric disorders after TBI compared to a control group without TBI, as well as attempted to determine if rehabilitation programs post-TBI decrease the risk of developing psychiatric disorders, such as anxiety. The authors found that those with TBI were at two times higher risk for developing psychiatric disorders compared to the non-TBI control group. The 15-year follow-up period revealed that those who participated in rehabilitation programs post-TBI, including physiotherapy and occupational therapy, were significantly less likely to develop psychiatric disorders than those who did not; in addition, medium- to high-intensity rehabilitation programs correlated with lower risk for psychiatric conditions, whereas low-intensity rehabilitation therapy did not have any significant findings. In a cohort study, Neumann et al. (2022) examined anxiety trajectories in individuals who attended inpatient rehabilitation post TBI and found that risk factors of anxiety included indicators of socioeconomic disadvantages, such as insurance

status, race and pre-injury mental health. In an RCT, Mendes et al. (2021) compared holistic neuropsychological rehabilitation delivered via virtual reality to conventional neuropsychological rehabilitation and a control group that received no intervention, and found no differences in anxiety, as measured by the HADS. Similarly, Powell et al. (2002) found no differences in measures of anxiety between those who received an outreach intervention in the community and those who only received an information booklet of resources.

Conclusions

There is 1b evidence (Borgen et al., 2023) that a home-based goal-oriented rehabilitation program delivered via phone call or videoconference may improve symptoms of anxiety at 12 months.

There is level 1b evidence (Hart & Vaccaro, 2017) that a goal intention intervention with reminders via text messages may not improve anxiety post severe TBI.

There is level 1b evidence (Mendes et al., 2021) that holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for anxiety than conventional neuropsychological rehabilitation.

There is level 1b evidence (Schmidt et al., 2013) that video feedback for self-awareness rehabilitation may not be different than verbal or experiential feedback for stress and anxiety post TBI.

There is level 2 evidence (Yeh et al., 2020) that participation in physiotherapy and occupational rehabilitation programs post TBI may prevent the development of anxiety post TBI.

There is level 2 evidence (Neumann et al., 2022) that factors such as insurance status, race and pre-TBI mental health status may impact anxiety trajectories following inpatient rehabilitation.

There is level 2 evidence (Powell et al., 2002) that an outreach community intervention may not improve anxiety post severe TBI, compared to an information booklet only.

KEY POINTS

- A home-based goal-oriented rehabilitation program may improve anxiety post severe TBI; however, goal intentions delivered via text message may not be effective.
- Participation in physiotherapy and occupational therapy may lower the risk of anxiety.
- Factors such as race, insurance status, and premorbid mental may impact anxiety trajectories following participation in inpatient rehabilitation.
- Holistic neuropsychological rehabilitation delivered via virtual reality may not be more effective for anxiety than conventional neuropsychological rehabilitation.
- Self-awareness training may not be effective for anxiety and stress post TBI.
- A community outreach program may not be more effective than an information booklet of resources for anxiety post severe TBI.

Cognitive Rehabilitation

Cognitive rehabilitation aims to help individual with ABI to regain cognitive function or to compensate for cognitive deficits, and it can be implemented using technologies such as computer-based cognitive tools and virtual reality (De Luca et al., 2018).

TABLE 52 | Cognitive Rehabilitation for the Management of Anxiety Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
De Luca et al. (2023) Italy RCT PEDro=6 N=20	**Population:** TBI; *Experimental group*(n=10): Gender: Male=5, Female=5; Mean Age=46.2yr; *Control Group* (n=10): Gender: Male=6, Female=4; Mean Age=43.1yr; Time Post-Injury=>6-mo **Intervention:** Participants were randomized to either the experimental group or the control group. The experimental group received innovative virtual reality training (VR-CT) whereas the control group received conventional cognitive treatment (C-CT). All participants received 24 sessions of the same standard cognitive rehabilitation 3x/wk for 8wk. All outcomes were assessed before and after the intervention. **Outcome Measure:** Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT), Frontal Assessment Battery (FAB), Hamilton Rating Scale for Depression (HRS-D), Psychological General Well Being Index (PGWBI) Coping Orientation to the Problems Experiences-new Italian version (COPE-NIV).	1. The virtual reality (VR-CT) group showed significant differences anxiety (p<.008), and positive well-being (p<.005), as well as in coping strategies, including social support (p<.01), avoidance strategies (p<.005) and positive attitude (p<.007). 2. Between-group post-treatment analysis revealed statistically significant differences in the COPE sub-items, including positive attitude (p<.02).
Corallo et al. (2022) Italy RCT PEDro=7 N=12	**Population:** Severe ABI, TBI=7, Vascular=5**;** Mean Age=46.9yr; *Intervention Group* (n=6): Gender: Male=3, Female=3; *Control Group* (n=6): Gender: Male=4, Female=2; Time Post-Injury=Not Reported. **Intervention:** Participants were randomly allocated to either an intervention group receiving cognitive rehabilitation and feedback from a humanoid robot or a control group receiving traditional cognitive rehabilitation 3x/wk for 8wk. Both groups received conventional physiotherapy and speech therapy in addition to cognitive rehabilitation. Outcomes were assessed at admission (T0), after 1 month (T1), and after an additional 2 months (T2). **Outcome Measure:** Level of Cognitive Functioning Scale (LCF) Mini Mental State Examination (MMSE) Severe Impairment Battery (SIB) Beck Depression Inventory (BDI-II) Hamilton Rating Scale for anxiety (HAM-A) Functional Independence Measure scale (FIM) EuroQol-5D (EQ-5D)	1. The experimental treatment significantly improved symptoms of anxiety (p<.001) and depression (p<.001) as measured by the HAM-A and BDI-II respectively.
Ownsworth et al. (2017) Australia	**Population:** Severe TBI. *EBL* (n=27): Male=20, Female=7; Mean age=37.37yr; Mean time post-injury=36.44mo.	1. EBL participants demonstrated better self-awareness than ELL participants (p<0.05).

Author Year Country Study Design Sample Size	Methods	Outcome
RCT PEDro=7 $N_{Initial}$=54, N_{Final}=50	*ELL* (n=27): Male=23, Female=4; Mean age=37.86yr; Mean time post- injury=40.81mo. **Intervention:** Participants were randomly allocated to the errorless learning (ELL) or error-based learning (EBL) groups and received eight 1.5h therapy sessions over 8wk. Outcomes were measured at baseline, and at 1wk, and 6mo. **Outcome Measures:** Chevignard's Cooking Task, Behavioural Assessment of Dysexecutive Syndrome (BADS), The Awareness Questionnaire (AQ), Patient Competency Rating Scale (PCRS), Sydney Psychosocial Reintegration Scale (SPRS), Care and Needs Scale (CANS), Depression Anxiety and Stress Scales-21 (DASS-21)	2. Behavioral competency on the PCRS was significantly better in the EBL group than in the ELL group (p<0.05). 3. There were no significant between-group differences observed in the Zoo Map task of BADS, or in anxiety and depression, as measured by the DASS-21 (p>0.05).
Chiaravalloti et al. (2016) USA RCT PEDro=9 $N_{Initial}$=69, N_{Final}=53	**Population:** TBI. *Treatment Group* (n=35): Mean Age=37.17yr; Gender: Male=27, Female=8; Mean Time Post Injury=120mo; Mean GCS=4.83. *Control Group* (n=34): Mean Age=40.68yr; Gender: Male=24, Female=10; Mean Time Post Injury=102mo; Mean GCS=5.0. **Intervention:** Participants were randomized to receive the modified Short Memory Technique (TG) to improve learning, or conventional therapy (CG) in 10 sessions x5 wk. Participants in the TG were randomized to receive 5 monthly booster sessions (BS) or control sessions (CS) after treatment. Outcomes were assessed before and after treatment, and at 6mo follow-up. **Outcome Measures:** California Verbal Learning Test (CVLT), Memory Assessment Scales (MAS), Rivermead Behavioural Memory Test (RBMT), Frontal System Behaviour Scale (FrSBe), State Trait Anxiety Inventory (STAI), Chicago Multidimensional Depression Inventory (CMDI)	1. There were no significant differences between the groups for depression [F (1, 61) = 0.024; CI = −12.62 to 14.72] or anxiety [F (1, 57) = .075; CI = −4.63 to 4.86] from before to after treatment
Dundon et al. (2015) Ireland RCT PEDro=3 N=26	**Population:** TBI; Mean Age=38.96yr; Gender: Male=19, Female=7, Length of PTA= >7d. **Intervention:** Participants were assessed during a dichotic listening task (DLT) (Study 1) presented at 6 levels of distraction difficulty and received either adaptive training (AT, n=9), non-adaptive training (NAT, n=8), or no training (NT, n=9) between sessions (Study 2). The cognitive training procedure was based on attention process training (APT). Outcomes were assessed before and after training. **Outcome Measures:** Perceived Stress Questionnaire (PSQ), Calgary Symptoms of Somatic Stress (C-SOSI), Test of Everyday Attention (TEA), Rivermead Behavioural Memory Test (RBMT), Wechsler Test of Adult Reading (WTAR), Speed and Capacity of Language	1. The main effect of Time was significant for the C-SOSI (p=0.066). 2. The interaction between Group and Time was not significant (p=0.114).

Author Year Country Study Design Sample Size	Methods	Outcome
	Processing Test (SCOLP), Wechsler Memory Scale (WMS), Hayling Sentence Completion Test, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI).	
McMillan et al. (2002) UK RCT PEDro=5 N=130	**Population:** TBI; *Mindfulness Training Attentional Control Training (ACT)* (n=44): Mean Age=34.6yr; Gender: Male=35, Female=9; Median GCS=9. *Physical Exercise (PE)* (n=38): Mean Age=31.4yr; Gender: Male=30, Female=8; Median GCS=10. *Control Group* (n=48): Mean Age=36.2yr; Gender: Male=36, Female=12; Median GCS=9. **Intervention:** The ACT group received supervised practice (5 sessions of 45min over 4wk) and were given an ACT audiotape to practice daily with. The PE group had the same amount of therapist contact, but the audiotape was based on physical training. The control group had no therapist contact. Outcomes were assessed post-training, at 6mo and 12mo. **Outcome Measures:** Test of Everyday Attention (TEA), Paced Auditory Serial Addition Test (PASAT), Adult Memory and Information Processing Battery (AMIPB), Trail Making Test A, Trail Making Test B, Sunderland Everyday Memory Questionnaire (EMQ), Cognitive Failures Questionnaire (CFQ), Hospital Anxiety and Depression (HADS), General Health Questionnaire (GHQ-28), Rivermead Post-Concussion Questionnaire (RPQ).	1. No significant differences in anxiety or depression, as measured by the Hospital Anxiety and Depression Scale (HADS).
Salazar et al. (2000) USA RCT PEDro=6 $N_{Initial}$=120, N_{Final}=107	**Population:** TBI; *Hospital rehabilitation* (n=67): Mean age=25yr; Gender: Male=62, Female=5; Mean Time post-injury=38d; Mean GCS=9.4; *Home rehabilitation* (n=53): Mean age=26yr; Gender: Male=51, Female=2; Mean Time post-injury=39d. Mean GCS=9.5. **Intervention:** Patients were randomly assigned to either an intensive, standardized, 8wk, in-hospital cognitive rehabilitation program or a limited home rehabilitation program with weekly telephone support from a psychiatric nurse. Outcomes were assessed at baseline and at the 1yr follow-up. **Outcomes:** Katz Adjustment scale (KAS), Halstead-Reitan Neuropsychological Battery, Buschke Selective Reminding Test (SRT), Continuous Visual Memory Test (CVMT), Paced Auditory Serial Addition Test (PASAT), Wisconsin Card Sorting Test (WCST), Wechsler Memory Scale Revised (WMS-R), Auditory Consonant Trigrams (ACT).	1. There were no significant differences between treatment groups reported at 1 year in measures of belligerence (p=0.19), social irresponsibility (p=0.99), antisocial behaviour (p=0.24), social withdrawal (p=0.40), and apathy (p=0.21). 2. At 1 year after randomization, no significant differences were found for verbal or physical aggression (p=0.82). 3. No significant differences were found at 1 year for major depression (p=0.26) and generalized anxiety (p=0.33), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
Afsar et al. (2021) India Pre-Post N=12	**Population:** TBI; Gender: Male=9, Female=3; Mean Age=32.33yr; Severity: Moderate=4, Severe=8; Mean Time Post-Injury=11.37yr. **Intervention:** Participants received an outpatient hospital-based Cognitive Retraining intervention with	1. Post intervention, the participants experienced significantly lower amounts of perceived stress (on the Perceived Stress Scale, p=0.028), and reported higher levels of

Author Year Country Study Design Sample Size	Methods	Outcome
	five tasks targeting cognitive domains such as processing speed, attention, response inhibition, working memory, learning, and memory. Participants received 20 sessions, 3x/wk for 2mo. Outcomes were assessed before and after the intervention. **Outcome Measure:** National Institute of Mental Health and Neurosciences (NIMHANS) Neuropsychology Battery, Perceived Stress Scale, Rivermead Post-Concussion Symptom Questionnaire, World Health Organization Quality of Life Scale—Brief (WHOQOL-Brief), Visual Analogue Scale (VAS).	psychological quality of life (on the WHOQoL-Brief Psychological, p=0.034).

Discussion

Cognitive rehabilitation assisted by technology was examined in two RCTs (Corallo et al., 2022; De Luca et al., 2023). De Luca et al. (2023) found that delivering cognitive rehabilitation via an innovative virtual reality training program resulted in significantly improved anxiety, well-being, and coping strategies, when compared to conventional cognitive training. Corallo et al. (2022) allocated participants with ABI to receive traditional cognitive rehabilitation or rehabilitation delivered with the assistance of a humanoid robot that provided feedback to individuals. The authors found that symptoms of anxiety significantly improved in the group that was assisted by the robot, as measured by the Hamilton Rating Scale for anxiety (HAM-A) (Corallo et al., 2022). In a pre-post study by Afsar et al. (2021), participants who received an outpatient hospital-based Cognitive Retraining intervention showed significantly lower amounts of stress, as measured by the Perceived Stress Scale.

In the RCT by Ownsworth et al. (2017), the authors found no differences in anxiety when comparing errorless training to error-based training following severe TBI. Similarly, attentional training and modified short memory techniques were found not to be effective for anxiety and stress post-TBI (Chiaravalloti et al., 2016; Dundon et al., 2015; McMillan et al., 2002). In the RCT by Salazar et al. (2000), the authors found no differences in generalized anxiety disorder when comparing in-hospital cognitive rehabilitation and a home program with telephone support from a psychiatric nurse.

Conclusions

There is level 1b evidence (Corallo et al., 2022; De Luca et al., 2023) and level 4 evidence (Afsar et al., 2021) that cognitive rehabilitation, either manualized or with the assistance of a humanoid robot or non-immersive virtual reality, may improve anxiety in individuals with ABI.

There is level 1b evidence (Chiaravalloti et al., 2016) and level 2 evidence (Dundon et al.; McMillan et al., 2002) that attentional training and modified short memory technique may not be effective for anxiety post TBI.

There is level 1b evidence (Ownsworth et al., 2017) that errorless learning may not improve anxiety post severe TBI, compared to error-based training.

There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for anxiety post moderate to severe TBI.

KEY POINTS

- Participation in cognitive rehabilitation programs, with or without the assistance of technology, may improve anxiety symptoms post moderate to severe ABI.
- Attentional training and modified short memory technique may not improve anxiety post TBI.
- Errorless learning may not improve anxiety, compared to error-based learning in individuals with severe TBI.
- In-hospital cognitive rehabilitation may not be different than home rehabilitation with telephone support for anxiety post TBI.

Peer Support

There is limited literature on peer support interventions in the TBI population. In a systematic review, Hughes et al. (2020) found that peer support groups for individuals with ABI result in several benefits such as feeling connected and interacting with others, as well as providing and receiving support.

TABLE 53 | Peer Support for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Hanks et al. (2012) USA RCT PEDro=5 N=96	**Population:** TBI=96; Gender: Male=74, Female=22; Caregivers=62; Peer Mentored Group: Mean Age=38.46yr; Mean GCS=9.39. TBI Control Group: Mean Age=40.90yr; Mean GCS=9.8. Caregiver Mentored Group: Mean Age=51.87 yr. Caregiver Control Group: Mean Age=50.18yr. **Intervention:** Participants and caregivers were randomly assigned to either a peer mentoring program or to a control group. Discussions in mentoring sessions included emotional well-being, post-TBI quality of life, and community integration.	1. There was no difference between groups in anxiety (p=0.31) and depression symptoms (p=07). 2. The mentored group had decreased somatic symptoms of emotional distress, less emotion-focused (p=0.04) and avoidance coping (p=0.03), as well as lower alcohol use (p=0.01) and fewer somatic symptoms of emotional distress. 3. Individuals who received mentoring had significantly better behavioral control and

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measures: Peer Mentoring Questionnaire, Family Assessment Device (FAD), Coping Inventory for Stressful Situations (CISS-21), 12-Item Short-Form Health Survey (SF-12), Brief Symptom Inventory-18 (BSI-18), Community Integration Measure (CIM), Short Michigan Alcoholism Screening Test (SMAST).	less chaos in the living environment (p=0.04).

Discussion

In an RCT, Hanks et al. (2012) assigned participants with TBI and their caregivers either to a peer mentoring program or a control group. The peer mentoring program included discussions on emotional well-being, quality of life post TBI and reintegration to the community. The authors found no group differences in anxiety (Hanks et al., 2012).

Conclusions

There is level 2 evidence (Hanks et al., 2012) that peer support may not improve anxiety symptoms in individuals with TBI.

KEY POINTS

- Peer support may not be effective for the management of anxiety post moderate to severe TBI.

Therapeutic Writing

Writing has been used as a therapeutic approach to help individuals process negative emotions associated with stressful or traumatic experiences (Smyth & Helm, 2003). Writing has been used to address persona trauma, mood disorders, bulimia symptoms, and chronic pain; writing therapy includes journaling, story writing, poetry, personal narratives, letter writing, and the use of online platforms (e.g., blogs) (Haertl & Ero-Phillips, 2019).

TABLE 54 | Therapeutic Writing for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Bugg et al. (2009) UK RCT PEDro=6 $N_{Initial}$=148, N_{Final}=67	**Population:** *Information group* (n=31); Gender: Male=3, Female=28; Mean age=36.65yr; Time post-injury<1mo; TBI severity: Not serious=1, Mild=9, Moderate=9, Very serious=9, Extremely serious=3. *Control group* (n=36); Gender: Male=16, Female=20; Mean age=38.14yr; Time post-injury<1mo; TBI severity: Not serious=3, Mild=7, Moderate=16, Very serious=8, Extremely serious=2; **Intervention:** Patients were randomized to a writing and information group or an information control group. Both groups received an information booklet 1mo post-injury, and participants in the writing group wrote about emotional aspects of their trauma over three 20min sessions 5-6wk post-injury. Outcomes were assessed at baseline, and at 3, and 6mo post-injury. **Outcome Measures:** Hospital Anxiety and Depression Scale (HADS), World Health Organization Quality of Life Measure (WHOQoL), Post-traumatic Diagnostic Scale (PDS).	1. There were no significant between group differences for the PDS scores. 2. There were no statistically significant differences between treatment groups for anxiety or depression, as measured by the HADS.

Discussion

In an RCT study, Bugg et al. (2009) examined the effect of writing as a self-help intervention on the severity of psychological symptoms in individuals who had a TBI and were at risk of developing PTSD symptoms. The intervention and the control group were given a self-help information booklet with a questionnaire, those in the intervention condition had sessions with a researcher and engaged in a writing activity that involved writing about emotions and feelings related to their injury. The authors found no group differences in anxiety symptoms, as measured by the Hospital Anxiety and Depression Scale HADS (Bugg et al., 2009).

Conclusion

There is level 1b evidence (Bugg et al., 2009) that writing as a self-help intervention may not improve anxiety post TBI.

KEY POINTS

- A writing intervention may not improve symptoms of anxiety in individuals with moderate to severe TBI.

Pharmacological Interventions

Sertraline

Sertraline is a selective serotonin reuptake inhibitor that has been used to treat chronic depression, with sustained efficacy as a treatment to prevent the emergence of depression in high risk patients (Keller et al., 1998). Sertraline has also been used to treat obsessive-compulsive disorder, post-traumatic stress disorder panic disorder, premenstrual dysphoric disorder in women, and social anxiety disorder (Singh & Saadabadi, 2019).

TABLE 55| Sertraline for the Management of Anxiety Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Fann et al. (2017) USA RCT PEDro=9 N=62	**Population:** *Sertraline* (n=31); Gender: Male=23, Female=8; Mean age=38yr; Mean time post-injury=4.3mo; Severity: Mild=16, Moderate=6, Severe=9. *Placebo* (n=31); Gender: Male=24, Female=7; Mean age=36.9yr; Mean time post-injury=4.9mo. TBI severity: Mild=13, Moderate=7; Severe=11. **Intervention:** Patients were randomized to receive either sertraline or placebo daily for 12wk. Outcomes were assessed at baseline, 1, 3, 6, 8, 10, and 12wk. **Outcome Measures:** Hamilton Anxiety and Depression Scale (HAM-D)-17 Item, Symptom Checklist-20, Clinician-rated Clinical Global Impression scale (CGI), Short Form 36 (SF-36), Sheehan Disability Scale, Trail Making Test B, Head Injury Symptom Checklist, Brief Anger and Aggression Questionnaire (BAAQ), Brief Pain Inventory, Hamilton Anxiety Rating Scale (HAM-A).	1. Depression significantly improved from baseline to 12 weeks in both treatment groups ($p<0.001$). 2. There were no statistically significant differences between treatment groups for depression (HAM-D), anxiety (HAM-A) or anger and aggression (BAAQ).
Ashman et al. (2009) USA RCT PEDro=10 N=41	**Population:** TBI; Mean Age=49.1yr; Gender: Male=24, Female=17; Mean Time Post Injury=17.7mo; Injury Severity: Mild=15, Moderate=16, Severe=10. **Intervention:** Patients were diagnosed with major depression. The treatment group (n=22) received sertraline (25mg adjusted every 2wk, up to 100 mg) and the control (n=19) received a placebo, both for 10wk. **Outcome Measures:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Hamilton Rating Scale for Depression (HAM-D), Beck Anxiety Inventory (BAI), Life-3 Scale.	1. No significant differences were found between sertraline and placebo for anxiety, as measured by the BAI.

Discussion

In an RCT, Fann et al. (2017) compared sertraline to placebo for the management of major depression and anxiety post-TBI. The authors found that, while participants in both groups showed improvements

in anxiety, no significant group differences were observed (Fann et al., 2017). In the RCT by Ashman et al. (2009) participants with major depression were randomized to receive sertraline or placebo. The authors found no statistically significant differences between sertraline and placebo groups on measures of anxiety.

Conclusions

There is level 1b evidence (Ashman et al., 2009; Fann et al., 2017) that sertraline may not be more effective than placebo for anxiety post TBI.

KEY POINTS

- Sertraline may not be effective to treat anxiety in individuals with moderate to severe TBI.

Amantadine

Amantadine is a antiviral agent originally used to treat influenza; however, it is now used mostly to treat Parkinson disease, particularly for the management of tremors, rigidity and bradykinesia (Chang & Ramphul, 2018). Amantadine has been used as a wakefulness-promoting agent with a positive effect on cognition (Plantier & Luaute, 2016). While Amantadine has been commonly prescribed for Parkinson's disease, and for cognitive recovery post ABI (Loggini et al., 2020); there is limited research on the use of amantadine for anxiety management in this population.

TABLE 56 | Amantadine for the Management of Anxiety Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Hammond et al. (2014) USA RCT PEDro=9 $N_{Initial}$=76, N_{Final}=72	**Population:** TBI. *Amantadine Group (n=38)*: Mean Age=34.7yr; Gender: Male=25, Female=13; Mean Time Post Injury=5.3yr; Mean GCS=9.5. *Placebo Group (n=38)*: Mean Age=42.1yr; Gender: Male=22, Female=16; Mean Time Post Injury=4.7yr; Mean GCS=7.5. **Intervention:** Participants were randomized to receive placebo or 100 mg of amantadine 2x/day for 28 days. Assessments were conducted at baseline and 28 days. **Outcome Measure:** Neuropsychiatric Inventory (NPI) Irritability (NPI-I), NPI Agitation/ Aggression (NPI-A), NPI Distress (NPI-D), Beck Depression Inventory-II (BDI-II), Brief Symptom Inventory (BSI), Global Mental Health Scale (GMHS).	1. Eighty-one percent of the amantadine group had improved irritability by at least 3 points on NPI-I, compared to 44% of placebo (p=0.0016). 2. Significant difference in frequency and severity of irritability on NPI-I between amantadine and placebo groups (p=.0085). 3. No significant differences between amantadine and placebo groups on NPI-D, BDI-II, BSI-Anxiety, or GMHS. 4. Only individuals with moderate to severe aggression at baseline on NPI-A had significant reduction in aggression after amantadine treatment compared to placebo (p=0.046).

Discussion

In an RCT, Hammond et al. (2014) found no significant differences between individuals who received amantadine and those who received placebo in anxiety symptoms, as measured by the Brief Symptom Inventory (BSI) anxiety sub-scale (Hammond et al., 2014).

Conclusion

There is level 1b (Hammond et al., 2014) that amantadine may not be effective for the management of anxiety post TBI.

KEY POINTS

- Amantadine may not be effective for the treatment of anxiety in individuals with moderate to severe TBI.

Methylphenidate

Methylphenidate is a stimulant that has been used for the treatment of behavioural disorders associated with attention deficit hyperactivity disorder (ADHD) (Britton, 2012). There is limited research on the use of methylphenidate for anxiety post-TBI.

TABLE 57 | Methylphenidate for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Jenkins et al. (2019) UK RCT Crossover PEDro=9 $N_{Initial}$=46, N_{Final}=40	**Population:** TBI=40; *Methylphenidate first* (n=20): Mean Age= 40yr; Gender: Male=18, Female=2; Mean Time Post Injury=67mo; Mean GCS=8.3. *Placebo First* (n=20): Mean Age=39yr; Gender: Male=16, Female=4; Mean Time Post Injury=67mo; Severity: Mean GCS=8.3. **Intervention:** Participants were randomized to receive 0.3mg/kg of methylphenidate (treatment group) 2x/d for 2wk with crossover to placebo (control group) 2x/d for 2wk and vice versa. Outcome measures were assessed at baseline, at 2 wk, and at 4wk. **Outcome Measures:** Choice Reaction Time (CRT) Task, Single-Photon Emission Computed Tomography (SPECT), Trail Making Test (TMT), Delis-Kaplan Executive Function System (D-KEFS), Stroop Color Word Test, Wechsler Memory Scale - People Test, Wechsler	1. Individuals with low caudate Dopamine Transporter (DaT) showed significant improvements in self-reported apathy (p=0.03). 2. No significant difference in behaviour, as measured by the Frontal Systems Behaviour Scale (FrSBe). 3. No significant difference were found in anxiety or depression, as measured by the HADS.

Author Year Country Study Design Sample Size	Methods	Outcome
	Abbreviated Scale for Intelligence (WASI), Lille Apathy Rating Scale (LARS), Visual Analogue Scale for Fatigue (VAS-F), Glasgow Outcome Scale-Extended (GOSE), Hospital Anxiety and Depression Scale (HADS), Frontal Systems Behaviour Scale (FrSBe), Cognitive Failures Questionnaire (CFQ), Rating Scale of Attentional Behaviour (RSAB).	

Discussion

In an RCT crossover, Jenkins et al. (2019) compared methylphenidate to placebo and found no significant group differences in anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS).

Conclusions

There is level 1a evidence (Jenkins et al., 2019) that methylphenidate may not improve anxiety in individuals with severe TBI; however, more research is needed.

KEY POINTS

- Methylphenidate may not improve anxiety post TBI; further research is needed.

Risperidone

Risperidone is an antipsychotic used for the management of psychosis-induced aggression or agitation (Ostinelli et al., 2018). It should be noted that, due to lack of evidence for antipsychotic effectiveness, prolonged post-traumatic amnesia and decreased cognitive function (Bogner et al., 2015; McKay et al., 2018; Mysiw et al., 2006), current recommendations and reviews advise against the use of antipsychotics to manage behaviour (Plantier & Luaute, 2016; Ponsford et al., 2014; Williamson et al., 2018). There is limited research on the use of risperidone for agitation, anger and aggression in individuals with ABI.

TABLE 58 | Risperidone for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Deb et al. (2020) UK RCT	**Population:** TBI=14, Severity: Mild=3, Moderate=4, Severe=5*; Risperidone Group (n=6)* Mean Age=39.3yr; Gender: Male=5, Female=1. *Placebo Group (n=8):* Mean Age=43.1yr; Gender: Male=5, Female=3.	2. The score changes in the HADS- Anxiety were slightly greater in the risperidone group whereas HADS- Depression score change was

Author Year Country Study Design Sample Size	Methods	Outcome
PEDro=6 N=14	**Intervention:** Participants were randomly allocated into two groups: Risperidone or Placebo. Those in the experimental group received 1mg once daily dose of Risperidone up to a dose of 4mg/day, if necessary. Those in the placebo group received an equivalent amount of placebo capsules. Follow-ups were done by telephone every week and at 12 weeks post-treatment to assess improvement. **Outcome Measure:** Modified Overt Aggression Scale (MOAS), Glasgow Outcome Scale - Extended (GOS-E), Irritability Questionnaire (IRQ), Hospital Anxiety and Depression Scale (HADS), Clinical Global Impression (CGI), Udvalg for Kliniske Undersogelser Scale (UKU), EQ- 5D, Short Form 12 (SF-12).	slightly greater in the placebo group; however, significance was not reached.

Discussion

In a small RCT by Deb et al. (2020), participants were randomized to receive either risperidone or a placebo in a dose of 1-4mg daily as necessary for 12 weeks. The authors found that the score changes in the HADS for anxiety score were slightly greater in the risperidone group; however, differences were not statistically significant (Deb et al., 2020). Given that some studies have suggested that frequent use of risperidone may reduce cognitive and functional recovery in individuals with TBI (Williamson et al., 2019), caution is recommended.

Conclusions

There is level 1b evidence (Deb et al., 2020) that risperidone may not be effective for the management of anxiety in individuals with TBI.

KEY POINTS

- Risperidone may not be effective in reducing symptoms of anxiety post TBI.

Cerebrolysin

Cerebrolysin is a neuropeptide preparation used to enhance neuroplasticity and neuroprotection in conditions such as TBI, stroke, subarachnoid hemorrhage, Parkinson's disease, Alzheimer disease, and multiple sclerosis (Jarosz et al., 2023).

TABLE 59 | Cerebrolysin for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Muresanu et al. (2020) Romania RCT PEDro=10 $N_{Initial}$=142, N_{Final}=139	**Population:** TBI; *Cerebrolysin* (n=80): Mean age=46.4yr; Gender: Male=72, Female=8; Time post-injury<4h; Mean GCS=10.2; *Control* (n=59): Mean age=48.8yr; Gender: Male=51, Female=8; Time Post-injury<4h. Mean GCS=10.6. **Intervention:** Participants were randomly allocated to receive either 50mL of Cerebrolysin or physiological saline solution per day for 10d, followed by an additional two 10d treatment cycles with 10mL. Outcomes were assessed at 10d, 30d and 90d post-TBI. **Outcomes:** Glasgow Outcome Scale Extended (GOS-E), Barthel Index, Mini-Mental State Examination (MMSE), Wechsler adult intelligence scale (WAIS), Stroop Color-Word Test—Victoria Version (VST), Color Trails Test (CTT), Hospital Anxiety and Depression Scale (HADS).	1. Only the HADS depression sub-scale showed a medium to large size effect at 30-day (p=0.0263) and at 90-day (p=0.0026), while HADS-anxiety did not show significance at 30 days (p=0.3453) and 90 days (p=0.4860).
Poon et al. (2020) Italy RCT PEDro=9 N=40	**Population:** TBI; Mean Age=38.1yr; Gender: Male=32, Female=8; Mean Time Post Injury <6hr; Mean GCS=9.9. **Intervention:** Participants were randomized to receive either Cerebrolysin (50mL) or placebo for 10d, followed by two additional treatment cycles (10mL dailyx10d). Outcomes were assessed at baseline, 10d, 30d, and 90d. **Outcome Measures:** Glasgow Outcome Scale Extended (GOS-E), Barthel Index (BI), Mini-Mental State Examination (MMSE), Wechsler adult intelligence scale - III (WAIS-III), Stroop Color-Word Test—Victoria version (VST), Finger Tapping Test (FTT), Color Trails Test (CTT), Hospital Anxiety and Depression Scale (HADS).	1. For the HADS Anxiety Scale, a stand-alone statistically significant superiority of Cerebrolysin was found with an effect size close to be considered "large" (p = 0.0378). 2. For the HADS depression subscale, a "large" treatment effect was shown at the final endpoint after 180 days (p=0.0204).

Discussion

In an RCT, Muresanu et al. (2020) found that cerebrolysin had no significant effects on anxiety compared to placebo. However, in another RCT, Poon et al. (2020) found that cerebrolysin had a significant effect on anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS).

Conclusion

There is conflicting level 1b evidence (Muresanu et al., 2020; Poon et al., 2020) that cerebrolysin may have an effect on anxiety; however, further research is needed.

KEY POINTS

- There is conflicting evidence regarding the efficacy of cerebrolysin for anxiety symptoms post TBI. More research is required.

Melatonin

Melatonin is a hormone involved in the regulation of the sleep-wake cycle that has been often used as a supplement to improve conditions such as insomnia and other sleep disorders (Xie et al., 2017).

TABLE 60| Melatonin for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Grima et al. (2018) Australia RCT Crossover PEDro=9 N=33	**Population:** TBI; *Melatonin-placebo group* (n=18): Mean Age=35yr; Gender: Male=61%, Female=39%; Median Time Post Injury=61mo; Severity: Median GCS= 5. *Placebo-melatonin group* (n=15): Mean Age=38yr; Gender: Male=73%, Female=27%; Median Time Post Injury= 25mo; Severity: Median GCS=8. **Intervention:** Participants with chronic insomnia were randomly allocated to a 4wk melatonin or placebo treatment before crossover. The melatonin formula was a prolonged release formula (2mg). Outcome were measured at baseline and at the end of each treatment phase. **Outcome Measures:** Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS), Hospital Anxiety Depression Scale (HADS), Short-Form Health Survey (SF-36).	1. Melatonin was also associated with a significant but small decrease in self-reported anxiety symptomatology, with no differences in depression. 2. The HADS anxiety scores were significantly lower in the melatonin arm compared to the placebo arm (p=0.0006). 3. HADS depression scores were not significantly different between treatments (p=0.68).
Kemp et al. (2004) UK RCT Crossover PEDro=5 N=7	**Population:** TBI; Mean age=39.6yr; Gender: Male=7; Mean time post-injury=36.3mo; Severity: Mild=2, Moderate=3, Severe=2. **Intervention:** Patients were randomized to receive either 5mg Melatonin or 25mg Amitriptyline daily for 1mo, with a 2wk washout period between treatments. Outcomes were assessed at baseline and after each treatment cycle. **Outcomes:** Speed and Capacity of Language-Processing Test (SCOLP), Adult Memory and Processing Batter (AMIPB), Hospital Anxiety and Depression Scale (HADS).	1. There were no significant treatment effects on anxiety (p=0.66) or depression (p=0.97), as measured by the HADS.

Discussion

In an RCT crossover, Grima et al. (2018) examined the effect of melatonin on sleep disturbances in individuals who had sustained a TBI. Participants were given prolonged-release melatonin formulation of 2mg and placebo capsules for 4 weeks, separated by a 48-hour washout period. The authors found a small but significant decrease in symptoms of anxiety, with lower anxiety in those in the melatonin arm, compared to the placebo arm.

In an RCT by Kemp et al. (2004), the authors compared melatonin to amitriptyline for the management of sleep disorders post-TBI, and found no significant differences for anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS).

Conclusions

There is level 1a evidence (Grima et al., 2018) that melatonin may decrease anxiety post TBI, compared to placebo.

There is level 1b evidence (Kemp et al., 2004) that melatonin may not decrease anxiety, compared to amitriptyline.

KEY POINTS

- Melatonin may be effective for anxiety following a moderate to severe TBI compared to placebo; however, it may not decrease anxiety when compared to amitriptyline.

Fish Oil Supplementation

Omega-3 fatty acids found in fish such as salmon, tuna and sardines, are considered beneficial dietary sources for the prevention of conditions such as coronary disease (Harris, 2004). There is limited research on fish oil supplementation and TBI.

TABLE 61| Fish Oil Supplementation for the Management of Anxiety Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Kagan et al. (2021) Israel RCT PEDro=6 $N_{Initial}$=150, N_{Final}=51	**Population:** Severe TBI; *Intervention* (n=25); Mean age=41.8y; Gender: Not Reported; Mean time post-injury=Not Reported; Mean ISS=34.5. *Control* (n=26); Mean age=45.6y; Gender: Not Reported; Mean time post-injury=Not Reported; Mean ISS=34.6. **Intervention:** Patients were randomized into groups that received enteral feeding with fish oil (treatment) or without (control) fish oil. Outcomes were assessed at baseline and 6mo after discharge. **Outcomes:** Fatty acids, Brief Illness Perceptions Questionnaire (IPQ), Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Post-traumatic Checklist Scale (PCL), Hospital Anxiety and Depression Scale (HADS), Rivermead Head Injury Follow-up Questionnaire (RHI).	1. Treatment groups did not significantly differ in presentation of anxiety and depression at 6 months. 2. No group differences in PTSD symptoms, as measured by the PCL scale were observed at 6 months.

Discussion

In an RCT by Kagan et al. (2021) examined the effects of enteral nutrition enriched with fish oil supplementation on the onset and development of PTSD. Patients with polytrauma who were admitted to the intensive care unit (ICU) received enteral feeding with or without fish oil. The authors found no differences in anxiety symptoms between groups at six months of follow-up.

Conclusions

There is level 1b evidence (Kagan et al., 2021) that enteral nutrition with fish oil supplementation may not prevent anxiety after ICU discharge in individuals with severe TBI.

KEY POINTS

- Enteral nutrition enriched with fish oil supplementation may not prevent the development of anxiety post ICU discharge in individuals with polytrauma and severe TBI.

Obsessive-Compulsive Disorder

Rates of Obsessive-Compulsive Disorder (OCD) in patients after ABI are similar to rates in the general population. Two prospective studies in patients after TBI reported similar incidence rates; Gould et al. (2011) found rates of 1% in the first year following injury in a population with mixed severity, and Alway et al. (2016) found incidences between 0-2.6% in the first five years following injury in patients with moderate to severe TBI. Retrospective studies have mixed results, reporting rates from 1 to 15% (Hibbard et al., 1998; Koponen et al., 2011; van Reekum et al., 1996; Whelan-Goodinson et al., 2009). Ponsford et al. (2018) suggested one possible reason for high reported rates of OCD is that behaviours related to TBI are similar to symptoms of OCD, such as frequent checking due to memory problems. Treatments for OCD include psychotherapy and antidepressant medications. No intervention studies examining the treatment of OCD in individuals with moderate to severe have been identified.

Post-Traumatic Stress Disorder

Early literature on Post Traumatic Stress Disorder (PTSD) focused on patients with mild TBI; this was based on the belief that PTSD could not develop in the presence of amnesia following a traumatic event (Bryant et al., 2001; Mayou et al., 1993; Warden et al., 1997; Zatzick et al., 2010). Since then, research has found that PTSD can occur in individuals with moderate and severe TBI as well (Al-Ozairi et al., 2014).

PTSD has been classified as a trauma-stressor-related disorder, rather than an anxiety disorder, often occurring after exposure to a traumatic event and includes symptoms such as intrusive thoughts, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity (Van Praag et al., 2019). In a population-based study of individuals with TBI, it was found that nearly 18% met the criteria for PTSD across the spectrum of TBI severity (Barker-Collo et al., 2013). Individuals with comorbid PTSD and TBI may experience cognitive impairment and sleep disruptions, along with anxiety and depressive symptoms (Balba et al., 2018; Bosma et al., 2018). PTSD and TBI are often comorbid, and misdiagnoses of one or the other can be a barrier to improvement (Rosen & Ayers, 2020).

Non-Pharmacological Interventions

For most individuals who have experienced a traumatic event, symptoms of PTSD may subside with time; however, a proportion of individuals experience symptoms that cause significant interference with their lives and require non-pharmacological interventions (National Guideline Alliance UK, 2018).

Interventions for the Management of PTSD

For those who have sustained a TBI, PTSD and TBI symptoms may overlap (Bryant, 2011), resulting in additional complications for the development of non-pharmacological interventions. In this section we present non-pharmacological interventions that have been used to treat PTSD in individuals with moderate to severe ABI including resilience interventions, neurofeedback and multidisciplinary rehabilitation.

TABLE 62| Management of Post-Traumatic Stress Disorder Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Resilience Programs		
Assonov et al. (2021) Ukraine RCT PEDro=6 N=70	**Population:** TBI; *Resilience Intervention Group* (n=35): Gender: Male=34, Female=1; Mean Age=47.22yr; *Control Group* (n=35): Gender: Male=34, Female=1; Mean Age=45.65yr. Severity: Moderate=56, Mild=14; Median Time Post Injury=6yr (IQR 5-6). **Intervention:** Participants received a structured treatment program (TROI -Two Step Resilience-Orientated Intervention) focused on enhancing resilience after TBI. The first step focused on the cognitive factors of resilience while the second factor focused on emotional factors of resilience. Sessions were 60min/d for 6d. Outcomes were assessed before and after the intervention. **Outcome Measure:** Connor-Davidson Resilience Scale (CD-RISC), Neurobehavioral Symptom Inventory (NSI), Montreal Cognitive Assessment Scale (MoCA), Hospital	1. The intervention group had a significantly greater decrease in post-traumatic symptoms as measured by the PCL-5 (p<.00). 2. Individuals in the intervention group also had significantly higher scores for resilience (p<.001), positive affect (p <.001) and quality of life (p=.017), and post-concussive symptoms (p=.03) compared to the control group.

Author Year Country Study Design Sample Size	Methods	Outcome
	Anxiety and Depression Scale (HADS), Positive and Negative Affect Scale (PANAS), Posttraumatic Stress Disorder Checklist 5 (PCL-5), Chaban Quality of Life Scale (CQLS).	
Cognitive Rehabilitation		
Elbogen et al. (2019) USA RCT PEDro=5 $N_{initial}$=224 N_{final}=178	**Population:** TBI=112; Severity: Moderate/Severe=64; Family/Friend=112; *CALM Group (n=57)* Mean Age=36.77yr; Gender: Male=53, Female=4. *Control Group (n=55)* Mean Age=36.25yr; Gender: Male=50, Female=5. **Intervention:** Veterans with PTSD and TBI received cognitive rehabilitation supported by technology. Veterans and families members were randomized to either the Cognitive Applications for Life Management (CALM), involving goal management training plus mobile devices for attentional control, or a Brain Health Training, involving psychoeducation plus mobile devices to train visual memory. **Outcome Measures:** Delis-Kaplan Executive Function System (DKEFS) Color-Word inhibition task, Barratt Impulsiveness Scale (BIS), Dimensions of Anger Reactions (DAR), Head Injury Behavior Scale (HIBS), Number of home visits, Clinician-Administered Posttraumatic stress Disorder Scale (CAPS).	1. Both the control and CALM groups experienced significant decreases in total symptom severity of the CAPS scores (p=0.002) and p<0.001) respectively. 2. No significant effects on PTSD intensity were revealed.
Multidisciplinary Rehabilitation		
Igoe et al. (2023) Ireland Cohort $N_{Initial}$=45, N_{Final}=32	**Population:** ABI, TBI=13, Other (e.g., encephalitis) =11, Stroke=8. Gender: Male=20, Female=12. Mean Time Post Injury at =1.28yr. **Intervention:** Longitudinal cohort of participants who received post-acute inpatient neurorehabilitation that included physiotherapy, occupational therapy, speech and language therapy, psychology, medical and social work lasting for 8wks to 16wks depending on individual needs. Individuals were assessed at 1yr (T1) and 8yr(T2). **Outcome Measure:** Post-Traumatic Growth Inventory (PTGI), Hospital Anxiety and Depression Scale (HADS), Brief Coping Orientation to Problems Experienced (Brief COPE), World Health Organization Quality of Life Brief version (WHOQOL-BREF), European Brain Injury Questionnaire (EBIQ).	1. Psychological (p<.001) quality of life scores were significantly higher at T2 for individuals with higher PTGI scores. 3. There was a positive, nonsignificant, association with adaptive coping and higher PTGI Scores. 4. At T2, there were significant positive associations between the WHOQOL psychological subscale (p<.001).
Neurofeedback		
Elbogen et al. (2021) USA Pre-Post $N_{Initial}$=41, N_{Final}=36	**Population:** TBI; Gender: Male=35, Female=6; Mean Age=38.57yr; Mean GCS=Not Reported; Time Post-Injury=13.11yr; PTA >1hr=64%. **Intervention:** Participants were instructed to perform "mobile neurofeedback" using a portable EEG headset linked to an application on a mobile device. The duration was 10min sessions, 4x/wk, for 3mo. Outcomes were assessed at baseline and at 3-mo.	1. At follow-up individuals reported significantly reduced PTSD symptoms (p=.019), depression (p,.001) and suicidal ideation (p=.033). 2. Veterans displayed significantly reduced anger scores as measured by PROMIS (p=.016) and reduced sleep disturbance (p=.010).

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: Regional Pain Scale, Patient-Reported Outcomes Measurement Information System (PROMIS), PTSD Checklist for DSM-5 (PCL-5), Patient Health Questionnaire (PHQ-9).	3. Analysis of the number of phone calls/ home visits revealed a significant correlation with number of staff and reduced depressive symptoms (p=.03).
	Therapeutic Writing	
Bugg et al. (2009) UK RCT PEDro=6 $N_{Initial}$=148, N_{Final}=67	**Population:** *Information group* (n=31); Gender: Male=3, Female=28; Mean age=36.65yr; Time post-injury<1mo; TBI severity: Not serious=1, Mild=9, Moderate=9, Very serious=9, Extremely serious=3. *Control group* (n=36); Gender: Male=16, Female=20; Mean age=38.14yr; Time post-injury<1mo; TBI severity: Not serious=3, Mild=7, Moderate=16, Very serious=8, Extremely serious=2; **Intervention:** Patients were randomized to a writing and information group or an information control group. Both groups received an information booklet 1mo post-injury, and participants in the writing group wrote about emotional aspects of their trauma over three 20min sessions 5-6wk post-injury. Outcomes were assessed at baseline, and at 3, and 6mo post-injury. **Outcome Measures:** Hospital Anxiety and Depression Scale (HADS), World Health Organization Quality of Life Measure (WHOQoL), Post-traumatic Diagnostic Scale (PDS).	1. There were no significant between group differences for the PDS scores. 2. There were no statistically significant differences between treatment groups for anxiety or depression, as measured by the HADS.

Discussion

In an RCT, Assonov et al. (2021) examined a resilience intervention (TROI -Two Step Resilience-Orientated Intervention) that focused on enhancing resilience after TBI, including cognitive factors and emotional factors of resilience. The authors found that those in the intervention group had a significantly greater decrease in post-traumatic symptoms as measured by the Posttraumatic Stress Disorder Checklist 5 (PCL-5). In the RCT by Elbogen et al. (2019), a cognitive rehabilitation intervention supported by technology resulted in significant decreases in total PTSD symptom severity among veterans, as measured by the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS).

Igoe et al. (2023) examined a longitudinal cohort of participants with moderate to severe ABI who received post-acute inpatient neurorehabilitation, including physiotherapy, occupational therapy, speech and language therapy, psychology, medical and social work, and assessed participants at 1 and 8 years. The authors found that psychological quality of life scores and the use of adaptative coping strategies were significantly higher at 8 years for individuals with higher Post-Traumatic Growth Inventory (PTGI) scores. The authors suggested the implementation of long-term neuropsychological support to promote post-traumatic growth in those with ABI. In a Pre-post study by Elbogen et al. (2021),

mobile neurofeedback using a portable EEG headset linked to an application on a mobile device was found to reduce PTSD symptoms, as measured by the PTSD Checklist for DSM-5 (PCL-5).

In an RCT, Bugg et al. (2009) examined a writing as a self-help intervention for individuals with TBI who were at risk of developing PTSD. The intervention and the control group were given a self-help information booklet with a questionnaire, those in the intervention condition had sessions with a researcher and engaged in a writing activity that involved writing about emotions and feelings related to their injury. The authors found no group differences in PTSD symptoms (Bugg et al., 2009).

Conclusions

There is level 1b evidence (Assonov et al., 2021) that a resilience intervention may help reduce PTSD symptoms in individuals with TBI.

There is level 1b evidence (Bugg et al., 2009) that writing as a self-help intervention may not improve symptoms of PTSD following a TBI.

There is level 2 evidence (Elbogen et al., 2019) that a cognitive rehabilitation intervention supported by technology may decrease PTSD symptoms in veterans with TBI.

There is level 2 evidence (Igoe et al., 2023) that long-term neuropsychological support that includes adaptative coping strategies may promote post-traumatic growth in individuals with ABI who attended post-acute inpatient multidisciplinary rehabilitation.

There is level 4 evidence (Elbogen et al, 2021) that mobile neurofeedback using a portable EEG headset linked to an application on a mobile device may reduce PTSD symptoms in individuals with TBI.

KEY POINTS

- A resilience intervention may help reduce PTSD symptoms post TBI.
- Cognitive rehabilitation supported by technology may decrease PTSD symptoms among veterans with TBI.
- Long-term neuropsychological support that includes adaptative coping strategies may promote post-traumatic growth in individuals with ABI.
- Mobile neurofeedback with a portable EEG headset may decrease PTSD symptoms post TBI.
- A writing intervention may not decrease PTSD symptoms in those with a TBI.

Pharmacological Interventions

Fish Oil Supplementation

Omega-3 fatty acids found in fish such as salmon, tuna and sardines, are considered beneficial dietary sources for the prevention of conditions such as coronary disease (Harris, 2004).

TABLE 63| Fish Oil Supplementation for the Management of Post-Traumatic Stress Disorder Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Kagan et al. (2021) Israel RCT PEDro=6 $N_{Initial}$=150, N_{Final}=51	**Population:** Severe TBI; *Intervention* (n=25); Mean age=41.8y; Gender: Not Reported; Mean time post-injury=Not Reported; Mean ISS=34.5. *Control* (n=26); Mean age=45.6y; Gender: Not Reported; Mean time post-injury=Not Reported; Mean ISS=34.6. **Intervention:** Patients were randomized into groups that received enteral feeding with fish oil (treatment) or without (control) fish oil. Outcomes were assessed at baseline and 6mo after discharge. **Outcomes:** Fatty acids, Brief Illness Perceptions Questionnaire (IPQ), Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Post-traumatic Checklist Scale (PCL), Hospital Anxiety and Depression Scale (HADS), Rivermead Head Injury Follow-up Questionnaire (RHI).	1. Treatment groups did not significantly differ in presentation of anxiety and depression at 6 months. 2. No group differences in PTSD symptoms, as measured by the PCL scale were observed at 6 months.

Discussion

In an RCT by Kagan et al. (2021) examined the effects of enteral nutrition enriched with fish oil supplementation on the onset and development of PTSD. Patients with polytrauma who were admitted to the intensive care unit (ICU) received enteral feeding with fish oil or without. The authors found no differences in PTSD between groups at six months follow-up.

Conclusions

There is level 1b evidence (Kagan et al., 2021) that enteral nutrition with fish oil supplementation may not prevent PTSD after ICU discharge in individuals with severe TBI.

KEY POINTS

- Enteral nutrition enriched with fish oil supplementation may not prevent the development of PTSD post ICU discharge in individuals with polytrauma and severe TBI.

Suicidal Ideation

Suicidal ideations are the thoughts or considerations of suicide that when left unattended, can lead to distress, and attempted suicide. Risk factors for suicide overlap with characteristics present after a TBI which explains, in part, why there is an increased risk of suicide following a TBI (Ahmedani et al., 2017; Bahraini et al., 2013; Simpson & Tate, 2007). Unfortunately, the risk for suicidal ideation and attempt remains high even 20 years post-injury (Fisher et al., 2016).

Incidence and Prevalence of Suicidal Ideation

The prevalence of suicide in individuals with ABI is much greater than in the general population. A large retrospective cohort estimated an incidence rate ratio of 2.38 in patients with severe TBI compared to controls (Madsen et al., 2018). Within other TBI populations, 23-28% of individuals report suicidal ideation post-injury (Mackelprang et al., 2014; Simpson & Tate, 2002; Tsaousides et al., 2011). Males are more likely to have suicidal ideation compared to females (Wisco et al., 2014), while age at the time of injury was not associated with suicidal ideation (Mackelprang et al., 2014; Simpson & Tate, 2002). The risk of suicidal ideation can be further augmented with a comorbid diagnosis of depression, anxiety, or PTSD (Tsaousides et al., 2011) and the number of sustained TBIs (Shura et al., 2018; Wisco et al., 2014).

Elevated suicidal ideation at one-year post-TBI has been associated with continual elevation of ideation at five years (Fisher et al., 2016), indicating the necessity for therapies targeting such ideations. If suicide ideation is not minimized, the risk of suicide attempts is high (Simpson & Tate, 2007) and is further increased when emotional distress is present (Gutierrez et al., 2008; Simpson & Tate, 2002). Within their lifetime, 26% of individuals post TBI attempt suicide, with half of these individuals making more than one attempt (Simpson & Tate, 2002, 2005). Moreover, emotional disturbance and substance abuse history increase the risk of attempted suicide by a factor of 21, compared to individuals with no history (Simpson & Tate, 2005).

Non-Pharmacological Interventions

In the general population, some strategies to reduce suicide deaths include reducing access to lethal means, programs that influence organizational policies and culture in police workplace settings, and screening for depression in the community settings (Sultan et al., 2021). Non-pharmacological interventions, such as psychotherapy, have been demonstrated effectiveness in reducing depressive symptoms and perceived stress, which may contribute to reducing risk of suicide in individuals with TBI (Wadhawan et al., 2019).

Interventions for Suicide Prevention

Non-pharmacological approaches have been used in TBI populations to prevent suicide by targeting symptoms such as mood disturbances and sleep difficulties, these approaches include cognitive behavioural therapy and other forms of psychotherapy and physical activity (Wadhawan et al., 2019).

TABLE 64| Interventions for Suicide Prevention Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
	Psychotherapy	
Brenner et al. (2018) Australia RCT PEDro=6 $N_{Initial}$=44, N_{Final}=35	**Population:** TBI; *Intervention Group (n=15)*: Mean Age=47.7yr; Gender: Male=13, Female=1, Transgender=1. *Waitlist Group (n=20)*: Mean Age=54.6yr; Gender: Male=19, Female=1, Transgender=0. **Intervention:** Participants were randomized to receive a manualized, small-group cognitive behavioural intervention focused on alleviating hopelessness or to a waitlist. The intervention was 2hr and delivered weekly for 10 wk. Participants were crossed over to the alternate intervention after 10 wk. Assessments occurred at baseline, 10wk, and20 wk. **Outcome Measure:** Beck Hopelessness Scale (BHS), Beck Depression Inventory (BDI), Beck Scale for Suicide Ideation (BSSI).	1. The intervention group had significantly lower hopelessness post intervention compared to those on the waitlist (p=0.03); these reductions were maintained at follow-up. 2. The waitlist group demonstrated significant reductions on the BHS (p=0.01) and depression (p=0.003) after completing the intervention. 3. There were no significant between-group differences for the BDI or BSSI.
Simpson et al. (2011) Australia RCT PEDro=8 N=17	**Population:** TBI; Severity: Severe. *Treatment Group (n=8)*: Mean Age=39.4yr; Mean Time Post Injury=6.3 yr. *Control Group (n=9)*: Mean Age=44.1yr; Mean Time Post Injury=7.6 yr. **Intervention:** Participants were randomized to receive a manualized, small-group cognitive behavioural intervention focused on alleviating hopelessness or to a waitlist. The intervention was 2 hr and delivered weekly for 10 wk. Participants were crossed over to the alternate intervention after 10 wk. Assessments occurred at baseline, 10wk, and 20 wk. **Outcome Measure:** Beck Hopelessness Scale (BHS), Beck Scale for Suicide Ideation (BSSI), Hospital Anxiety and Depression Scale (HADS), Herth Hope Index (HHI), Rosenberg Self-Esteem (RSE), Social Problem-Solving Inventory-Revised (SPSI-R).	1. Significant group-by-time interaction on BHS (p=0.002) but no significant main effects for either group or time. 2. Individuals receiving treatment had larger improvements in hopelessness (BHS scores) at 10wk; 75% reduced hopelessness by 1 severity band and 50% maintained/reduced severity by 20 wk. 3. Hopelessness on BHS improved significantly from pre to post treatment for all participants (p=0.008), a clinical improvement from moderate to mild severity. 4. Suicidal ideation according to mean BSSI scores was stable in the treatment group but increased in the control group. 5. No significant change on BSSI, HADS, HHI, RSE, and SPSI-R were found.
Barnes et al. (2017) USA Post-Test $N_{Initial}$=17, N_{Final}=13	**Population:** TBI; Median Age=54.5yr; Gender: Male=12, Female=2; Severity: Moderate=4, Severe=10. **Intervention:** Participants received 10 sessions of problem-solving therapy for suicide prevention. Assessments occurred after the intervention. **Outcome Measure:** Client Satisfaction Questionnaire-8 (CSQ-8), Narrative Evaluation of Intervention Interview (NEII).	1. On the CSQ-8, participants reported high satisfaction with the program (mean score=27.8). 2. On the NEII, participants reported that they found the intervention valuable, beneficial, and without negative effects.

Author Year Country Study Design Sample Size	Methods	Outcome
Neurofeedback		
Elbogen et al. (2021) USA Pre-Post $N_{Initial}$=41, N_{Final}=36	**Population:** TBI; Gender: Male=35, Female=6; Mean Age=38.57yr; Mean GCS=Not Reported; Time Post-Injury=13.11yr; PTA >1hr=64%. **Intervention:** Participants were instructed to perform "mobile neurofeedback" using a portable EEG headset linked to an application on a mobile device. The duration was 10min sessions, 4x/wk, for 3mo. Outcomes were assessed at baseline and at 3-mo. **Outcome Measure:** Regional Pain Scale, Patient-Reported Outcomes Measurement Information System (PROMIS), PTSD Checklist for DSM-5 (PCL-5), Patient Health Questionnaire (PHQ-9).	1. At follow-up individuals reported significantly reduced suicidal ideation (p=.033).

Discussion

Hopelessness is a precursor to suicidal ideation, which in turn increases the risk of suicide. In two RCTs (Brenner et al., 2018; Simpson et al., 2011), group-based CBT therapy was effective at reducing feelings of hopelessness after severe TBI. In the study by Brenner et al. (2018), while the intervention significantly reduced feelings of hopelessness compared to the waitlist, no significant group differences were found for suicidal ideation, as measured by the Beck Scale for Suicide Ideation (BSSI). Similarly, in the study by Simpson et al. (2011), individuals receiving CBT had larger improvements in hopelessness that were maintained at follow-up. In both RCTs, the authors noted significant reductions in depressive symptoms and suicidal ideation following treatment, although these reductions were not significant when compared to the control group over time (Brenner et al., 2018; Simpson et al., 2011).

In a post-test study by Barnes et al. (2017) individuals with moderate to severe TBI received ten sessions of problem-solving therapy for suicide prevention. The authors found that the participants were highly satisfied with the program and found it to be valuable and beneficial; however, the study did not measure symptoms of suicidal ideation, hopelessness, or depression, so the effectiveness of the program in reducing risk of suicide is unknown (Barnes et al., 2017).

In a pre-post study by Elbogen et al. (2021), participants were instructed to perform "mobile neurofeedback" using a portable EEG headset linked to an application on a mobile device. The mobile neurofeedback application was configured to provide auditory feedback to participants through a relaxing sound to indicate brainwave patterns associated with a relaxed brain state. The authors found a significant reduction in suicidal ideation (Elbogen et al., 2021).

Conclusions

There is level 1a evidence (Brenner et al., 2018; Simpson et al., 2011) that CBT may be effective in reducing hopelessness; however, it may not be effective for suicide ideation.

There is level 4 evidence (Barnes et al., 2017) that problem-solving therapy may be a feasible intervention for suicide prevention post TBI; however more research is needed to determine its efficacy.

There is level 4 evidence (Elbogen et al., 2021) that mobile neurofeedback may decrease suicidal ideation in veterans with TBI and PTSD.

KEY POINTS

- Group-based Cognitive Behavioural Therapy (CBT) may be an effective intervention for reducing feelings of hopelessness, a precursor of suicidal ideation, post TBI.
- Problem-solving therapy may be a feasible intervention for reducing suicidal ideation post TBI; further research is required to determine its efficacy.
- Mobile neurofeedback using a portable EEG headset may reduce suicidal ideation in veterans with TBI and PTSD.

Substance Use Disorders

Incidence and Prevalence of Substance Use

Rates of pre-injury substance abuse in those who have sustained a TBI are high. Substance use disorders and TBI are most common in young male individuals, and substance intoxication is a leading contributor to accident-related injury (Kraus et al., 1989; Ponsford et al., 2018). Studies differ in the criteria used to determine if an individual is dealing with addiction, dependence, or abuse. Studies that only include individuals with a positive Blood Alcohol Concentration (BAC) at the time of admission report an inflated incidence compared to patient reported substance use disorders. Additionally, prevalence rates are variable between populations. Rates of pre-injury alcohol abuse in Australian and North American populations have been recorded at 20-40%, whereas rates in Finland are reported at 8%, which likely reflects cultural differences in alcohol consumption (Alway et al., 2016; Gould et al., 2011; Hibbard et al., 1998; Koponen et al., 2002).

Among those who sustain their injury in a motor vehicle collision, one of the leading causes of TBI, almost half were found to be intoxicated (DeLambo et al., 2008; Wehman et al., 2000; West et al., 2009). Studies have suggested that alcohol and substance abuse decline within the first year of injury (Bombardier et al., 2003; Jorge, 2005; Kelly et al., 1997; Ponsford et al., 2007), but those who returned to drinking two

years post-injury are likely to consume more than before the injury (Bombardier et al., 2002; Ponsford et al., 2007). In addition, individuals who abused alcohol pre-injury have reported to be ten times more likely to demonstrate problematic alcohol use post injury (Bombardier et al., 2003). Individuals who drink excessively are more likely to report alcohol as the cause of their TBI and are more likely to report pre-injury substance abuse (Turner et al., 2003). Moreover, the correlation between mood disorders and substance abuse has also been shown to be quite strong both before and after injury (Jorge, 2005).

Intoxication and Initial Assessments

Several issues have been raised about assessing the severity of injury, particularly with the use of the GCS. It has been suggested that the GCS is unreliable when used to establish functioning level at time of injury for those who have been drinking and/or using other substances (Jagger et al., 1984). Some studies have reported a negative correlation between GCS score and BAC among individuals admitted to hospital post-TBI (Alexander et al., 2004; Berry et al., 2010; O'Phelan et al., 2008; Schutte & Hanks, 2010; Shahin et al., 2010); a positive correlation has been noted between BAC and Injury Severity Scale score (Salim, Ley, et al., 2009; Salim, Teixeira, et al., 2009). Andelic et al. (2010) noted that patients diagnosed with a less severe TBI more frequently reported substance use at the time of injury, while those diagnosed with a more severe injury frequently reported pre-injury substance abuse. Of note, other studies did not find a correlation between the two variables (Kelly et al., 1997; Sperry et al., 2006; Stuke et al., 2007). To date, there is conflicting evidence regarding the effects of alcohol on injury severity.

Intoxication and Mortality

The protective role of elevated serum ethanol levels and TBI is a controversial topic. It has been suggested that alcohol acts as a neuroprotective agent and plays a role in survival post-injury (Berry et al., 2010). Several studies reported lower mortality rates among individuals who were intoxicated at the time of injury than those who were not intoxicated (Berry et al., 2010; O'Phelan et al., 2008; Salim, Ley, et al., 2009; Salim, Teixeira, et al., 2009; Tien et al., 2006). A retrospective study reported that BAC was higher for survivors than non-survivors of TBI (Salim, Ley, et al., 2009), while another study found that low to moderate BAC was associated with lower risk of mortality in those who had sustained a severe TBI (Tien et al., 2006). These studies primarily focus on alcohol intoxication; however, their findings can also apply to illicit drug intoxication at the time of injury (O'Phelan et al., 2008; Salim, Teixeira, et al., 2009). Overall, further research needs to be conducted to conclusively determine the effects of alcohol and other substances on survival following ABI.

Substance Abuse and Recovery

Recovery following a brain injury may be negatively impacted when individuals continue to abuse alcohol or other substances, often resulting in increased risk of seizures, reduced efficacy of rehabilitation and

risk of subsequent TBI (VanderVeen, 2021). Individuals with substance use disorders have been found to spend more time in rehabilitation programs due to accentuated deficits in sensory, motor, cognitive, and communication functions (Wehman et al., 2000). Additionally, continued abuse of alcohol and other substances increases the risk of developing medical complications (Salim, Ley, et al., 2009). Involvement in rehabilitation deters or prevents individuals from using various substances given that patients are often closely monitored (Bjork & Grant, 2009). However, once patients are discharged from inpatient rehabilitation, individuals may return to their previous substance use behaviours as a coping strategy. During acute recovery, high BAC is predictive of poorer performance on a variety of neuropsychological measures, including orientation, concentration, reasoning, and memory (Bombardier & Thurber, 1998; Kelly et al., 1997; Tate et al., 1999; Wilde et al., 2004). In addition, acute BAC may be correlated with Functional Independence Measure (FIM) score upon admission to rehabilitation, but not with FIM at discharge or one-year post-injury (Schutte & Hanks, 2010). Cognitive measures were also negatively impacted by hazardous drinking both before and after injury (Ponsford et al., 2013). Vickery et al. (2008) reported that acute BAC and a history of hazardous drinking were associated with outcomes on the Disability Rating Scale (DRS) but not the FIM. Interestingly, while high acute BAC was associated with a lower score on the DRS, a history of hazardous drinking was associated with a higher score (Vickery et al., 2008).

Non-Pharmacological Interventions

Programs for the Management of Substance Use

Individuals with TBI may be particularly vulnerable to negative consequences of alcohol and substance misuse; therefore, since many patients reduce their drinking shortly after their injury, there is an opportunity for screening and intervention (Weil et al., 2018). There are several programs that have been implemented for the management of substance use among individuals with brain injuries.

TABLE 65 | Programs for the Management of Substance Use Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Bogner et al. (2021) USA RCT PEDro=6 $N_{Initial}$=58, N_{Final}=49	**Population**: Moderate to Severe TBI; Gender: Male=40, Female=18; Mean Age: *SBI Group*=38.1yr, *SEA Group*=40.4yr; Mean GCS=Not Reported; Time Post-Injury=33.8d **Intervention:** Participants were randomly allocated to either an Adapted Screening and Brief Intervention group (ASBI) or a Screening and Education with Attention control group (SEA). The duration of the intervention was 1 initial session, (25-30min), 1 session (10-15min) 1-mo post discharge. Outcomes were	1. No significant differences were found between treatment conditions for the number of drinks consumed per week. 2. A nonsignificant difference was found for adherence to abstinence between both treatment conditions, with more participants in the Adapted SBI group remaining abstinent.

Author Year Country Study Design Sample Size	Methods	Outcome
	assessed pre-intervention and then at 3-mo, 6-mo, and 12-mo follow-up. **Outcome Measure:** The primary outcome was the number of alcoholic drinks per week (Behavioral Risk Factor Surveillance System). Alcohol binging, use of illicit drugs, number of facts recalled from the video/intervention.	3. Those who did resume drinking in the Adapted SBI condition consumed significantly more drinks at 3 months (p=.03). 4. There were no significant group differences for binge use, drug use or the number of facts recalled about the negative effects of substance misuse.
Sander et al. (2012) USA RCT PEDro=5 N=104	**Population:** TBI. *Intervention Group (n=54)*: Mean Age=36.1yr; Gender: Male=44, Female=10; Median GCS Score=14. *Control Group (n=50)*: Mean Age=35.4yr; Gender: Male=41, Female=9; Median GCS Score=12. **Intervention:** Participants were randomly assigned to receive intervention or control. The intervention group received a motivational interview and education: they watched a 10min educational video about potential negative effects of substance abuse after TBI and were then asked to consider pros/cons of substance abuse. The control group received standard care: information and referrals typically given to those with substance issues. Assessments were conducted at 3mo follow-up. **Outcome Measure:** CAGE Alcohol Questionnaire (CAGE-AQ), Alcohol Expectancy Questionnaire-III (AEQ), Readiness to Change Question (RTC).	1. There was no treatment effect on CAGE-AQ, AEQ, or RTC. 2. After treatment, individuals with severe injury indicated alcohol use could result in physical and cognitive impairment. 3. Individuals who attributed their TBI to alcohol use indicated alcohol use could result in physical and cognitive impairment.
Tweedly et al. (2012) USA RCT PEDro=5 N=60	**Population:** TBI; *ID Group (n=20)*: Mean Age=36.5yr; Gender: Male=15, Female=5; Mean Time Post Injury=8 mo. *INFO Group (n=20)*: Mean Age=35.1yr; Gender: Male=14, Female=6; Mean Time Post Injury=7.95 mo. *MI Group (n=20)*: Mean Age=33.9yr; Gender: Male=16, Female=4; Mean Time Post Injury=7.79mo. **Intervention:** Participants were randomly assigned to one of three conditions: Informal Discussion (ID), a general 30min discussion about changes that had occurred since injury; Information (INFO), a package outlining cognitive, physiological, and behavioural changes that can occur following injury, plus ID; or Motivational Interviewing (MI), plus ID and INFO. Assessments were conducted at baseline and 6mo follow-up. **Outcome Measure:** Alcohol Use Disorders Identification Test (AUDIT), Timeline Follow-Back (TLFB), Readiness to Change Questionnaire (RTCQ), Hospital and Anxiety and Depression Scale (HADS).	1. Both MI and INFO groups were drinking less frequently and consuming fewer drinks than ID at follow-up, but the differences were not significant.
Ponsford et al. (2012) Australia	**Population:** TBI; Mean age=35yr; Gender: Not Reported; Time post-injury=6-9mo; Severity: Moderate=24, Severe=36.	1. There were no significant differences in alcohol consumption over time based on treatment group (p>0.05).

Author Year Country Study Design Sample Size	Methods	Outcome
RCT PEDro=5 N*initial*=60, N*final*=50	**Intervention:** Participants were randomly assigned in groups of 20 to receive either discussion plus information, brief motivational interview plus information, or informal discussion as control condition. Outcomes were assessed at baseline and 6mo after the initial assessment. **Outcomes:** Alcohol Use Disorders Identification Test (AUDIT), Alcohol Timeline Follow back Method (TLFB), California Verbal Learning Test–II (CVLT-II), Readiness to Change Questionnaire, The Hospital Anxiety and Depression Scale (HADS) – depression scores.	
Wiart et al. (2012) France Case Series N= 47	**Population:** TBI; Mean Age=33.4yr; Gender: Male=35, Female=12; Mean GCS=6.4, Mean Time Post Injury=11.1yr. **Intervention:** Retrospective review of patients with mood disorders referred to a single physician for at least 1yr of neuro-systemic psychotherapy. **Outcome Measure:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Glasgow Outcome Scale.	1. No improvements were seen in addictive disorders.
Bogner et al. (1997) USA Case Series N=72	**Population:** TBI; Mean Age=26yr; Gender: Male=56, Female=16; Mean Time Post Injury=44.3mo; Mean Loss of Consciousness=10.5d. **Intervention:** Participants received a substance abuse treatment plan and were monitored for 1yr. Some individuals had support of a community team. **Outcome Measure:** Quantity-Frequency-Variability Index, General Health and History Questionnaire, Addiction Severity Index.	1. A positive substance abuse outcome was found in 75% of participants: 18% maintained abstinence, 32% attained abstinence, and 25% reduced alcohol use. 2. A significant difference in abstinence was found between initial assessment and 1yr follow-up ($p<0.05$). 3. Participants with a community team had more positive substance abuse outcomes than those without ($p<0.05$). 4. A greater proportion of participants with community teams attained abstinence.

Discussion

Four studies examined interventions for the management of substance use disorders. In an RCT, Bogner et al. (2021) allocated participants to either an Adapted Screening and Brief Intervention group (ASBI) or a Screening and Education with Attention control group (SEA). The authors found no significant differences between groups for the number of drinks consumed per week, and no significant differences were observed for binge alcohol use, drug use or the number of facts recalled about the negative effects of substance misuse (Bogner et al., 2021). In an RCT, Sander et al. (2012) reported that a combination of motivational interviewing (MI) and educational information did not reduce excessive drinking; in addition, positive expectancies and readiness to change were not improved after treatment. However, participants demonstrated awareness regarding the negative impact of their substance abuse on their physical and cognitive impairments. In the RCT by Tweedly et al. (2012), the authors found no significant

differences between a group that received Information (INFO), a package outlining cognitive, physiological, and behavioural changes that can occur following injury, plus informal discussion (ID); or Motivational Interviewing (MI), plus ID and INFO. In a similar RCT, Ponsford et al. (2012) found no significant differences in alcohol consumption between groups that received MI or discussion and information, compared to informal discussion only.

In a case series by Wiart et al. (2012), neuro-systemic psychotherapy was not found to improve addictive disorders post-severe TBI. In a case series study by Bogner et al. (1997), a substance abuse treatment program for individuals with TBI was found to be effective at assisting individuals to attain or maintain abstinence, as well as to reduce consumption. The authors reported a positive substance abuse outcome in 75% of participants, 18% maintained abstinence, 32% attained abstinence, and 25% reduced alcohol use; in addition, those who received community support had significantly more positive substance abuse outcomes (Bogner et al., 1997).

Conclusions

There is level 1b evidence (Bogner et al., 2021) that an Adapted Screening and Brief Intervention (ASBI) may not be more effective than a Screening and Education with Attention control (SEA) intervention for alcohol misuse following a TBI.

There is level 2 evidence (Ponsford et al., 2012; Sander et al., 2012; Tweedly et al., 2012) that motivational interviewing and education may not reduce frequency or intensity of substance consumption post TBI.

There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may not improve addictive disorders post severe TBI

There is level 4 evidence (Bogner et al., 1997) that a long-term substance abuse program may reduce substance consumptions and may increase abstinence post TBI.

KEY POINTS

- An Adapted Screening and Brief Intervention (ASBI) may not be more effective than a Screening and Education with Attention control (SEA) intervention for number of drinks consumed or alcohol abstinence in individuals with moderate to severe TBI.
- Motivational interviewing and education may not reduce substance abuse following a TBI.
- Neuro-systemic therapy may not improve addictive disorders in those with severe TBI.
- Long-term substance use programs may reduce substance consumption and may increase abstinence in individuals with TBI.

Peer Support

There is limited literature on peer support interventions in the TBI population. In a systematic review, Hughes et al. (2020) found that peer support groups for individuals with ABI result in several benefits such as feeling connected and interacting with others, as well as providing and receiving support.

TABLE 66 | Peer Support for the Management of Substance Use Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Hanks et al. (2012) USA RCT PEDro=5 N=96	**Population:** TBI; Gender: Male=74, Female=22; Caregivers=62; Peer Mentored Group: Mean Age=38.46yr; Mean GCS=9.39. TBI Control Group: Mean Age=40.90yr; Mean GCS=9.8. Caregiver Mentored Group: Mean Age=51.87 yr. Caregiver Control Group: Mean Age=50.18yr. **Intervention:** Participants and caregivers were randomly assigned to either a peer mentoring program or to a control group. Discussions in mentoring sessions included emotional well-being, post-TBI quality of life, and community integration. **Outcome Measures:** Peer Mentoring Questionnaire, Family Assessment Device (FAD), Coping Inventory for Stressful Situations (CISS-21), 12-Item Short-Form Health Survey (SF-12), Brief Symptom Inventory-18 (BSI-18), Community Integration Measure (CIM), Short Michigan Alcoholism Screening Test (SMAST).	1. There was no difference between groups in anxiety (p=0.31) and depression symptoms (p=07). 2. The mentored group had decreased somatic symptoms of emotional distress, less emotion-focused (p=0.04) and avoidance coping (p=0.03), as well as lower alcohol use (p=0.01) and fewer somatic symptoms of emotional distress. 3. Individuals who received mentoring had significantly better behavioral control and less chaos in the living environment (p=0.04).

Discussion

In an RCT, Hanks et al. (2012) assigned participants with TBI and their caregivers either to a peer mentoring program or a control group. The peer mentoring program included discussions on emotional well-being, quality of life post TBI and reintegration to the community. The authors found that the mentored group reported less alcohol abuse, compared to the control group (Hanks et al., 2012).

Conclusions

There is level 2 evidence (Hanks et al., 2012) that peer support may decrease alcohol use in individuals with TBI.

KEY POINTS

- Peer support may be effective for the management of alcohol use post moderate to severe TBI. However, more research is needed.

BEHAVIOUR

Agitation, Anger and Aggression

Challenging behaviour following ABI occurs with a relatively high frequency (25-50%), which often includes anger, agitation, aggression, and non-compliance with treatment. The emergence of these behaviours likely arises from injury to the frontal lobes, which results in disinhibited behaviour and a lack of recognition of the consequences (Kim, 2002). Individuals found to have poorer social functioning often engage in a variety of aggressive or agitated behaviours, including refusing participation, hitting, kicking, throwing objects, verbal abuse, and self-harm (McNett et al., 2012; Rao et al., 2009). Typically, behavioural management techniques and pharmacological interventions are used to alleviate these challenges with varying degrees of success.

Prevalence and Predictors of Agitation, Anger and Aggression

Agitation and aggression occur in approximately 33% to 70% of patients with TBI (Janzen et al., 2014; Nott et al., 2006; Sabaz et al., 2014; Singh et al., 2014). Agitation is generally defined as restlessness, impulsiveness, edginess, distractibility, wandering, and/or non-compliance; in contrast, aggression is defined as physical or verbal violence that may put the individual and others at risk for injury (Eisenberg et al., 2009). These behaviours have been associated with several clinical factors in individuals with ABI, including younger age (Baguley et al., 2006; Jean-Bay, 2000; Wolffbrandt et al., 2013), frontal lobe lesions (Tateno et al., 2003; Warriner & Velikonja, 2006), premorbid major depression (Baguley et al., 2006; Bakchine et al., 1989; Jean-Bay, 2000; Kim & Humaran, 2002; Sabaz et al., 2014; Tateno et al., 2003), and premorbid substance abuse (Sabaz et al., 2014; Tateno et al., 2003). During rehabilitation, the severity and duration of these challenging behaviours can have a negative impact on functional outcomes (Jean-Bay, 2000; Singh et al., 2014).

Behaviours such as agitation and aggression can be managed via non-pharmacological and pharmacological interventions. In an international survey by Carrier et al. (2021), 331 clinicians responded regarding their experience with treating agitation and aggression in the adult TBI population. The authors found that the majority (90%) of clinicians reported the use of pharmaceuticals, especially atypical antipsychotics; in addition, 52% of clinicians reported that they were satisfied with the current management practices (Carrier et al., 2021). A systematic review of reviews by Rahmani et al. (2021) found that amantadine, beta-blockers (propranolol and pindolol), antiepileptics, and methylphenidate can be used for scheduled treatment of agitation and aggression in patients with TBI; while the use of benzodiazepines and haloperidol should be avoided for treating agitation and aggression.

Non-Pharmacological Interventions

Psychotherapy

Aggressive behaviour following TBI has been associated with factors such as major depression, substance abuse, disconnection from social support networks and poor work performance; therefore, timely access to counseling, therapy and psychiatric services can help address psychosocial factors impacting aggressive behaviour (Maresca et al., 2023). In a meta-analysis, Byrne and Coetzer (2016) found that psychological interventions had a moderate effect on aggressive behavior following ABI.

TABLE 67 | Psychotherapy for Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Cognitive Behavioural Therapy (CBT)		
Anson & Ponsford (2006) Australia RCT PEDro=5 N=33	**Population:** TBI; Gender: Male=27, Female=6. *Group A (n=17)*: Mean Age=38.9yr; Mean Time Post Injury=755.8d. *Group B (n=16)*: Mean Age=37.8yr; Mean Time Post Injury=340.8d. **Intervention:** Participants were randomized to receive a CBT-based Coping Skills Group (CSG) in two groups with different duration. For Group A (n=15), baseline phase was 5wk, followed by 5wk of intervention, and a 5wk follow-up phase. For Group B (n=16), baseline was 10wk, followed by 5wk of intervention and a 10wk follow-up phase. The CSG consisted of 10 group sessions and ran for 900min 2×/wk. **Outcome Measure:** Coping Scale for Adults (CSA), Hospital Anxiety and Depression Scale (HADS), Rosenberg Self Esteem scale (RSE), The Sickness Impact Profile (SIP), The State-Trait Anger Expression Inventory, 2nd ed. (STAXI-2), National Adult Reading Test (NART), Rey Auditory Verbal Learning Test (RAVLT), Six Elements sub-test from the Behavioural Assessment of the Dysexecutive Syndrome (BADS).	1. There was no significant difference in anger, as measured by the State-Trait Anger Expression Inventory, 2nd Ed. (STAXI-2) (p=0.174).
Medd & Tate (2000) Australia RCT PEDro=5 N=16	**Population:** TBI; Gender: Male=14, Female=2; *Treatment Group (n=8),* Mean Age=35.88yr; Mean Time Post Injury=37.25mo; *Waitlist Group (n=8),* Mean Age=34yr; Mean Time Post Injury=74.25mo; Mean PTA=2wk. **Intervention:** Participants were randomly allocated to either the treatment group or the waitlist group. The treatment group received 5-8 individualized sessions of cognitive behavioural therapy based on the Commonwealth Rehabilitation Service Anger Management Program. **Outcome Measure:** State-Trait Anger Expression Inventory (STAXI), Hospital Anxiety and Depression	1. The treatment group had significantly higher pre-intervention levels of Anger Expression-Out (AX-O) on the STAXI than the waitlist group (p=0.004). 2. The treatment group showed a greater improvement in AX-O (p=0.006) and trait anger (p=0.054) from pre to post treatment when compared to the waitlist group. 3. No significant differences were found on HADS, SEI, or PCRS between groups.

Author Year Country Study Design Sample Size	Methods	Outcome
	Scale (HADS), Self-Esteem Inventories (SEI), Patient Competency Rating Scale (PCRS).	
Aboulafia-Brakha et al. (2013) Switzerland Pre-Post $N_{Initial}$=10, N_{Final}=9	**Population:** TBI; Median Age=47yr; Gender: Male=8, Female=2; Median Time Post Injury=27.5mo; Median GCS=5. **Intervention:** Participants completed a semi-structured group treatment program for the management of anger and aggressiveness (1 hr, 1 day/wk for 8wk). The program was based on a cognitive behavioural therapy framework as led by a therapist. Inter-session homework was encouraged to apply new strategies. Outcomes were assessed at baseline, immediately after treatment, and at 4-5mo follow-up. **Outcome Measure**: Buss and Perry Aggression Questionnaire (AQ-12), UPPS Impulsive Behaviour Scale (UPPS-P), Frontal System Behavioural Scale (FrSBe), Cambridge Behaviour Scale (EQ), Hospital Anxiety Depression Scale (HADS), Quality of Life Assessment (SF-36).	1. Significant improvement in feelings of aggression on AQ-12 was found from baseline to 4-month follow-up (p=0.02). 2. No significant improvement on AQ-12 was found from baseline to post treatment (p=0.84). 3. No significant improvements were found for UPPS-P, FrSBe, EQ, HADS, or SF-36 between baseline and post treatment (p>0.05).
Walker et al. (2010) Australia Pre-Post N=52	**Population:** TBI; Mean Age=32.3yr; Gender: Male=40, Female=12; Mean Time Post Injury=4.1yr; Injury Severity: Severe. **Intervention:** Participants received 2hr sessions of group-based CBT focused on anger management, 1 x/wk for 12wk. Assessments were conducted at baseline, 12wk, and 3-16mo follow-up. **Outcome Measure:** State-Trait Anger Expression Inventory (STAXI).	1. At post treatment, there were significant reductions in trait anger (p=0.002), anger expression-out (p=0.003), and anger control (p=0.005), but not in state anger or anger expression-in. 2. At follow-up (n=31), the improvements from baseline were maintained, but there were no further improvements from post treatment.
Neuro-Systemic Psychotherapy		
Wiart et al. (2012) France Case Series N= 47	**Population:** TBI; Mean Age=33.4yr; Gender: Male=35, Female=12; Mean GCS=6.4; Mean Time Post Injury=11.1yr. **Intervention:** Retrospective review of patients with mood disorders referred to a single physician for at least 1yr of neuro-systemic psychotherapy. **Outcome Measure:** Diagnostic and Statistical Manual of Mental Disorders (DSM), Glasgow Outcome Scale.	1. A significant improvement was found in hostility (p<0.01). 2. No improvements were seen in apathy, bipolar symptomatology, or loss of control.
Motivational Interviewing		
Bell et al. (2005) USA RCT PEDro=6 $N_{Initial}$=171, N_{Final}=157	**Population:** Moderately severe TBI; *Telephone intervention* (n=85): Mean age=34; Male=64, Female=21; *Standard control* (n=86) Mean age=37; Male=65, Female=21. Time post-injury= Not reported. **Intervention:** Participants were randomly assigned to receive motivational interviewing via telephone follow-up calls after discharge or no contact. Calls were made 2 and 4wk, 2, 3, 5, 7, and 9mo after discharge. **Outcome Measures:** Functional Independence Measure (FIM), Disability Rating Scale (DRS), Community Integration Questionnaire (CIQ),	1. Significant improvements were found in the composite score that combined the outcome measures (FIM, DRS, CIQ, FSE, GOS-E, EuroQol, NFI, PQOL, SF-36, and BSI) (p=0.012). 2. No significant differences between the two groups were found for individual measures.

Author Year Country Study Design Sample Size	Methods	Outcome
	Neurobehavioral Functioning Inventory (NFI), Functional Status Examination (FSE), Glasgow Outcome Scale Extended (GOSE), 36 Short-Form (SF-36), Brief Symptom Inventory (BSI), EuroQOL, Perceived Quality of Life (PQOL).	

Discussion

Two RCTs (Anson & Ponsford, 2006; Medd & Tate, 2000) and two pre-post studies (Aboulafia-Brakha et al., 2013; Walker et al., 2010) examined Cognitive Behavioral Therapy (CBT) interventions. Medd and Tate (2000) found that the CBT group had significantly improved in anger, as measured by the State-Trait Anger Expression Inventory (STAXI) when compared to the waitlist control. In the study by Aboulafia-Brakha et al. (2013), significant improvements in feelings of aggression were observed from baseline to the 4-month follow-up; however, no significant improvements were found for other challenging behaviours such as impulsivity.

In the study by Walker et al. (2010), significant reductions in anger, anger expression and anger control were observed after the CBT intervention, with improvements maintained at follow-up. In a case series study, Wiart et al. (2012) examined the use of neuro-systemic psychotherapy and reported a significant improvement in hostility. In the RCT by Anson and Ponsford (2006), the authors found that duration of CBT had no impact on anger, as measured by the State-Trait Anger Expression Inventory, 2nd Ed. (STAXI-2).

Bell et al. (2005) examined motivational interviewing delivered over the phone and reported that the group that received the telephone intervention showed significant improvements in behaviour. However, results from this study need to be interpreted with caution given that behaviour was assessed in a composite score including multiple outcome measures.

Conclusions

There is 1b evidence (Bell et al., 2005) that motivational interviewing via follow-up telephone calls may improve behaviour post TBI.

There is level 2 evidence (Medd & Tate, 2000) and level 4 evidence (Aboulafia-Brakha et al., 2013; Walker et al., 2010) that CBT may improve anger expression and feelings of aggression post TBI.

There is level 2 evidence (Anson & Ponsford, 2006) that duration of CBT interventions may have no impact on depression in individuals post TBI.

There is level 4 evidence (Wiart et al., 2012) that neuro-systemic psychotherapy may improve hostility in individuals with TBI.

KEY POINTS

- Cognitive Behavioural Therapy (CBT) may be effective for the management of anger expression and feelings of aggression in individual with moderate to severe TBI.
- The duration of CBT may not have an impact on anger post TBI.
- Neuro-systemic psychotherapy may improve hostility following a moderate to severe TBI.
- Motivational Interviewing delivered over the phone post discharge may improve behaviour in individuals with moderate to severe TBI.

Rehabilitation Programs

An approach that helps individuals acquire coping strategies and to develop skills to use during stressful situations has been suggested as treatment option for individuals with challenging behaviour, such as anger and aggression; other therapies may include cognitive therapies, relaxation-based therapies, skills-training, exposure-based treatments, cathartic treatments, and multicomponent treatments (Demark & Gemeinhardt, 2002).

TABLE 68 | Rehabilitation Programs for Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Ponsford et al. (2022) Australia RCT PEDro=7 $N_{Initial}$=49, N_{Final}=44	**Population:** ABI, TBI=30, Stroke=13, Hypoxia=5, non-progressive brain tumor=1; Intervention Group (n=24): Gender: Male=22, Female=2, Mean Age=42.92yr, Severe, Time Post Injury=8.71yr. Control Group (n=25): Gender: Male=15, Female=10, Mean Age=43.60yr, Severe, Time Post Injury=8.68yr. **Intervention:** Participants were randomly allocated to either a Positive Behavior Support (PBS) intervention or Waitlist treatment group. The intervention consisted of initial meeting, GAS/goal setting, PBS+PLUS sessions, and occasionally included other therapists, and focused on approaches to achieve goals. The intervention lasted 12mo, and participants had to receive at least 6 sessions over 3 months. Outcomes were assessed at baseline, 4-mo intervals, post-intervention and at 12-mo follow-up. **Outcome Measures:** Overt Behavior Scale (OBS), Challenging Behavior Self-Efficacy Scale (CBSES), Mini International Neuropsychiatric Interview, Hospital	1. On the OBS, Intervention group showed significant reduction in challenging behavior (p<.05) over 12-mo intervention. However, the waitlist group showed a similar improvement on the OBS over the 12mo waitlist period. 2. PBS+PLUS intervention resulted in significantly greater gains in close others' confidence in addressing challenging behaviors on the CBSES, relative to those in the Waitlist group who showed no gains (p=.000 to .03).

Author Year Country Study Design Sample Size	Methods	Outcome
	Anxiety and Depression Scale (HADS), Community Integration Questionnaire - Revised (CIQ), Care and Needs Scale (CANS).	
Hart et al. (2017) USA RCT PEDro=7 $N_{Initial}$=90, N_{Final}=84	**Population:** TBI; Severity: Severe. *Treatment Group (n=60):* Mean Age=30.4yr; Gender: Male=49, Female=11; Median Time Post Injury=69mo. *Control Group (n=30):* Mean Age=36.2yr; Gender: Male=24, Female=6; Median Time Post Injury=72mo. **Intervention:** Participants were randomized to receive anger self-management training (treatment) or personal readjustment and education (control) in 90min weekly sessions for 8wk. Assessments were conducted at baseline, 4wk, 8wk, and 16wk. **Outcome Measure:** State-Trait Anger Expression Inventory 2 (STAXI-2); Brief Anger-Aggression Questionnaire (BAAQ).	1. At 8wk, the proportion of responders on self-reported STAXI-2 Trait Anger was significantly greater in the treatment group than control group for intention-to-treat analysis (68.3% versus 46.7%, p=0.047) and per protocol analysis (71.9% versus 51.9%, p=0.031); these improvements were maintained at 16wk. 2. There were no significant differences in response rates between groups on self-reported STAXI-2 Anger Expression-Out or BAAQ at 8wk or 16wk. 3. There were no significant differences in response rates between groups on STAXI-2 or BAAQ as rated by a significant other at 8wk or 16wk. 4. There were no significant differences between groups in mean scores on STAXI-2 or BAAQ by self-report over time.
Aboulafia-Brakha & Ptak (2016) Switzerland RCT Crossover $N_{Initial}$=24, N_{Final}=19	**Population:** ABI: TBI=78.9%, Stroke=21.1%; Gender: Male=16, Female=3; Mean GCS=10.1; *Intervention First Group* (N=8): Mean Age=46.1yr; Mean Time Post Injury=12.7mo; *Control First Group* (N=11): Mean Age=39.3yr; Mean Time Post Injury=19.45mo. **Intervention:** Patients self-reporting increased anger were randomized to one of two groups (AB or BA). The AB group received an 8-wk anger management programme (60 min, 1x/wk), followed by a 4wk psycho-educational programme. For group BA, the order was reversed. Outcomes were assessed at baseline: 6–12wk prior intervention (T0), first session (T1), 4wk after beginning the intervention (T2), 8wk after beginning the intervention (T3), 12wk after the intervention, and final assessment (T4). **Outcome Measures:** The Aggression Questionnaire (AQ-12), State-Trait Anger and Expression Inventory-2 (STAXI-2), Multidimensional Anger Reaction Scale (MARS), Frontal System Five-Point Test Behaviour Scale (FrSBe), 16 items-UPPS Impulsive Behaviour Scale, Fatigue Assessment Inventory (FAI), Wechsler Memory Scale-III (WMS-III), Trail Making Test A, Trail Making Test B, D-KEFS Color Word Interference Test (CWIT), Five Point Test.	1. AQ-12 scores significantly improved from TI to T4 ($p = 0.01$). 2. All STAXI-2 subscales showed significant improvement from T1 to T4 ($p < 0.01$). 3. Rumination and venting showed significant improvement from T1 to T4 ($p = 0.01$; $p = 0.04$). 4. Other subscales were non-significant ($p > 0.05$).

Author Year Country Study Design Sample Size	Methods	Outcome
Carnevale et al. (2006) USA RCT PEDro=5 N=37	**Population:** TBI=24, ABI=13; Mean Age=40.5yr; Gender: Male=28, Female=7; Mean Time Post Injury=7.6yr, Loss of Consciousness >24hr = 91.9%. **Intervention:** Participants were randomized to a control group (n=12) that received no treatment, an education group (n=13) that received education only, and a Natural Setting Behaviour Management (NSBM) group (n=12) that received both education and an individualized behaviour modification program. Target behaviours included aggression, disinhibition and inappropriate social behaviour. **Outcome Measure:** Maslach Burnout Inventory (MBI), Questionnaire on Resources and Stress for Families with Chronically Ill or Handicapped Members (QRS), Neurobehavioral Functioning Inventory–Revised (NFI-R).	1. NSBM had more improvement in behaviour than the other two groups at 30wk ($p<0.002$). 2. A significant difference was noted between the education group and the NSBM group ($p<0.04$).
McDonald et al. (2021) Australia Post-Test N=12	**Population:** ABI=5), Stroke=1; Mean Age=37yr; Gender: Male=6, Female=0; Mean Time Post Injury=5.3yr. *Caregivers (n=6):* Mean Age=54.3yr; Gender: Male=0, Female=6. **Intervention:** Participants and their caregivers were given an online treatment program "Carer's Way Ahead" that provides psychoeducation about TBI and challenging behaviours and specific management approaches. Following completion, all participants were directed to complete the post intervention self-report measures. **Outcome Measure:** Depression Anxiety and Stress Scale (DASS), Carer Strain Index (CSI), Family Assessment Device-General Functioning (FAD-GF), Family Environment Scale (FES) Form R, Overt Behaviour Scale-Adult (OBS-Adult).	1. Prior to commencing the program, carers thought and felt that the program would lead to some improvement (ranging from 20-80% improvement). 2. Some participants identified that the program either validated or reinforced approaches they had already taken or helped them refocus on their management approach. 3. No significant change in OBS scores at post-intervention. 4. In 5/6 cases, the FAD-GF pre-treatment scores fell within the range suggestive of unhealthy family functioning, as observed post-treatment and no change.
Pachalska et al., (2019) Poland PCT N=60	**Population:** Moderate to Severe TBI=60; *Treatment Group A (Comprehensive Rehabilitation, n=20):* Mean Age=26.7±6.79yr; Gender: Male=11, Female=9; Mean Time Post Injury=Not Reported; *Treatment Group B (Early Neuropsychological Rehabilitation, n=20):* Mean Age=25.6±6.39yr; Gender: Male=11, Female=9; Mean Time Post Injury=Not Reported; *Treatment Group C (Academy of Life Program, n=20):* Mean Age=26.3±8.69yr; Gender: Male=11, Female=9; Mean Time Post Injury=Not Reported. **Intervention:** Participants were received one of three different rehabilitation protocols focused on behaviours: comprehensive rehabilitation (cognitive and social skills rehabilitation), cognitive rehabilitation	1. No statistically significant difference was found between women and men in terms of behavioral disorders. 2. At follow-up, individuals in comprehensive rehabilitation group (Group A) showed less severe aggressiveness compared to the other groups. 3. Those in group A showed lower scores in behavioural disorders and higher social cultivation in behaviour, as well as lower impulsive levels compared to group B and group C.

Author Year Country Study Design Sample Size	Methods	Outcome
	(neuropsychological rehabilitation) or social skills rehabilitation (Academy of Life Program). **Outcome Measures:** Frontal Behavioral Inventory (FBInv).	
Hart et al. (2012) USA Pre-Post N=10	**Population:** TBI; Mean Age=43.3yr; Gender: Male=8, Female=2; Range of Time Post Injury=6-243mo; Range of Injury Severity: Moderate to Severe. **Intervention:** 8 sessions that consisted of self-monitoring training to build awareness of anger problem and training of specific problem-solving skills (anger self-management training). **Outcome Measure:** State Trait Anger Expression Inventory 2 (STAXI-2), Brief Anger-Aggression Questionnaire (BAAQ).	1. Following the intervention, there were significant reductions on self-reported STAXI-2 Trait Anger (p=0.02), STAXI-2 Anger Expression-Out (p=0.002), and BAAQ (p=0.01). There were no significant improvements on STAXI-2 or BAAQ as rated by a significant other.
Feeney & Ylvisaker (1995) USA Case Series N=3	**Population:** TBI; Mean Age=18.3yr; Injury Severity: Severe. **Intervention:** Patients received antecedent interventions, comprised of photographic and written cues, for managing aggression. **Outcome Measure:** Aberrant Behaviour Checklist (ABC).	1. All three patients showed a decrease in aggressive behaviours and ABC ratings indicated decreased intensity. 2. Two patients showed a mild increase in aggressive behaviours with written cues, which decreased when substituted with photographic cues.
Burke et al. (1988) USA Pre-Post N=5	**Population:** TBI; Mean Age=23.2yr; Gender: Male=5, Female=0. **Intervention:** Patients received behaviour therapy, with emphasis on reinforcement and antecedent conditions, for managing aggression. **Outcome Measure:** Frequency of aggression.	1. Measurements showed a 97% decrease in aggressive behaviour from baseline levels at 1wk and 100% at 3 wk. 2. There was a significant reduction in behaviour at all time-points compared to baseline (p<0.001). 3. No incidents of aggression were recorded during a 6mo follow-up.

Discussion

Behaviour management programs were evaluated in nine studies. In an RCT, Ponsford et al. (2022) allocated participants to either a Positive Behavior Support (PBS) intervention or Waitlist group. The intervention focused on approaches to achieve goals and lasted for 12 months. The authors found a significant reduction in challenging behavior in the intervention group, as measured by the Overt Behavior Scale (OBS); however, the waitlist group showed a similar reduction over the 12-months. The PBS+PLUS intervention resulted in more significant gains in close others' confidence in addressing challenging behaviors than the waitlist group (Ponsford et al., 2022).

In an RCT, Hart et al. (2017) compared the anger management program to a personal readjustment and education program. The authors reported that there was significantly greater improvement in self-reported trait anger with self-management training than with the control program. These improvements were maintained at follow-up. However, there was no significant improvement in outward anger expression with treatment compared to control (Hart et al., 2017). In another RCT, Aboulafia-Brakha and Ptak (2016) compared an eight-week anger management program to a psycho-educational program. There were no differences in anger between the treatment programs; however, both groups showed significant improvements in anger scores after completing both programs (Aboulafia-Brakha & Ptak, 2016). In an RCT, Carnevale et al. (2006) found significant improvements in aggressive behaviour and disinhibition for participants who received an individualized education and behaviour modification program in the natural community setting compared to those who only received education.

In a pre-post study, McDonald et al. (2021) examined the use of a psychoeducational program called Carer's Way Ahead for the management of aggressive and agitated behaviours in those with ABI as reported by their caregivers. The authors found no significant change in Over Behaviour Scale (OBS) scores were observed at post-intervention. In a pre-post study, Hart et al. (2012) found that all measures of self-reported anger and aggression significantly improved following treatment; however, there were no improvements in outcomes as reported by a significant other (Hart et al., 2012). In a PCT study, Pachalska et al. (2019) found that a comprehensive rehabilitation program that included both social skills and cognitive rehabilitation significantly improved behavioural disorders when compared to cognitive or social rehabilitation alone. In a case series, Feeney and Ylvisaker (1995) found that an antecedent behavioural intervention significantly reduced aggressive behaviour (Feeney & Ylvisaker, 1995). An earlier pre-post study found that a program incorporating self-management, antecedent interventions, and positive reinforcement significantly reduced aggressive behaviours (Burke et al., 1988).

Conclusions

There is level 1b (Ponsford et al., 2022) that a positive behaviour support intervention with a focus on goal achievement may improve confidence of close others in addressing challenging behaviour.

There is level 1b evidence (Hart et al., 2017; Aboulafia-Brakha & Ptak, 2016; McDonald et al., 2021; Hart et al., 2012) that anger self-management training may help reduce anger and aggression post TBI.

There is level 2 evidence (Carnevale et al., 2006) that behavioural modification programs may improve aggressive behaviour and disinhibition post TBI.

There is level 2 evidence (Pachalska et al., 2019) that comprehensive rehabilitation including both social skills and cognitive rehabilitation may be more effective than social or cognitive rehabilitation alone for behavioural disorders associated with TBI.

There is level 4 evidence (Feeney & Ylvisaker, 1995; Burke et al., 1988) that a behavioral intervention addressing antecedent conditions may decrease aggressive behaviour post TBI.

KEY POINTS

- Anger self-management training programs, comprehensive social and behavioural support interventions may be effective for behavioral disorders such as anger and aggression management following TBI, with additional benefits for significant others.

Cognitive Rehabilitation

Cognitive rehabilitation aims to help individual with ABI to regain cognitive function or to compensate for cognitive deficits, and it can be implemented using technologies such as computer-based cognitive tools and virtual reality (De Luca et al., 2018).

TABLE 69 | Cognitive Rehabilitation for Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Elbogen et al. (2019) USA RCT PEDro=5 $N_{initial}$=224 N_{final}=178	**Population:** TBI=112; Severity: Moderate/Severe=64; Family/Friend=112; *CALM Group (n=57)* Mean Age=36.77yr; Gender: Male=53, Female=4. *Control Group (n=55)* Mean Age=36.25yr; Gender: Male=50, Female=5. **Intervention:** Veterans with PTSD and TBI received cognitive rehabilitation supported by technology. Veterans and families members were randomized to either the Cognitive Applications for Life Management (CALM), involving goal management training plus mobile devices for attentional control, or a Brain Health Training, involving psychoeducation plus mobile devices to train visual memory. **Outcome Measures:** Delis-Kaplan Executive Function System (DKEFS) Color-Word inhibition task, Barratt Impulsiveness Scale (BIS), Dimensions of Anger Reactions (DAR), Head Injury Behavior Scale (HIBS), Number of home visits, Clinician-Administered Posttraumatic stress Disorder Scale (CAPS).	1. Significant treatment effects were observed for anger and TBI-related behavioral issues. 2. Veterans randomized to CALM reported an average 7.89-point decrease in anger toward others over 6 months on the DAR compared with 2.62-point reduction in veterans in the control group (p= .008).

Author Year Country Study Design Sample Size	Methods	Outcome
Ownsworth et al. (2017) Australia RCT PEDro=7 $N_{Initial}$=54, N_{Final}=50	**Population:** Severe TBI. *EBL* (n=27): Male=20, Female=7; Mean age=37.37yr; Mean time post-injury=36.44mo. *ELL* (n=27): Male=23, Female=4; Mean age=37.86yr; Mean time post- injury=40.81mo. **Intervention:** Participants were randomly allocated to the errorless learning (ELL) or error-based learning (EBL) groups and received eight 1.5h therapy sessions over 8wk. Outcomes were measured at baseline, and at 1wk, and 6mo. **Outcome Measures:** Chevignard's Cooking Task, Behavioural Assessment of Dysexecutive Syndrome (BADS), The Awareness Questionnaire (AQ), Patient Competency Rating Scale (PCRS), Sydney Psychosocial Reintegration Scale (SPRS), Care and Needs Scale (CANS), Depression Anxiety and Stress Scales-21 (DASS-21)	1. EBL participants demonstrated better self-awareness than ELL participants ($p<0.05$). 2. Behavioral competency on the PCRS was significantly better in the EBL group than in the ELL group ($p<0.05$). 3. There were no significant between-group differences observed in the Zoo Map task of BADS, or in anxiety and depression, as measured by the DASS-21 ($p>0.05$).
Cantor et al. (2014) USA RCT PEDro=6 N=98	**Population:** TBI; Mean Age=45.3yr; Gender: Male=37, Female=61; Mean Time Post Injury=12.6yr; Severity: Mild=49, Moderate=19, Severe=30. **Intervention:** Participants were randomly assigned to either the Short-Term Executive Plus (STEP) cognitive rehabilitation program or to a waitlist control. Participants received group sessions of emotional regulation (2 sessions, 45min) and an individual problem-solving session of attention training (1 session, 60min) per day (3d/wk for 12wk). Group sizes were generally 4-6 participants. **Outcome Measures:** Problem Solving Inventory (PSI), Frontal System Behavioural Scale (FrSBe), Behavioural Assessment of the Dysexecutive Syndrome (BADS), Self-awareness of Deficits Interview (SADI), Attention Rating and Monitoring Scale (ARMS), Difficulties in Emotion Regulation Scale (DERS), Stroop Color and Word Test (SCWT), Controlled Oral Word Association Test (COWAT), Animal Naming Test, Wechsler Adult Intelligence Scale (WAIS-III), Short Category Test (SCT), Trail Making Test B, Symbol Digit Modalities Test (SDMT), Auditory Consonant Trigrams (ACT), Test of Reading Speed, Woodcock Johnson III Tests of Cognitive Ability auditory attention scale (WJ-III-COG), Beck Depression Inventory-Second Edition (BDI-II), State-Trait Anxiety Inventory (STAI), Hopkins Verbal Learning Test-Revised (HVLT-R), Participation Objective Participation Subjective (POPS), Life-3 Scale, Self-Efficacy Questionnaire (GSE).	1. There were significant treatment effects for the composite executive function measure ($p=0.008$) and the Frontal Systems Behavior Scale (FrSBe) ($p=.049$). 2. There were no other significant treatment effects.
Vanderploeg et al. (2008) USA	**Population:** TBI; Mean Age=32.4yr; Gender: Male=335, Female=25; GCS <12.	1. No significant differences were found in depressed mood, as measured by the Present State Examination ($p=0.50$).

Author Year Country Study Design Sample Size	Methods	Outcome
RCT PEDro=7 N=360	**Intervention:** Patients were randomly assigned to specific cognitive-didactic therapy (n=180) or functional-experiential rehabilitation therapy (n=180) for 1.5-2.5hr/d over 20-60d. **Outcome Measure:** Functional Independence Measure (FIM), Disability Rating Scale (DRS), Present State Examination (PSE), Apathy Evaluation Scale, Neurobehavioral Rating Scale, Rancho Los Amigos Scale (RLAS).	2. No differences in irritable behaviour (p=0.53) and angry behaviour were found (p=0.31).
Salazar et al. (2000) USA RCT PEDro=6 $N_{Initial}$=120, N_{Final}=107	**Population:** TBI; *Hospital rehabilitation* (n=67): Mean age=25yr; Gender: Male=62, Female=5; Mean Time post-injury=38d; Mean GCS=9.4; *Home rehabilitation* (n=53): Mean age=26yr; Gender: Male=51, Female=2; Mean Time post-injury=39d. Mean GCS=9.5. **Intervention:** Patients were randomly assigned to either an intensive, standardized, 8wk, in-hospital cognitive rehabilitation program or a limited home rehabilitation program with weekly telephone support from a psychiatric nurse. Outcomes were assessed at baseline and at the 1yr follow-up. **Outcomes:** Katz Adjustment scale (KAS), Halstead-Reitan Neuropsychological Battery, Buschke Selective Reminding Test (SRT), Continuous Visual Memory Test (CVMT), Paced Auditory Serial Addition Test (PASAT), Wisconsin Card Sorting Test (WCST), Wechsler Memory Scale Revised (WMS-R), Auditory Consonant Trigrams (ACT).	1. There were no significant differences between treatment groups reported at 1 year in measures of belligerence (p=0.19), social irresponsibility (p=0.99), antisocial behaviour (p=0.24), social withdrawal (p=0.40), and apathy (p=0.21). 2. At 1 year after randomization, no significant differences were found for verbal or physical aggression (p=0.82). 3. No significant differences were found at 1 year for major depression (p=0.26) and generalized anxiety (p=0.33), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Discussion

In an RCT, Elbogen et al. (2019) looked at the use of Cognitive Applications for Life Management (CALM), an intervention involving goal management training plus mobile devices for cueing and training attentional control compared to a visual memory training control via mobile devices for Brain Health Training. The authors found significant differences between groups in favour of CALM for anger, as measured by the DAR scores, as well as fewer maladaptive interpersonal behaviours.

Cognitive training was also examined by Cantor et al. (2014) in an RCT study. The authors found significant treatment effects for behaviour, as measured by the Frontal Systems Behavior Scale (FrSBe). In another RCT study, Vanderploeg et al. (2008) compared cognitive-didactic training to experiential-functional training and found no group differences in irritable and angry behaviour. Similarly, Salazar et al. (2000) found no differences in aggressive behaviour when comparing in-hospital cognitive rehabilitation and a home program with telephone support. In the RCT by Ownsworth et al. (2017), participants were allocated to errorless learning or error-based learning and received therapy involving goal-directed activities and meal preparation. Participants in the error-based learning demonstrated

greater self-awareness and behavioral competency, compared to those in the errorless learning group. However, no differences were found for self-regulatory behaviour, as measured by the Zoo map test of the Behavioural Assessment of Dysexecutive Syndrome.

Conclusions

There is level 1b evidence (Cantor et al., 2014) and level 2 evidence (Elbogen et al., 2019) that a cognitive rehabilitation may be effective for the management of behaviour, including disinhibition and anger post TBI.

There is level 1b evidence (Vanderploeg et al., 2008) that cognitive-didactic training may not improve irritability and anger post TBI, compared to functional-experiential training.

There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for social behaviour post TBI.

There is level 1b evidence (Ownsworth et al., 2017) that error-based learning may improve behavioral competency post severe TBI, compared to errorless learning.

KEY POINTS

- Cognitive rehabilitation may be effective for behavioral disorders such as anger and disinhibition following TBI.
- Cognitive-didactic training may not improve anger or irritable behaviour post moderate to severe TBI, when compared to functional-experiential training.
- Error-based learning may be more effective for behavioural competency in individuals with severe TBI., compared to errorless learning.
- In-hospital cognitive rehabilitation may not be different than home rehabilitation with telephone support for aggressive behaviour post TBI.

Emotion Recognition

Emotion recognition is an essential aspect of social cognition that mediates affiliative behaviours and social interactions in both animals and humans (Ferretti & Papaleo, 2019).

TABLE 70| Emotion Recognition for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Neumann et al. (2015) USA RCT PEDro=8 N=71	**Population:** TBI=71; *Faces group (n=24)* Mean Age=41.0yr; Gender: Male=23, Female=1; Mean Time Post Injury=10.5yr; Mean GCS=6.0. *Stories group (n=23)* Mean Age=41.5yr; Gender: Male=18, Female=5; Mean Time Post Injury=10.9yr; Mean GCS=4.4. *Control group (n=24)* Mean Age=39.5yr; Gender: Male=16, Female=7; Mean Time Post Injury=9.8yr; Mean GCS=5.3. **Intervention:** Participants were randomly allocated to either a Faces group (n=24) in which they were completed recognition of emotions by facial expressions, a Stories group (n=23) in which they were taught to infer emotions from contextual information in short stories, or a Control group (n=24) in which they played a variety of online, publicly available computer games that targeted speed of processing, visual scanning, attention, memory, reasoning, and problem-solving skills. All interventions consisted of 9 hours of computer-based training with a therapist and outcomes were taken at post-intervention, 3-month, and 6-month follow-up. **Outcome Measures:** Diagnostic Assessment of Nonverbal Accuracy 2-Adult Faces (DANVA 2-AF), Emotional Inference From Stories Test (EIST), Interpersonal Reactivity Index (IRI), Neuropsychiatric Reactivity Index (NPI).	1. Significant improvement in DANVA 2-AF scores in the Faces group (p=0.031) compared to the Control group. 2. So significant difference between the Faces group and control or the Stories group and control for EIST scores. 3. Faces and Stories groups were not significantly different than control for informant ratings of IRI perspective talking (PT) or empathic concern (EC). 4. Faces and Stories groups were not significantly different than control for informant ratings of NPI Irritability and Aggression.
Radice-Neumann et al. (2009) USA RCT PEDro=5 $N_{Initial}$=21, N_{Final}=19	**Population:** TBI=19, ABI=2; Mean Age=43yr; Gender: Male=12, Female=8; Mean Time Post Injury=12yr; Mean GCS=4.08. **Intervention:** Participants were randomly assigned to receive either the facial affect recognition (FAR; n=10) training or the stories of emotional inference training (SEI; n=9). In the FAR training, individuals practiced identifying and discriminating emotions from facial expressions and focused on processing their internal emotions. SEI involved reading stories and answering questions. Sessions were 1:1 for 1hr, 3 x/wk for 2-3 wk. **Outcome Measures:** Levels of Emotional Awareness Scale (LEAS), Diagnostic Assessment of Nonverbal Affect – adult faces/adult paralanguage (DANVA2-AF and DANVA2-AP), Brock Adaptive Functioning Questionnaire (BAFQ).	1. Both groups improved their ability to infer emotions from contextual situations (LEAS; p=0.019). 2. On the BAFQ, caregivers indicated those in the FAR group showed improvement in the behaviour of participants (p=0.042); out of 4 emotional behaviours, only aggression changed significantly (p=0.047); SEI did not improve in perceived behaviour. 3. No significant changes were noted in empathy (p=o.115).

Discussion

In an RCT, Radice-Neumann et al. (2009) found that while both groups improved their ability to infer emotions from context, individuals who received facial recognition training showed improvements in emotional behaviours, significantly reduced aggression; however, no changes were observed for empathy. In a subsequent RCT, Neumann et al. (2015) randomly allocated participants to either a Faces group that completed recognition of emotions by facial expressions, a Stories group that taught

participants to infer emotions via contextual information within short stories, or a control group that played a series of online computer games that targeted speed of processing, visual scanning, attention, memory, reasoning, and problem-solving skills. The authors found no significant differences in Neuropsychiatric Reactivity Index (NPI) scores specifically for subcategories of irritability and aggression.

Conclusions

There is conflicting evidence (Neumann et al., 2015; Radice-Neumann et al., 2009) that a program addressing recognition of facial emotions may be effective for irritability and aggression in individuals with TBI.

KEY POINTS

- There is conflicting evidence regarding the effectiveness of facial emotion recognition programs for behaviour post TBI.

Psychoeducation

Psychoeducation interventions have been used in healthcare to help patients understand and manage their mental health condition by reinforcing their individual skills and resources to be able to better cope with their situation (Casañas et al., 2012). Psychoeducation is based on providing patients and families with information about their illness to enable them to understand their condition better and to adhere to medical treatment; for instance, psychoeducation has been used to help individuals with bipolar disorder and their family members to identify mood episodes (Rabelo et al., 2021).

TABLE 71 | Psychoeducation for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Neumann et al. (2017) USA Pre-Post N=17	**Population:** TBI=17; Mean Age=46.12yr; Gender: Male=13, Female=4; Mean Time Post Injury=8.73yr; Mean PTA=95.35d; Mean LOC=14.18d. **Intervention:** Eight lessons incorporated psycho-educational information and skill-building exercises teaching emotional vocabulary, labeling, and differentiating self-emotions; interoceptive awareness; and distinguishing emotions from thoughts, actions, and sensations. **Outcome Measures:** Toronto Alexithymia Scale (TAS-	1. There was a small but significant effect on anger as measured by the STAXI.

Author Year Country Study Design Sample Size	Methods	Outcome
	20), Levels of Emotional Awareness Scale (LEAS), State Trait Anxiety Inventory (STAI), Patient Health Questionnaire (PHQ-9) - Depression, State Trait Anger Expression Inventory (STAX-2I), Positive and Negative Affect Scale (PANAS), Difficulty with Emotion Regulation Scale (DERS), Satisfaction Questionnaires.	

Discussion

In a pre-post study, Neumann et al. (2017) implemented a psychoeducational information and skill-building exercises program for post TBI individuals. The program involved teaching emotional vocabulary, labelling and differentiating emotions, as well as the distinction between actions, sensations and emotions. The authors found a small but significant effect in anger, as measured by the State Trait Anger Expression Inventory (STAX-2I) (Neumann et al., 2017). Further research with larger sample sizes is needed to determine the effectiveness of this intervention.

Conclusions

There is level 4 evidence (Neumann et al., 2017) that psychoeducation may be effective for the management of anger in individuals with TBI.

KEY POINTS

- Psychoeducation may be effective for anger post TBI; however, further research is needed.

Music Therapy

Music therapy has been used to reduce agitation and other intrusive behaviours in individuals with Alzheimer's disease (Zare et al., 2010). However, there is limited research on the use of music therapy for the management of agitation, anger and aggression post ABI.

TABLE 72| Music Therapy for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Park et al. (2016) USA RCT Crossover	**Population:** Severe TBI; Male=11, Female=3; Mean age=34.64yr; Mean time post-injury=40d. **Intervention:** Patients with cognitive impairment and agitation post severe TBI listened to either preferred	1. Patients listening to preferred music demonstrated a significantly greater decrease in ABS scores when compared

Author Year Country Study Design Sample Size	Methods	Outcome
PEDro=8 N=14	music or classical "relaxation" music for 1h in a randomized order with a 1d washout period between conditions. Outcome measures were assessed 3hxd. **Outcome Measures:** Agitated Behavior Scale (ABS).	with the effect of "relaxation" music (p=0.046).
Formisano et al. (2001) Italy Case Series N=34	**Population:** TBI=18, Other=16; Mean Age=35.9yr; Gender: Male=17, Female=17; GCS Score<8. **Intervention**: Patients received music therapy treatment based on Nordoff & Robbins, 20-40min for 3x/wk during rehabilitation. Evaluation occurred at six different time points. **Outcome Measure:** Undesired behaviours, Glasgow Outcome Scale, Disability Rating Scale (DRS), Coma Recovery Scale (CRS).	1. During music therapy, patients showed a reduction in undesired behaviours. 2. Positive effects were reported in 27 of 34 patients 1mo after starting treatment and at follow-up. 3. No improved interaction with the environment was recorded (DRS, CRS).

Discussion

In an RCT crossover, Park et al. (2016) allocated individuals with severe TBI and agitation to either their preferred music or classical 'relaxation' music. The authors found that participants who listened to their preferred music showed a greater decrease in agitation scores, compared to classical music. It should be noted that the intervention was delivered by a researcher, as opposed to a music therapist (Park et al., 2016).

In a case series study, Formisano et al. (2001) reported that music therapy had a beneficial effect in reducing post-coma agitation following ABI. However, given the lack of both prospective data and statistical analysis in this study, further research is required to determine the effect of music therapy on agitation or aggressive behaviour post ABI.

Conclusions

There is level 1a evidence (Park et al., 2016) that preferred music may reduce agitation in individuals with severe TBI who present with agitated behaviour in acute care.

There is level 4 evidence (Formisano et al., 2001) that music therapy may reduce post-coma agitation in individuals with ABI; however, further research is needed.

KEY POINTS

- Listening to preferred music may decrease agitation in individuals with severe TBI.
- Music therapy may reduce post-coma agitation following ABI.

Biofeedback Training

Biofeedback training is a promising intervention for the management of anxiety and stress. In a meta-analysis, Goessl et al. (2017) found that heart rate variability biofeedback was associated with a reduction in stress and anxiety in both clinical settings and in the community. Neurofeedback is a type of biofeedback that has been used for the treatment of depression and anxiety in non-TBI populations (Hammond, 2005). There is limited information evaluating the role for neurofeedback training in individuals with ABI.

TABLE 73 | Biofeedback Training for the Management of Agitation, Anger and Aggression post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Elbogen et al. (2021) USA Pre-Post $N_{Initial}$=41, N_{Final}=36	**Population:** TBI; Gender: Male=35, Female=6; Mean Age=38.57yr; Mean GCS=Not Reported; Time Post-Injury=13.11yr; PTA >1hr=64%. **Intervention:** Participants were instructed to perform "mobile neurofeedback" using a portable EEG headset linked to an application on a mobile device. The duration was 10min sessions, 4x/wk, for 3mo. Outcomes were assessed at baseline and at 3-mo. **Outcome Measure:** Regional Pain Scale, Patient-Reported Outcomes Measurement Information System (PROMIS), PTSD Checklist for DSM-5 (PCL-5), Patient Health Questionnaire (PHQ-9).	1. Veterans displayed significantly reduced anger scores as measured by PROMIS (p=.016).

Discussion

In a pre-post by Elbogen et al., 2021) participants used a portable EEG neurofeedback headset linked to an application on a mobile device. The authors found that, at follow-up, participants reported significantly reduced anger scores, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) (Elbogen et al., 2021).

Conclusion

There is level 4 evidence (Elbogen et al., 2021) that a mobile neurofeedback device may reduce anger in individuals with TBI.

KEY POINTS

- Biofeedback training may be effective for anger in individuals with moderate to severe TBI.

Peer Support

There is limited literature on peer support interventions in the TBI population. In a systematic review, Hughes et al. (2020) found that peer support groups for individuals with ABI result in several benefits such as feeling connected and interacting with others, as well as providing and receiving support.

TABLE 74 | Peer Support for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Hanks et al. (2012) USA RCT PEDro=5 N=96	**Population:** TBI=96; Gender: Male=74, Female=22; Caregivers=62; Peer Mentored Group: Mean Age=38.46yr; Mean GCS=9.39. TBI Control Group: Mean Age=40.90yr; Mean GCS=9.8. Caregiver Mentored Group: Mean Age=51.87 yr. Caregiver Control Group: Mean Age=50.18yr. **Intervention:** Participants and caregivers were randomly assigned to either a peer mentoring program or to a control group. Discussions in mentoring sessions included emotional well-being, post-TBI quality of life, and community integration. **Outcome Measures:** Peer Mentoring Questionnaire, Family Assessment Device (FAD), Coping Inventory for Stressful Situations (CISS-21), 12-Item Short-Form Health Survey (SF-12), Brief Symptom Inventory-18 (BSI-18), Community Integration Measure (CIM), Short Michigan Alcoholism Screening Test (SMAST).	1. There was no difference between groups in anxiety (p=0.31) and depression symptoms (p=07). 2. The mentored group had decreased somatic symptoms of emotional distress, less emotion-focused (p=0.04) and avoidance coping (p=0.03), as well as lower alcohol use (p=0.01) and fewer somatic symptoms of emotional distress. 3. Individuals who received mentoring had significantly better behavioral control and less chaos in the living environment (p=0.04).

Discussion

In an RCT by Hanks et al. (2012), participants with TBI and their caregivers were randomly assigned either to a peer mentoring program or a control group. The peer mentoring program included discussions on emotional well-being, quality of life post TBI and reintegration to the community. The authors found that the mentored group reported significantly better behavioural control and less chaos in the living environment, compared to the control group (Hanks et al., 2012).

Conclusions

There is level 2 evidence (Hanks et al., 2012) that peer support may decrease behavioural dyscontrol in those with moderate to severe TBI.

KEY POINTS

- Peer support may be effective for the management of behavioural dyscontrol post moderate to severe TBI. However, more research is needed.

Sensory Stimulation

Sensory stimulation programs provide sensory-specific stimuli to individuals with disorders of consciousness post ABI, including sound, familiar and unfamiliar voices, music, and touch (Padilla & Domina, 2016).

TABLE 75 | Sensory Stimulation for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Sedghi et al. (2020) Iran RCT PEDro=7 N=80	**Population:** Severe TBI; *Intervention* (n=40); Gender: Male=26, Female=14; Mean age=36.4yr; *Control* (n=40); Gender: Male=24, Female=16; Mean age=40.22yr; Time post-injury=24-48h. **Intervention:** Patients were randomly allocated to the intervention or control group. Those in the intervention group received auditory and sensory stimulation from a family member 10min/d for 7d. Data was collected at baseline, prior to each intervention session, and 30min postintervention. **Outcome Measures:** Richmond Agitation and Sedation Scale (RASS).	1. Patients who received stimulation from their family members demonstrated significantly lower RASS scores ($p<0.01$).

Discussion

In an RCT study, Sedghi et al. (2020) examined the effect of auditory and tactile stimulation on agitation in individuals with severe TBI who presented with decrease consciousness in the intensive care unit (ICU). Participants in the intervention group received stimulation from a family member, who shared happy memories with the patient and touched their hand. The authors found that individuals who received sensory stimulation had significantly lower agitation scores, as measured by the Richmond Agitation and Sedation Scale RASS).

Conclusions

There is level 1b evidence (Sedghi et al., 2020) that auditory and tactile stimulation may decrease agitation in individuals with decreased consciousness.

KEY POINTS

- Auditory and tactile stimulation delivered by a family member may decrease agitation in individuals admitted to the ICU with decreased consciousness post severe TBI.

Post-Traumatic Amnesia Interventions

Behavioural disturbances are common during the period of post-traumatic amnesia (PTA), especially agitated behaviour that is characterized by disinhibition, impulsivity, aggression, restlessness and emotional liability (Ponsford et al., 2023).

TABLE 76| Post-Traumatic Amnesia Interventions for Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Trevena-Peters et al. (2018) Australia RCT PEDro=7 $N_{initial}$=134, N_{final}=104	**Population:** Severe TBI. *Treatment* (n=49): Male=36, Female=13; Mean age=45.78yr; Mean time post-injury=16.12d. *Control* (n=55): Male=41, Female=14; Mean age=40.24yr; Mean time post-injury=16.76d. **Intervention:** Patients were randomized to receive either daily activities of daily living (ADL) retraining in addition to standard care, or standard care alone. Patients were assessed at baseline, Posttraumatic amnesia emergence, discharge, and 2mo follow-up. **Outcome Measures:** Functional Independence Measure (FIM), Agitated Behavior Scale (ABS), Community Integration Questionnaire (CIQ), Westmead Post-Traumatic Amnesia Scale (WPTAS).	1. There were no significant results observed between the groups using ABS, CIQ, or WPTAS scores (p>0.05). 2. Stimulation received by the treatment condition did not affect agitation levels on the ABS.

Discussion

In an RCT, Trevena-Peters et al. (2018) examined the effectiveness of activities of daily living retraining during the post-traumatic amnesia (PTA) period, compared to retraining after emergence from PTA. The authors found no significant group differences in agitation, as measured by the Agitated Behavior Scale (ABS).

Conclusions

There is level 1b evidence (Trevena-Peters et al., 2018) that activities of daily living retraining during the period of PTA or after emergence from PTA may not be different for agitation in individuals with TBI.

KEY POINTS

- Activities of daily living retraining during or after PTA may not have an effect on agitated behaviour in individuals with severe TBI.

Pharmacological Interventions

Agitation is often a recovery-limiting factor, as it creates both a disruptive and unsafe environment for rehabilitation (Rosati, 2002). An ideal medication should have "a rapid onset of action, achieve maximal effect with a single dose, cause minimal adverse effects, and allow the patient to resume normal daily activities as quickly as possible without causing protracted sedation or cognitive impairments" (Stanislav & Childs, 2000). Pharmacological interventions used to treat agitation include a variety of medications such as: antidepressants, stimulants, anticonvulsants, antipsychotics, and beta-blockers. Ideally, the safety and efficacy of pharmacological interventions for agitation and aggression would be studied using an RCT design; however, few of these trials have been conducted in ABI (Levy et al., 2005; Williamson et al., 2018). Moreover, due to the lack of consistency in measuring agitation and aggression (Baguley et al., 2006), comparing studies is challenging.

In a systematic review, Williamson et al. (2018) examined controlled trials of pharmacological interventions for agitated behaviours in patients with mixed severity of TBI. The authors concluded that propranolol, methylphenidate, valproic acid and olanzapine may offer some benefit, where as sertraline, lisdexamfetamine and dextroamphetamine were not supported. Additionally, antipsychotics could increase the length of post traumatic amnesia and decrease cognitive function (Williamson et al., 2018). In another systematic review that included case-series and case-report studies, Nash et al. (2018) reported weak support for the use of propranolol and antiepileptics. Nash et al. (2018) concluded that amantadine was among the best supported medications in acute management of behavioral and emotional dysregulation. Williamson et al. (2018) reported mixed findings for the use of amantadine and cautioned that it may increase agitation in acutely ill patients. Overall, both reviews commented on the paucity of high-quality primary research, expressing a need for more tailored trials, in various stages of recovery, and standardized assessments of agitated behaviours (Nash et al., 2018; Williamson et al., 2018).

Sertraline

Depression is a common correlate of agitation and aggression following ABI, which may be linked to serotonergic , dopaminergic, and noradrenergic dysfunction resulting from injury (Jorge, 2005). Sertraline is an antidepressant within the selective serotonin reuptake inhibitors (SSRIs) class, and it has been used to treat conditions such as major depressive disorder, panic disorder, PTSD and social anxiety (Singh & Saadabadi, 2019). While antidepressants such as sertraline have been recommended to treat agitation and aggression in individuals with TBI, antidepressants may also have adverse effects and increase confusion, sleepiness and/or anxiety, nausea and may potentially increase the risk of suicidal attempts (Plantier & Luaute, 2016). There is limited research on the use of sertraline for agitation, anger and aggression post ABI.

TABLE 77 | Sertraline for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Fann et al. (2017) USA RCT PEDro=9 N=62	**Population:** *Sertraline* (n=31); Gender: Male=23, Female=8; Mean age=38yr; Mean time post-injury=4.3mo; Severity: Mild=16, Moderate=6, Severe=9. *Placebo* (n=31); Gender: Male=24, Female=7; Mean age=36.9yr; Mean time post-injury=4.9mo. TBI severity: Mild=13, Moderate=7; Severe=11. **Intervention:** Patients were randomized to receive either sertraline or placebo daily for 12wk. Outcomes were assessed at baseline, 1, 3, 6, 8, 10, and 12wk. **Outcome Measures:** Hamilton Anxiety and Depression Scale (HAM-D)-17 Item, Symptom Checklist-20, Clinician-rated Clinical Global Impression scale (CGI), Short Form 36 (SF-36), Sheehan Disability Scale, Trail Making Test B, Head Injury Symptom Checklist, Brief Anger and Aggression Questionnaire (BAAQ), Brief Pain Inventory, Hamilton Anxiety Rating Scale (HAM-A).	1. Depression significantly improved from baseline to 12 weeks in both treatment groups ($p<0.001$). 2. There were no statistically significant differences between treatment groups for depression (HAM-D), anxiety (HAM-A) or anger and aggression (BAAQ).
Banos et al. (2010) USA RCT PEDro=9 N=99	**Population:** Severe TBI; *Treatment* (n=49): Mean age=35.3; Male=39, Female=10; Mean time post-injury=21.5d. *Placebo* (n=50): Mean age=34.5; Male=33, Female=17 Mean time post-injury=19.2d. **Intervention:** Participants were randomly assigned to receive 50mg of sertraline or placebo daily for 3mo. Outcomes were assessed at 3, 6, and 12mo after injury. **Outcome Measures:** Wechsler Adult Intelligence Scale-III (WAIS-III), Symbol Digit Modalities Test (SDMT), Wechsler Memory Scale-III (WMS-III), Trail Making Test A, Trail Making Test B, Wisconsin Card Sorting Test (WCST), Neurobehavioral Functioning Inventory (NFI).	1. There were no significant between-group treatment effects on challenging behaviour, as measured by the NFI scores ($p>0.05$).
Meythaler et al. (2001) USA RCT PEDro=5 N=9	**Population:** Severe TBI; Time post-injury < 2wks; Age=14-65y. Sertraline group: n=6. Placebo group: n=3. **Intervention:** Patients were randomized to receive 50mg of sertraline or placebo in the morning and afternoon every day for 2 weeks. Subjects were assessed at baseline and post-intervention. **Outcome Measures:** Orientation Log (O-Log), Agitated Behaviour Scale (ABS), Galveston Orientation and Amnesia Test (GOAT)	1. There were no significant effects of sertraline use observed in the treatment group when compared to the control ($p>0.05$) on agitation, as measured by the ABS.
Kant et al. (1998) USA Pre-Post N=13	**Population:** TBI; Mean Age=37.6yr; Gender: Male=10, Female=3; Injury Severity: Mild=5, Moderate=6, Severe=6; Mean Time Post Injury=2yr. **Intervention:** Participants with aggression received sertraline (50-200 mg/day) for 8 wk. Assessments were conducted at 4wk and 8wk. **Outcome Measure:** Overt Aggression Scale-Modified (OAS-M), Anger Irritability Assault Questionnaire (AIAQ), Beck Depression Inventory (BDI).	1. Significant improvement on OAS-M ($p<0.001$) and AIAQ ($p<0.01$) found at 4wk and 8wk. 2. Significant improvement on BDI found at 4wk ($p=0.04$) but not 8wk ($p=0.14$).

Discussion

In an RCT study, Banos et al. (2010) examined the effects of sertraline, compared to placebo, for cognition and behavioural recovery post TBI. The authors found no significant differences in challenging behaviour, such as aggression, as measured by Neurobehavioural Functioning Inventory (NFI). Similarly, in an RCT by Fann et al. (2017), sertraline was no different than placebo for the treatment of major depression following a TBI. In a pre-post study, Kant et al. (1998) found that patients who received sertraline responded positively at both four and eight week follow-ups, showing significant reductions in aggressive and irritable behaviour. As for agitated behaviour, sertraline was not found to be effective compared to placebo in an RCT by Meythaler et al. (2001).

Conclusions

There is level 1b evidence (Banos et al., 2010; Fann et al., 2017) that sertraline may not reduce challenging behaviours such as aggression and anger, compared to placebo, post moderate to severe TBI.

There is level 2 evidence (Meythaler et al., 2001) that sertraline may not reduce agitation, compared to placebo, in individuals with severe TBI.

There is level 4 evidence (Kant et al., 1998) that sertraline may reduce irritability post TBI.

KEY POINTS

- Sertraline may be an effective treatment for irritability; however, it may not be effective for the management of aggression and anger in those with moderate to severe TBI.
- Sertraline may not be effective for agitation post severe TBI.

Amitriptyline

Amitriptyline is a tricyclic antidepressant (TCA) drug that acts by blocking the reuptake of both serotonin and norepinephrine neurotransmitters, and it has been commonly used to treat conditions such as depression, PTSD, insomnia, diabetic neuropathy, fibromyalgia (Thour & Marwaha, 2019). Amitriptyline is an antidepressant that has not been commonly used to treat agitation after TBI; however, a low dose during the awakening period has been reported to reduce agitation (Plantier & Luaute, 2016). There is limited research on the use of amitriptyline for agitation, anger and aggression post ABI.

TABLE 78 | Amitriptyline for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Mysiw et al. (1988) USA Cohort N=58	**Population:** TBI; *Amitriptyline* (n=20), Mean Age=29.4yr, Gender: Male=18, Female=2, Mean PTA=11.9wk; *No Durg* (n=38), Mean Age=25.6yr, Gender: Male=25, Female=13; Mean PTA=9.8wk. Mean Age=29.4yr; Gender: Male=18, Female=2; **Intervention:** Participants with persistent agitation failing to respond to conventional behavioural techniques received amitriptyline (25-150 mg/day). Assessments were conducted at 1wk and follow-up. **Outcome Measure:** Orientation Group Monitoring Scale (OGMS).	1. Thirteen patients experienced significantly reduced levels of agitation after 1wk ($p<0.001$), which was maintained in the ensuing weeks ($p<0.001$) but did not significantly decrease from 1wk ($p>0.6$). 2. Thirty percent of patients (n=6) experienced no significant change in agitation levels, despite increasing the dose at 1wk ($p>0.7$) and beyond ($p>0.3$).

Discussion

In a cohort study, Mysiw et al. (1988) found that 65% of patients displayed significant reductions in agitation within the first week of treatment with amitriptyline (Mysiw et al., 1988). However, given the scarcity of more recent evidence, findings should be interpreted with caution.

Conclusions

There is level 2 evidence (Mysiw et al., 1998) that amitriptyline may reduce agitation post TBI.

KEY POINTS

- Amitriptyline may be an effective treatment for reducing agitation post TBI; however, further research is needed.

Amantadine

Amantadine is a antiviral agent originally used to treat influenza; however, it is now used mostly to treat Parkinson disease, particularly for the management of tremors, rigidity and bradykinesia (Chang & Ramphul, 2018). Amantadine has been used as a wakefulness-promoting agent with a positive effect on cognition (Plantier & Luaute, 2016). While Amantadine has been commonly prescribed for Parkinson's disease, and for cognitive recovery post ABI (Loggini et al., 2020); there is limited research on the use of amantadine for challenging behaviours in this population.

TABLE 79 | Amantadine for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Hammond et al. (2017) USA RCT PEDro=9 $N_{initial}$=168, N_{final}=112	**Population:** *Amantadine 100mg (n=82)*: TBI: Mild=22, Moderate=1, Severe=27, Other=36; Male=64, Female=22; Median age=38.1yr; Median time post-injury=7.6yr. *Placebo (n=86):* TBI: Mild=20, Moderate=, Severe=18, Other=40; Male=66, Female=16; Median age=38.6yr; Median time post-injury=6.3yr. **Intervention:** Patients were randomly allocated to take either 100mg of Amantadine or placebo every morning and noon for 6d. Outcomes were assessed at baseline and at 28d and 60d. **Outcome Measures:** Neuropsychiatric Inventory (NPI), State-Trait Anger Expression Inventory (STAXI-2).	1. Change in Participant-rated NPI-A Most Problematic was statistically significant (p=0.0118) in favor of amantadine. 2. There were no significant differences in anger, as measured by the STAXI-2 scores.
Hammond et al. (2015) USA RCT PEDro=10 $N_{Initial}$=168, N_{Final}=157	**Population:** TBI. *Amantadine Group (n=82)*: Mean Age=40.2yr; Gender: Male=66, Female=16; Severity: Mild=20, Moderate=3, Severe=59. *Placebo Group (n=86)*: Mean Age=38.2yr; Gender: Male=64, Female=22; Severity: Mild=22, Moderate=1, Severe=63. **Intervention:** Participants were randomized to receive either placebo or 100 mg of amantadine 2x/day for 60 days. Assessments were conducted at baseline, 28 days, and 60 days. **Outcome Measure:** Neuropsychiatric Inventory Irritability (NPI-I).	1. Observer-rated NPI-I scores showed no significant differences between groups at 28d or 60d, but both groups showed improvement in irritability. 2. Participant-rated NPI-I Most Problematic (p=0.0353) and Distress (p=0.0362) scores were significantly different between amantadine and placebo at 60d, but there was no significant difference after adjustment for multiple comparisons.
Hammond et al. (2014) USA RCT PEDro=9 $N_{Initial}$=76, N_{Final}=72	**Population:** TBI. *Amantadine Group (n=38)*: Mean Age=34.7yr; Gender: Male=25, Female=13; Mean Time Post Injury=5.3yr; Mean GCS=9.5. *Placebo Group (n=38)*: Mean Age=42.1yr; Gender: Male=22, Female=16; Mean Time Post Injury=4.7yr; Mean GCS=7.5. **Intervention:** Participants were randomized to receive placebo or 100 mg of amantadine 2x/day for 28 days. Assessments were conducted at baseline and 28 days. **Outcome Measure:** Neuropsychiatric Inventory (NPI) Irritability (NPI-I), NPI Agitation/ Aggression (NPI-A), NPI Distress (NPI-D), Beck Depression Inventory-II (BDI-II), Brief Symptom Inventory (BSI), Global Mental Health Scale (GMHS).	1. Eighty-one percent of the amantadine group had improved irritability by at least 3 points on NPI-I, compared to 44% of placebo (p=0.0016). 2. Significant difference in frequency and severity of irritability on NPI-I between amantadine and placebo groups (p=.0085). 3. No significant differences between amantadine and placebo groups on NPI-D, BDI-II, BSI-Anxiety, or GMHS. 4. Only individuals with moderate to severe aggression at baseline on NPI-A had significant reduction in aggression after amantadine treatment compared to placebo (p=0.046).
Meythaler et al. (2002) USA RCT Crossover PEDro=6 N=35	**Population:** TBI; Mean Age=31yr; Gender: Male=26, Female=9; Time Post Injury<6 wk; Mean GCS=5.4. **Intervention:** Patients received amantadine at 200mg/ day (Group 1, n=15) or placebo (Group 2, n=20) for 6 wk, after which they received the alternate treatment for 6 wk. **Outcome Measures:** Disability Rating Scale (DRS), Mini mental Status Test (MMSE), Glasgow Outcome Scale (GOS), Galveston Orientation and Amnesia Test (GOAT), and Functional Independence Measure (FIM), Agitated Behavioral Scale (ABS).	1. No significant group difference in agitated behaviour as measured by the ABS.

Author Year Country Study Design Sample Size	Methods	Outcome
Schneider et al. (1999) USA RCT Crossover PEDro=5 N=10	**Population:** TBI; Mean Age=31yr; Gender: Male=7, Female=3; GCS Score Range=3-11. **Intervention:** Patients were randomized to either amantadine (50-150mg 2x/d) or placebo for 2wk in a crossover design with a 2wk washout period. **Outcome Measures:** Battery of Neuropsychological tests, Neurobehavioural Rating Scale.	1. There was a general trend towards improvement in the study sample over the 6wk. 2. There were no significant differences between groups (p=0.737) in behaviour such as inattention, disinhibition, and agitation.

Discussion

Five RCTs examined the effects of amantadine on behaviour post-TBI. Hammond et al. (2014) found that the frequency and severity of irritability were reduced when individuals received amantadine for 28 days compared to placebo. However, amantadine only significantly reduced aggression in individuals who had moderate to severe aggression at baseline (Hammond et al., 2014). A subsequent trial by Hammond et al. (2015) found that amantadine produced a non-significant reduction in irritability compared to placebo at 28 and 60 days (Hammond et al., 2015). Hammond et al. (2017) found that participants who received 100mg twice daily of amantadine showed decreased aggression; however, no beneficial impact on anger was observed. In two RCTs, the authors found that amantadine was not effective for the management of agitated behaviour compared to placebo (Meythaler et al., 2002; Schneider et al., 1999).

Conclusions

There is level 1b evidence (Hammond et al., 2014; 2015) that amantadine may reduce aggressive behaviour among those with moderate to severe aggression post TBI. However, evidence is conflicting regarding the use of amantadine for the reduction of irritability.

There is level 1b evidence (Hammond et al., 2017) that amantadine may not reduce anger post TBI.

There is level 1b evidence (Meythaler et al., 2002) and level 2 evidence (Schneider et al., 1999) that amantadine may not be effective for the management of agitation post TBI.

KEY POINTS

- Amantadine may be effective for the treatment of aggression in individuals with TBI; however, evidence is conflicting regarding its effectiveness in reducing irritability. Amantadine may not be effective for the management of anger.
- Amantadine may not improve agitated behaviour following a moderate to severe TBI.

Methylphenidate

In a systematic review, Fleminger et al. (2006) found that the evidence in favor of the use of psychostimulants, such as methylphenidate, for the management of agitation and aggression is poor and it must be weighed against the risks of adverse mental side effects, particularly in individuals vulnerable to drug abuse. There is limited research on the use of methylphenidate for agitation, anger and aggression post ABI.

TABLE 80 | Methylphenidate for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Jenkins et al. (2019) UK RCT Crossover PEDro=9 $N_{Initial}$=46, N_{Final}=40	**Population:** TBI=40; *Methylphenidate first* (n=20): Mean Age= 40yr; Gender: Male=18, Female=2; Mean Time Post Injury=67mo; Mean GCS=8.3. *Placebo First* (n=20): Mean Age=39yr; Gender: Male=16, Female=4; Mean Time Post Injury=67mo; Severity: Mean GCS=8.3. **Intervention:** Participants were randomized to receive 0.3mg/kg of methylphenidate (treatment group) 2x/d for 2wk with crossover to placebo (control group) 2x/d for 2wk and vice versa. Outcome measures were assessed at baseline, at 2 wk, and at 4wk. **Outcome Measures:** Choice Reaction Time (CRT) Task, Single-Photon Emission Computed Tomography (SPECT), Trail Making Test (TMT), Delis-Kaplan Executive Function System (D-KEFS), Stroop Color Word Test, Wechsler Memory Scale - People Test, Wechsler Abbreviated Scale for Intelligence (WASI), Lille Apathy Rating Scale (LARS), Visual Analogue Scale for Fatigue (VAS-F), Glasgow Outcome Scale-Extended (GOSE), Hospital Anxiety and Depression Scale (HADS), Frontal Systems Behaviour Scale (FrSBe), Cognitive Failures Questionnaire (CFQ), Rating Scale of Attentional Behaviour (RSAB).	1. Individuals with low caudate Dopamine Transporter (DaT) showed significant improvements in self-reported apathy (p=0.03). 2. No significant difference in challenging behaviour, as measured by the Frontal Systems Behaviour Scale (FrSBe).
Mooney & Haas (1993) USA RCT PEDro=5 N=38	**Population:** Severe TBI; Mean Age=29.45yr; Gender: Male=38, Female=0; Mean Time Post Injury=27.08mo. **Intervention:** Patients received methylphenidate (30 mg/day; n=19) or placebo (n=19) for 6 wk. **Outcome Measure:** State Trait Anger Expression (STAXI), Katz Adjustment Scale (KAS), Profile of Mood State Questionnaire (POMS).	1. After controlling for differences in baseline anger scores, there was a significant main effect for the drug treatment (p<0.001). 2. For all of the anger outcome measures, a significant drug by time interaction effect was noted (p=0.002).

Discussion

In an RCT, Mooney and Haas (1993) found that methylphenidate significantly reduced anger following brain injury, as measured by several anger outcome measures. Despite the differences between the

groups on one measure at baseline, the authors found a significant treatment effect. In an RCT, Jenkins et al. (2019) found no significant differences in challenging behaviour, as measured by the Frontal Systems Behaviour Scale (FrSBe).

Conclusions

There is conflicting evidence (Jenkins et al., 2019; Mooney & Haas, 1993) regarding the effectiveness of methylphenidate for the management of challenging behaviours such as disinhibition, executive dysfunction and anger post TBI. Further research is needed.

KEY POINTS

- Further Research is needed to determine whether or not methylphenidate is effective for the management of challenging behaviours following a moderate to severe TBI.

Dextroamphetamine

Amphetamine is a stimulant drug used to mange narcolepsy and attention deficit hyperactivity disorder (ADHD) (Martin & Le, 2020). There is very limited research on the use of dextroamphetamine for agitation, anger and aggression post ABI.

TABLE 81 | Dextroamphetamine for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Hart et al. (2018) USA RCT PEDro=10 N=32	**Population:** TBI=32; *DEX group (n=17)* Mean Age=39.6yr; Gender: Male=11, Female=6; Mean Time Post Injury=53.6d; Mean GCS=8.2. *Placebo group (n=15)* Mean Age=38.7yr; Gender: Male=15, Female=0; Mean Time Post Injury=60.2d; Mean GCS=7.5. **Intervention:** Participants were randomly allocated to either be administered 10mg of dextroamphetamine (DEX), or an identical placebo daily for 3 weeks. Outcome measures were completed at weekly intervals. **Outcome Measures:** Moss Attention Rating Scale (MARS), Hopkins Rehabilitation Rating Scale (HRER), Cognitive Failures Questionnaire (CFQ), Rating Scale of Attentional Behavior (RSAB), Finger Tapping Test (FT), Symbol Digit Modalities Test (SDMT), Functional Independence Measure (FIM), Disability Rating Scale (DRS), Agitated Behavior Scale (ABS), Profile of Mood States (POMS).	1. Significant group differences for ABS score between DEX and placebo group (p=0.04). 2. Between group difference approached significance (p=0.07) for SDMT score 3. No other significant between group differences were detected.

Discussion

In an RCT, Hart et al. (2018) compared the effects of 10mg of dextroamphetamine (DEX) to an identical placebo for the management of agitation and aggression post TBI. Each intervention condition was implemented for 3 weeks with outcome measures taken each week. The authors found that the Agitated Behavior Scale (ABS) slope was positive in the intervention group, indicating more agitation over time, while the placebo indicated the opposite trend; however, the differences showed no statistical significance.

Conclusions

There is level 1b evidence (Hart et al., 2018) that dextroamphetamine may not reduce agitated behaviour in individuals with TBI.

KEY POINTS

- Dextroamphetamine may not reduce agitation post severe TBI.

Carbamazepine

Carbamazepine is an anticonvulsant often well tolerated by patients and with low risk of adverse neurological side effects (Fleminger et al., 2006). There is limited research on the use of carbamazepine for agitation, anger and aggression post ABI.

TABLE 82 | Carbamazepine for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Azouvi et al. (1999) France Pre-Post N=10	**Population:** TBI; Mean Age=33.7yr; Gender: Male=8, Female=2; Mean GCS Score=5.3; Mean Time Post Injury=58 wk. **Intervention:** Patients received carbamazepine (mean dose=9.47±2.9 mg/kg/day) for 8 wk. **Outcome Measure:** Neurobehavioural Rating Scale (NRS), Agitated Behaviour Scale (ABS), Katz Adjustment Scale (KAS), Mini-Mental Status Examination (MMSE).	1. Total NRS-R and ABS scores showed significant improvement (p=0.02); improvements plateaued after 2 wk. 2. At follow-up, significant improvements were shown for only the irritability (p<0.01) and disinhibition (p<0.05) portions of NRS-R. 3. Global NRS-R significantly decreased from baseline (p=0.01). 4. No significant changes on MMSE were observed (p>0.01).

Discussion

In pre-post study, Azouvi et al. (1999) examined the use of carbamazepine to treat 10 individuals with severe brain injury and significant behavioural challenges that were interfering with care and/or family

integration. After two weeks, results indicated improvement on behavioural scales but only the improvements in irritability and disinhibition were maintained by the end of the trial. Overall neurobehavioural and social functioning outcomes had improved. It should be noted that drowsiness was a frequent adverse event which limited a dosage increase in 40% of the participants.

Conclusions

There is level 4 evidence (Azouvi et al., 1999) that carbamazepine may reduce agitation, irritability and disinhibited behaviour post TBI.

KEY POINTS

- Carbamazepine may reduce agitated behaviour, disinhibition and irritability post TBI. However, more research with larger samples is needed.

Lamotrigine

Lamotrigine is anticonvulsant that has been used to manage in mood in individuals with bipolar disorders (Pachet et al., 2003). Off-label uses of this medication include fibromyalgia, schizophrenia, and unipolar depression (Betchel et al., 2023). There is limited research on the use of lamotrigine for agitation, anger and aggression.

TABLE 83 | Lamotrigine for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Chahine & Chemali (2006) Lebanon Case Series N=4	**Population:** Severe TBI; Mean Age=26yr; Gender: Male=4, Female=0. **Intervention:** Lamotrigine (range 125 to 300mg/d) to reduce inappropriate behaviours (e.g., laughing, impulsivity or verbal aggression). **Outcome Measure:** Frequency of crying, pathological laughing, behaviours of impulsivity, and seizures. Also, notes of depression.	1. All behaviours decreased once the patient was placed on lamotrigine. 2. Crying decreased and inappropriate laughing ceased. 3. Impulsivity did not cease.

Discussion

In a case study, Chahine and Chemali (Chahine & Chemali, 2006) found that lamotrigine may help to reduce challenging behaviours post severe TBI, such as pathologic laughter and crying. All four participants in this study were on other medications to control for additional behaviours, but these

medications were eventually eliminated once lamotrigine was introduced. No formal outcome assessments were conducted; therefore, results from this study need to be interpreted with caution.

Conclusions

There is level 4 evidence (Chahine & Chemali, 2006) that lamotrigine may reduce pathological laughter and crying post severe TBI; however, it may not decrease impulsivity.

KEY POINTS

- Lamotrigine may be effective in reducing challenging behaviours in individuals with severe TBI. However, further research with larger samples and standardized outcome measures is needed.

Valproic Acid

Valproic acid is a medication that has been used for the treatment of epilepsy, with some off-label applications including management of bipolar disorder, migraine prophylaxis and behavior disorders. In a systematic review, Williamson et al. (2019) found that while valproate acid may have a potential benefit in reducing agitation, anger or irritability, the majority of the studies on this medication have been conducted in heterogenous populations with limited sample sizes (Williamson et al., 2019). There is limited research on the use of valproic acid for agitation, anger and aggression in individuals with TBI.

TABLE 84 | Valproic Acid for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Wroblewski et al. (1997) USA Case Series N=5	**Population:** Moderate to Severe TBI; Mean Age=38.2yr; Gender: Male=4, Female=1. **Intervention:** Patients received valproic acid for destructive and aggressive behaviours. **Outcome Measure:** Aberrant Behaviour Checklist.	1. All patients showed a substantial reduction in destructive and aggressive behaviours.

Discussion

Wroblewski et al. (1997) examined the effects of valproic acid on reducing aggressive behaviour in a case series of five patients. The study reported that all patients showed a substantial reduction in challenging behaviour (i.e., outbursts, agitation, and anger) within one to two weeks, even when other medications were not successful. No statistical analyses were conducted, making it difficult to draw conclusions from

these findings. In addition, patients in thus study were part of a specialized neurobehavioural unit, which may have contributed to the positive results.

Conclusions

There is level 4 evidence (Wroblewski et al., 1997) that valproic acid may reduce aggression post moderate to severe TBI; however, further research is needed.

KEY POINTS

- Valproic acid may be effective in reducing aggression and agitation in individuals with a TBI; however, further research with larger sample sizes and standardized outcome measures is needed.

Divalproex

Divalproex is an anticonvulsant frequently prescribed for individuals with bipolar disorder, particularly to treat depression (Bond et al., 2010). There is limited research on the use of divalproex for agitation, anger and aggression in individuals with TBI.

TABLE 85 | Divalproex for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Chatham Showalter & Kimmel (2000) USA Case Series N=29	**Population:** Severe ABI, TBI=28; Mean Age=48.2yr; Mean Time Post Injury=28.6d. **Intervention:** A retrospective chart review of patients receiving divalproex treatment for a 22-mo period in an attempt to reduce symptoms of agitation following injury. Symptoms of agitations included easily aggravated, escalating temper, biting, punching, restless, etc. **Outcome Measure:** Agitated Behaviour Scale (ABS).	1. Eight patients had treatment with divalproex (mean 714 mg) that led to rapid resolution of symptoms and near total recovery. 2. For a second subgroup of patients(n=18), progress notes prior to and during treatment demonstrated decreased and significant improvement in symptoms within 7d of receiving divalproex (mean dose 1,257 mg). 3. Most patients were discharged to their homes (n=23) or to other community sites (n=4).

Discussion

In a case series study, Chatham Showalter and Kimmel (2000) examined the use of divalproex to treat symptoms of agitation in 29 patients post severe ABI. Symptoms decreased in the majority of patients,

with a portion showing near total resolution of symptoms. Due to a lack of statistical analysis, it is difficult make firm conclusions based on these results.

Conclusions

There is level 4 evidence (Chatham Showalter & Kimmel, 2000) that divalproex may improve symptoms of agitation in individuals with severe ABI; however, further research is necessary to confirm its effectiveness.

KEY POINTS

- Divalproex may be effective in reducing agitation post severe ABI; however, further research is needed.

Risperidone

Risperidone is an antipsychotic used for the management of psychosis-induced aggression or agitation (Ostinelli et al., 2018). It should be noted that, due to lack of evidence for antipsychotic effectiveness, prolonged post-traumatic amnesia and decreased cognitive function (Bogner et al., 2015; McKay et al., 2018; Mysiw et al., 2006), current recommendations and reviews advise against the use of antipsychotics to manage behaviour (Plantier & Luaute, 2016; Ponsford et al., 2014; Williamson et al., 2018). There is limited research on the use of risperidone for agitation, anger and aggression in individuals with ABI.

TABLE 86 | Risperidone for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Deb et al. (2020) UK RCT PEDro=6 N=14	**Population:** TBI=14, Severity: Mild=3, Moderate=4, Severe=5*; Risperidone Group (n=6)* Mean Age=39.3yr; Gender: Male=5, Female=1. *Placebo Group (n=8):* Mean Age=43.1yr; Gender: Male=5, Female=3. **Intervention:** Participants were randomly allocated into two groups: Risperidone or Placebo. Those in the experimental group received 1mg once daily dose of Risperidone up to a dose of 4mg/day, if necessary. Those in the placebo group received an equivalent amount of placebo capsules. Follow-ups were done by telephone every week and at 12 weeks post-treatment to assess improvement. **Outcome Measure:** Modified Overt Aggression Scale (MOAS), Glasgow Outcome Scale - Extended (GOS-E), Irritability Questionnaire (IRQ), Hospital Anxiety and	1. At 12 weeks, MOAS values had reduced in both groups, to a similar level. The Placebo group showed a larger change in total MOAS values and its sub-scores. 2. According to CGI-I, 40% in the risperidone group and 33% in the placebo group, respectively, were very much improved at follow-up. 3. Patient MOAS scores positively correlated with follow-up patient IRQ severity score (p=0.03). 4. Given the small sample, it was not possible to draw any definitive conclusion about risperidone's efficacy.

Author Year Country Study Design Sample Size	Methods	Outcome
	Depression Scale (HADS), Clinical Global Impression (CGI), Udvalg for Kliniske Undersogelser Scale (UKU), EQ- 5D, Short Form 12 (SF-12).	

Discussion

In a small RCT, Deb et al. (2020) examined the efficacy of risperidone for the management of aggression in individuals with TBI. Participants were randomized to receive either risperidone or a placebo in a dose of 1-4mg daily as necessary for 12 weeks. The authors found that the Modified Over Aggression Scale (MOAS) scores decreased for both the risperidone and the placebo group, with a larger change in MOAS scores and sub scores in the placebo condition. The score changes in the IRQ were found to be slightly greater in the risperidone group, compared to placebo and there was a correlation between MOAS and IRQ scores suggesting an association between irritability and aggression (Deb et al., 2020). Given that some studies have suggested that frequent use of risperidone may reduce cognitive and functional recovery in individuals with TBI (Williamson et al., 2019), caution is recommended.

Conclusions

There is level 1b evidence (Deb et al., 2020) that risperidone may not be effective for the management of aggression in individuals with TBI.

KEY POINTS

- Risperidone may not be effective in reducing aggression post TBI; further research is needed.

Rivastigmine

Rivastigmine is an acetylcholine inhibitor that increases the levels of a brain chemical called acetylcholine which allows communication of the nerve cells(Birks & Evans, 2015). Rivastigmine has been used to treat cognitive and behavioral symptoms in Alzheimer disease and diffuse Lewy body disease, as well as other conditions such as in vascular dementia and Parkinson's disease (Farlow, 2003).

TABLE 87| Rivastigmine for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Tenovuo et al. (2009) Finland RCT Crossover PEDro=9 N=102	**Population:** TBI; Mean age=45.5yr; Gender: Males=61, Female=39; Mean time post-injury=8yr; Mean GCS=11. **Intervention:** Individuals were randomized to receive one of two dosing rivastigmine schedules (placebo then rivastigmine or rivastigmine then placebo). Treatment lasted 8wk once a max dose of 12mg/d was reached. **Outcome Measures**: Symptom Checklist-90, Satisfaction with Life Scale (SWLS), Finnish Traumatic Brain Injury Questionnaire (FITBIQ), Simple Reaction Time Test, Ten-choice reaction time (10CRT), The Subtraction Test, Vigilance Test.	1. No significant difference (Finnish Traumatic Brain Injury Questionnaire-physical symptoms including irritation and impulsiveness; FITBIQ-physical symptoms).
Silver et al. (2006) USA RCT PEDro=9 N=123	**Population:** TBI; Mean GCS=6.5. *Rivastigmine* (n=80): Mean Age=37yr, Gender: Male=53, Female=27, Mean Loss of Consciousness=23.3d; *Placebo* (n=77): Mean Age=37.1yr, Gender: Male=53, Female=24, Mean loss of Consciousness=22.5d. **Intervention:** Participants were randomized to receive either rivastigmine (3-6 mg/d) or placebo. At the end of the first 4 wk, rivastigmine doses were increased to 3.0 mg, 2x/d. If necessary, doses were decreased to 1.5 mg or 4.5 mg 2x/d. **Outcome Measures:** Trail Making Test A, Trail Making Test B, Hopkins verbal learning test (HVLT), Cambridge Neuropsychological Test Automated Battery (CANTAB), Wechsler Adult Intelligence Scale-III (WAIS-III), Neurobehavioral Functioning Inventory (NFI), Beck Depression Inventory II (BDI-II), Satisfaction with Life Scale (SWLS), Clinical Global Impression of Change.	1. No significant differences in aggression, as measured by the Neurobehavioral Functioning Inventory (NFI).

Discussion

Two RCTs examined the effectiveness of rivastigmine compared to placebo. Tenovuo et al. (2009) reported no significant differences in behaviour, including irritability and impulsiveness, as measured by the Finnish Traumatic Brain Injury Questionnaire. Similarly, Silver et al. (2006) found no differences in the Neurobehavioral Functioning Inventory (NFI), including aggression.

Conclusion

There is level 1a evidence (Tenovuo et al., 2009) and level 1b evidence (Silver et al., 2006) that rivastigmine may not improve aggressive, irritable and impulsive behaviour post TBI.

KEY POINTS

- Rivastigmine may not be effective for managing aggression, irritability and impulsivity in individuals with moderate to severe TBI.

Ziprasidone

Ziprasidone is an antipsychotic medication commonly used to manage agitation, aggression or violent behaviours (Muir-Cochrane et al., 2020). There is limited research on the use of ziprasidone for agitation, anger and aggression in individuals with brain injuries.

TABLE 88 | Ziprasidone for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Noe et al. (2007) USA Case Series N=5	**Population:** TBI; Mean Age=26.8yr; Gender: Male=3, Female=2; Mean Time Post Injury=54.6 days; Mean GCS Score=6. **Intervention:** Ziprasidone (30-80 mg/day for 35-68 days) was given to participants. **Outcome Measure:** Agitation Behaviour Scale (ABS).	1. Mean dose of the drug was 52.8 mg/day. 2. Scores on the ABS decreased within the first 14 days (27.3 to 18). 3. Scores on the disinhibition portion of the ABS decreased from 28.6 to 17.1, while scores on the aggressiveness subsection of the scale decreased from 26.1 to 20.4. 4. No side effects were noted.

Discussion

In one case series, Noe et al. (2007) examined individuals who were still in post-traumatic amnesia upon admission to rehabilitation, which involves disorientation and behavioural alteration (Brooke et al., 1992). The authors found a decrease in agitation during the first two weeks of ziprasidone administration. In addition, it was noted that all patients tolerated the medication, with no clinical side effects observed (Noé et al., 2007).

Conclusions

There is level 4 evidence (Noé et al., 2007) that ziprasidone may reduce agitation among those with posttraumatic amnesia. However, additional further research is required to determine its effectiveness.

KEY POINTS

- Ziprasidone may be effective for the management of agitation in those with post-traumatic amnesia following a TBI; however, additional research with larger sample sizes is needed.

Methotrimeprazine

Methotrimeprazine is an antipsychotic medication that has been used in the management of schizophrenia (Blin et al., 1996). There is limited research on the use of methotrimeprazine for the management of agitation, anger and aggression in individuals with brain injuries.

TABLE 89 |Methotrimeprazine for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Maryniak et al. (2001) Canada Case Series N=120	**Population:** Moderate to Severe ABI; TBI=95; Mean Age=37.8yr; Gender: Male=89, Female=31. **Intervention:** Retrospective review of patients attending an inpatient ABI rehabilitation unit, and some received methotrimeprazine (MTZ). **Outcome Measure:** Agitated Behaviour Scale.	1. Fifty-eight percent had agitation, but 56 patients were treated with MTZ (10-25 mg, 4x/day) with a mean length of treatment of 41.9 days. 2. MTZ, was both safe and effective for controlling agitation in 96% of patients.

Discussion

Maryniak et al. (Maryniak et al., 2001) examined the oral administration of methotrimeprazine for agitation in a case series of 56 patients with moderate to severe ABI. The authors found that methotrimeprazine was both safe and effective for controlling agitation in nearly all cases. However, more rigorous studies, including RCTs, examining the safety and efficacy of methotrimeprazine within an ABI population are necessary to determine its effectiveness.

Conclusions

There is level 4 evidence (Maryniak et al., 2001) that methotrimeprazine may reduce agitation post ABI. However, further research is needed.

KEY POINTS

- Methotrimeprazine may be effective for the management of agitation post moderate to severe ABI; however, additional research is needed.

Dexmedetomidine

Dexmedetomidine is a medication indicated for the sedation of individuals who are mechanically ventilated in the intensive care unit (ICU) or those non-intubated patients who need peri-procedural or

peri-operative sedation; off-label uses include prevention of delirium, therapy for insomnia in the ICU and to manage alcohol withdrawal (Reel & Maani, 2023).

TABLE 90 | Dexmedetomidine for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Feng et al. (2022) China RCT PEDro=6 N=60	**Population:** TBI; Male=36, Female=24; Mean age=44.7yr; Time post-injury=1-6hr; GCS=9-12. **Intervention:** Patients were randomly assigned to receive dexmedetomidine (DEX) group or normal saline group (control) for post-operative agitation. **Outcome Measures:** Extubation time/weaning from ventilation, Heart rate, Mean Arterial Pressure (MAP), Riker Sedation-Agitation Scale (SAS), Ramsay Sedation Scale.	1. Riker Sedation-Agitation Scale scores were significantly lower in the DEX group, compared to the control ($p<0.05$). 2. The incidence of agitation in the DEX group was significantly lower than in the control ($p<0.05$).
Soltani et al. (2021) Iran RCT PEDro=7 N=60	**Population:** TBI; Gender: Male=46, Female=14; *Haloperidol:* Mean Age=36.8yr, Mean GCS=9; *Dexmedetomidine:* Mean Age=40.1yr; Mean GCS=8.9; Mean Time Post-Injury=Not Reported **Intervention:** Patients were randomized to either the haloperidol or dexmedetomidine group to assess pharmacological effect on delirium and agitation. Haloperidol was given 2.5mg/8hr for 10min. Dexmedetomidine was given 0.5 µg/kg/2d. Outcomes were assessed daily for 7d. **Outcome Measure:** Glascow Coma Scale (GCS), Richmond Agitation Sedation Scale (RASS), Acute Physiologic and Chronic Health Evaluation II (APACHE II), Confusion Assessment Method-ICU (CAM-ICU), Ventilation days, ICU length of stay.	1. RASS scores were significantly different in a between group comparison wherein patients in the dexmedetomidine group with lower agitation were calmer and more stable ($p<.05$). 2. Between days 5-7, it was found that the incidence of delirium was lower in the dexmedetomidine group than the haloperidol group ($p<.05$).
Bilodeau et al. (2021) Canada Case Series N=41	**Population:** TBI; Gender: Male=37, Female=4; Median Age=49yr (IQR:26-64yr); Median GCS=9 (IQR:6-14) Time Post-Injury=Not Reported **Intervention:** Retrospective review of medical records of patients admitted to the ICU who received dexmedetomidine for the management of agitation for a median duration of 3d (ranging from 3 to 6d). Outcomes were monitored post initiation of dexmedetomidine for up to 6d. **Outcome Measure**: Incidence of agitation, bradycardia, hypotension, administration of other psychoactive medication.	1. There was a statistically significant decrease in agitation between days 0 and 2 ($p=.01$), and days 0 and 3 ($p=.01$) after administration of dexmedetomidine 2. Use of concomitant propofol and benzodiazepine progressively decreased from day 0 to day 3.

Discussion

The use of dexmedetomidine was examined in three studies. In an RCT, Soltani et al. (2021) compared haloperidol to dexmedetomidine to manage delirium and agitation in individuals with TBI. The authors found that there was a significant reduction in agitation, as well as a reduction in delirium between days 5 and 7, in favor of the dexmedetomidine group (Soltani et al., 2021). Similarly, Feng et al. (2022) found that dexmedetomidine was effective for the management of postoperative agitation, compared to normal saline. In a case series, Bilodeau et al. (2021) retrospectively examined medical records of ICU patients who received dexmedetomidine for the treatment of agitation and found that there was a significant decrease in agitation between days 0 and 2, and days 0 and 3 after participants received dexmedetomidine.

Conclusions

There is level 1b evidence (Feng et al., 2022; Soltani et al., 2021) and level 4 evidence (Bilodeau et al., 2021) that dexmedetomidine may reduce agitation and delirium post TBI.

KEY POINTS

- Dexmedetomidine may be more effective for the management of agitation and delirium post moderate to severe TBI.
- Dexmedetomidine may be more effective for agitation and delirium than haloperidol.

Haloperidol

Haloperidol is an antipsychotic commonly used for the treatment of hallucinations and delusions in individuals with schizophrenia; off-label uses include acute mania episodes, agitation in psychiatric disorders, intractable hiccups, and chemotherapy-induced nausea and vomiting (Rahman & Marwaha, 2023).

TABLE 91 | Haloperidol for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Soltani et al. (2021) Iran RCT PEDro=7 N=60	**Population:** TBI; Gender: Male=46, Female=14; *Haloperidol:* Mean Age=36.8yr, *Dexmedetomidine:* Mean Age=40.1yr; Mean GCS at baseline: *Haloperidol*=9.0, Dexmedetomidine=8.9; Mean Time Post-Injury=Not Reported **Intervention:** Patients were randomized to either the haloperidol or dexmedetomidine group to assess	1. RASS scores were significantly different in a between group comparison wherein patients in the dexmedetomidine group with lower agitation were calmer and more stable ($p<.05$). 2. Between days 5-7, it was found that the incidence of delirium was lower in the

Author Year Country Study Design Sample Size	Methods	Outcome
	pharmacological effect on delirium and agitation. Haloperidol was given 2.5mg/8hr for 10 min. Dexmedetomidine was given 0.5 µg/kg/2d. Outcomes were assessed daily for 7d. **Outcome Measure:** Glascow Coma Scale (GCS), Richmond Agitation Sedation Scale (RASS), Acute Physiologic and Chronic Health Evaluation II (APACHE II), Confusion Assessment Method-ICU (CAM-ICU), Ventilation days, ICU length of stay.	dexmedetomidine group than the haloperidol group ($p<.05$).

Discussion

The use of haloperidol, compared to dexmedetomidine, was examined in one RCT. Soltani et al. (2021) randomized participants to either the haloperidol or dexmedetomidine group for the management of delirium and agitation. The authors found that the agitation scores, as measured by the Richmond Agitation Sedation Scale (RASS), were significantly different between groups, in favor of with those in the dexmedetomidine group. Haloperidol was found to be less effective than dexmedetomidine for the management of agitation and delirium.

Conclusions

There is level 1b evidence (Soltani et al., 2021) that haloperidol may not be less effective than dexmedetomidine for the management of agitation and delirium post TBI.

KEY POINTS

- Compared to haloperidol, dexmedetomidine may be more effective for the treatment of agitated behaviour and delirium in individuals with moderate to severe TBI.

Propranolol

Propranolol is a non-selective beta-blocker that has been used for the management of conditions such as hypertension, cardiac arrhythmias and hyperthyroidism (Al-Majed et al., 2017). Propranolol has been used to treat agitation in individuals with brain injuries, without the serious cognitive and affective side effects associated with other medications or the use of restraints used in patients with agitation post injury (Levy et al., 2005).

TABLE 92| Propranolol for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Brooke et al. (1992) USA RCT PEDro=7 N=21	**Population:** TBI; Severity of Injury: GCS <8. **Intervention:** Patients were randomized to receive either propranolol (n=11; 60 mg/day, max 420mg) or placebo (n=10). **Outcome Measure:** Overt Aggression Scale.	1. No significant differences between the two treatments in terms of agitation episodes per wk. 2. More intense episodes of agitation with placebo than propranolol ($p<0.05$). 3. More participants were placed in restraints with placebo than propranolol ($p<0.05$). 4. No differences between the two treatments in the proportion receiving sedating drugs or drugs for agitation.

Discussion

In a small Brooke et al. (1992) found that propranolol was effective in reducing the intensity of the agitation and use of restraints when compared to placebo. However, no significant differences were found between propranolol and placebo in reducing the frequency of agitation episodes.

Conclusions

There is level 1b evidence (Brooke et al., 1992) that propranolol may reduce the intensity of agitation episodes in individuals with severe TBI.

KEY POINTS

- Propranolol may be effective in reducing the intensity of agitation following a moderate to severe TBI.

Lithium Carbonate

Lithium has been used for many years in the treatment of mania and bipolar disorder (Kim, 2002). Lithium was the first mood stabilizer, and it is also prescribed as an adjunct therapy for major depressive disorder, vascular headaches, and neutropenia (Chokhawala et al., 2023). There is limited research on the use of lithium carbonate for the management of agitation, anger and aggression in individuals with brain injuries.

TABLE 93 | Lithium Carbonate for the Management of Agitation, Anger and Aggression Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Glenn et al. (1989) USA Case Series N=10	**Population:** Severe ABI; TBI=8, CVA=2; Mean Age=31.6yr; Gender: Male=5, Female=5. **Intervention:** Patients showing mood disorders and unstable, aggressive, combative, or self-destructive behaviour were administered lithium. **Outcome Measure:** Observed improvement.	1. Five participants showed a significant improvement with no decrease in motor or cognitive performance, one showed moderate response, and one improved dramatically but regressed after 7wk. 2. Four participants regressed after medications stopped. 3. Three participants had neurotoxic side effects.

Discussion

In a case series study, Glenn et al. (1989) examined the use of lithium in ten individuals with either TBI or stroke. The authors reported favourable outcomes for the majority of patients, indicating that lithium carbonate may decrease observed unstable, aggressive, combative, or self-destructive behaviour (Glenn et al., 1989). However, it may be associated with high risk of neurotoxicity. Given the lack of recent evidence and high quality studies, findings related to the use of lithium carbonate should be interpreted with caution.

Conclusions

There is level 4 evidence (Glenn et al., 1989) that lithium carbonate may reduce aggression post ABI.

KEY POINTS

- Lithium carbonate may reduce aggressive behaviour in individuals with ABI; however, further research is needed.

Olanzapine

Olanzapine is an antipsychotic medication that is commonly used for the treatment of schizophrenia and bipolar disorder; off-label uses include acute agitation, delirium, anorexia and nausea and vomiting associated with chemotherapy (Thomas & Saadabadi, 2023).

TABLE 94 | Olanzapine for the Management of Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Phyland et al. (2023) Australia RCT PEDro=6 $N_{Initial}$=13, N_{Final}=11	**Population:** TBI; Gender: Male=8, Female=3; Mean Age=39.9yr; Mean GCS=5.45; Mean Time Post-Injury=46.09d **Intervention:** Participants who were in Post-traumatic Amnesia (PTA) and clinically agitated were randomly allocated to either olanzapine (Titrated every 3-4 days, 1. 5mg at night, 2. 5mg -10mg morning and night, 3. 5mg morning 10 mg night, 4. 10 mg morning and night) or a placebo each day until the emergence from PTA. Doses were titrated every 3/4d until PTA emergence. Outcomes were assessed at baseline, throughout PTA, emergence from PTA, and at hospital discharge. **Outcome Measure:** Agitated Behavior Scale (ABS), Westmead Post-Traumatic Amnesia Scale (WPTAS), Rey Auditory Verbal Learning Test (RAVLT), Length of hospital stay, Number of Adverse Events, Simpson-Angus Scale.	1. All participants demonstrated at least one instance of significant reduction in agitation between phases. 2. No significant group differences were revealed for measures of agitation, mean ABS score, number of agitated days and agitation at discharge. However, a moderate effect size for mean ABS score was found in favor of olanzapine.

Discussion

In an RCT, Phyland et al. (2023) examined the effectiveness of olanzapine, compared to placebo, for the treatment of agitation in individuals who were in post-traumatic amnesia (PTA). The authors found a moderate effect size for mean ABS score was found in favor of the olanzapine group and all participants demonstrated at least one instance of significant reduction in agitation; however, no significant group differences were observed for measures of agitation, mean Agitated Behaviour Scale (ABS) score, number of agitated days and agitation at discharge (Phyland et al., 2023).

Conclusions

There is level 1b evidence (Phyland et al., 2023) that olanzapine may be not effective in reducing agitation during PTA, and it may be associated with poorer cognitive performance.

KEY POINTS

- Olanzapine may not be effective for agitated behaviour during post-traumatic amnesia in individuals with severe TBI. Further research is needed.

Lisdexamfetamine Dimesylate

Lisdexamfetamine is an amphetamine drug used for the treatment of attention-deficit hyperactivity disorder (ADHD) in children (Blick & Keating, 2007). There is limited research on Lisdexamfetamine Dimesylate in individuals with moderate to severe TBI.

TABLE 95 | Lisdexamfetamine Dimesylate for Agitation, Anger and Aggression Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Tramontana et al. (2014) USA RCT Crossover PEDro=7 $N_{Initial}$=22, N_{Final}=13	**Population:** Mean age=28.85y; Gender: Male=9, Female=4; Mean Time post-injury=15.58mo. Severity: Moderate=9, Severe=4. **Intervention:** Patients were randomly assigned to Lisdexamfetamine Dimesylate (LDX) (dosage as needed) or placebo for 6wk each, 12wk of treatment. Outcomes were assessed at baseline and at 6wk and 12wk. **Outcomes:** Wechsler Abbreviated Scale of Intelligence (WASI), Frontal Systems Behavioural Evaluation (FrSBE), Wisconsin Card Sorting Test (WCST), Finger Oscillation (Tapping test), Trail Making Test A, Trail Making Test B, Continuous Performance Test (CPT), Digit Span, Stroop Color Word Test, Digit Symbol Test, Paced Auditory Serial Addition Test (PASAT), Benton Visual Retentions Test, Conners Adult ADHD Rating Scale (CAARS), Behaviour Rating Inventory of Executive Function Adult Version (BRIEF-A), Quality of Life Inventory (QOLI), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI).	1. Cases with lower self-ratings of depression on the BDI-II pre-treatment tended to do better on LDX in planning and organization (p=0.03). 2. In the BRIEF-A, scores on the Inhibit scale predicted treatment outcomes on measures such as self-ratings of depression on the BDI-II (p=0.031).

Discussion

In an RCT, Tramontana et al. (2014) examined the effects of Lisdexamfetamine Dimesylate (LDX) compared to placebo on cognitive and neurobehavioural measures in individuals with moderate to severe TBI. The authors found no significant effects or interactions in the Behaviour Rating Inventory of Executive Function Adult Version (BRIEF-A), except for the organization subscale.

Conclusions

There is level 1a evidence (Tramontana et al., 2014) that Lisdexamfetamine Dimesylate may not have an effect on behaviour post TBI; however, further research is needed.

KEY POINTS

- Further research is needed to determine the effects of Lisdexamfetamine Dimesylate on behaviour following a moderate to severe TBI.

Use of Restraints

Due to the continued concern regarding the safety of patients and staff in hospitals and long-term care facilities, the use of restraints continues to be part of clinical practice; however, their use remains controversial. Reasons for the use of a restraint often include impulsiveness, pulling at devices, or removing endotracheal tubes, central venous lines, and other life support measures (McNett et al., 2012). Additionally, restraints may be used to control agitation, aggression, and behaviour related to confusion and altered mental status; increase patient safety related to impaired mobility; supporting patient posture or sitting balance; preventing disruption of therapy; and protecting the safety of family and staff (Evans & FitzGerald, 2002; Kow & Hogan, 2000; Minnick et al., 2007; Mion et al., 1996; Sandhu et al., 2010).

Policies related to the application of restraints often state that the use of restraints should meet the following criteria: (1) be individualized and offer as much dignity to the individual as the situation allows; (2) be humanely and professionally administered; (3) have safety protocols in place; (4) patient must be monitored; (5) careful documentation of the type of restraint, the reason for it, and the means for observation while in the restraint; (6) the method or choice of restraint must be the least restrictive option available (American Nurses Association, 2012; College of Nurses of Ontario, 2009; Ministry of Health and Long Term Care for the Province of Ontario, 2001; St. Joseph's Health Care, 2012). In accordance with provincial legislation, the College of Nurses for Ontario suggests that the following information is to be recorded when using restraints: type used, alternatives considered and used, date and time of application, reason given to patient, significant patient behaviours, and patient response.

Restraints may be considered acceptable if the restraint is used to ensure patient safety, the restraint is implemented safely, less restrictive interventions have been ineffective in preventing harm, and appropriate techniques are used as determined by hospital or organizational policy (Recupero et al., 2011). However, when an agitation crisis occurs physical restraints should be discarded if possible (Luauté et al., 2016). Currently, there is insufficient data available to determine the efficacy of using physical restraints to reduce agitated or aggressive behaviour post ABI (Duxbury & Wright, 2011).

Sexually Disinhibited Behaviour

Sexual dysfunction following TBI has been reported to occur in at least 50% of patients (Emory et al., 1995). Hypersexuality is less common than hyposexuality but results in a more significant negative effect for the individual and a greater burden of care. Hypersexual behaviour can encompass a range of behaviours, from promiscuity, exhibitionism, and indiscriminate sexual advances, to assault and/or rape (Mania et al., 2006), with inappropriate sexual talk one the most common inappropriate sexual behaviours post-TBI (Simpson et al., 2013). Treatment for sexual offenders without brain injuries often involves pharmacological intervention, counselling, and education. Typically, medication is used to

reduce the sexual drive, but it is unclear if it affects cognitive processing. In a review, Clay et al. (2018) concluded there was insufficient evidence to consider any specific treatment effective for decreasing inappropriate sexual behaviour in individuals with ABI; however, the authors suggested that some behavior analytic approaches may be effective.

Social Behaviour

Changes in social behaviour are common following a brain injury, including emotional changes that create challenges for establishing and maintaining social relationships (May et al., 2017). Changes in emotional and social behaviour post-TBI, such as indifference, egocentric behaviour, or lack of empathy, may have several negative consequences for individuals, including difficulties reintegrating into their communities or their workplaces (Milders, 2019). In addition, individuals living with TBI may also experience difficulties with their social communication ability, including verbal and nonverbal skills, resulting in poor social integration, lower levels of occupational activity and loneliness (Sherer et al., 2022).

Non-Pharmacological Interventions

Behavioural Modification Programs

Context-sensitive interventions have shown benefits for individuals experiencing difficulties with social communication skills, particularly interventions that promote the practice of skills in naturalistic settings as part of rehabilitation programs (Finch et al., 2016). Interventions that address behavioural challenges in the natural settings may also involve families and caregivers of individuals with brain injuries (Carnevale et al., 2006).

TABLE 96 | Behavioural Modification Programs for Social Behaviour Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Westerhof-Evers et al. (2017) Netherlands RCT PEDro=7 $N_{Initial}$=61, N_{Final}=56	**Population:** TBI; Mean Age=43.2yr; Gender: Male=83, Female=17; Severity: Moderate to severe. **Intervention:** Participants were randomly assigned to receive Treatment for Impairments in Social Cognition and Emotion Regulation (T-ScEmo) protocol or Cogniplus training. The T-ScEmo protocol aimed at enhancing emotion perception, perspective taking, theory of mind, goal-directed social behaviour (20 sessions 1-2x/wk) Cogniplus involved computerized attention training. Outcomes were assessed baseline (T0), post-intervention (T1), and 3-5 mo follow-up (T2).	1. There was no improvement for either group on the Dutch short version of The Awareness of Social Inferences Test (TASIT-short). 2. The T-ScEmo group had significant improvements in empathetic behaviour. 3. A decrease of social-behavioral problems was found for both groups over time.

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measures: The Awareness of Social Inferences Test (TASIT-short), Sixty faces test (FEEST), Cartoon test, Faux Pas test (FP), Wechsler Adult Intelligence Scale (WAIS-III), Trail Making Test A and B, Test of Everyday Attention Lottery (TEA), Dysexecutive Questionnaire-Social scales (DEX), Brock's Adaptive Functioning Questionnaire-Social monitoring scale (BAFQ), Role Resumption List (RRL), Quality of Life after Brain Injury (QOLIBRI), Treatment Goal Attainment (TGA), Relationship Quality Scale (RQS).	
Carnevale et al. (2006) USA RCT PEDro=5 N=37	**Population:** TBI=24, ABI=13; Mean Age=40.5yr; Gender: Male=28, Female=7; Mean Time Post Injury=7.6yr, Loss of Consciousness >24hr = 91.9%. **Intervention:** Participants were randomized to a control group (n=12) that received no treatment, an education group (n=13) that received education only, and a Natural Setting Behaviour Management (NSBM) group (n=12) that received both education and an individualized behaviour modification program. Target behaviours included aggression, disinhibition and inappropriate social behaviour. **Outcome Measure:** Maslach Burnout Inventory (MBI), Questionnaire on Resources and Stress for Families with Chronically Ill or Handicapped Members (QRS), Neurobehavioral Functioning Inventory–Revised (NFI-R)	1. NSBM had more improvement in behaviour than the other two groups at 30wk ($p<0.002$). 2. A significant difference was noted between the education group and the NSBM group ($p<0.04$).
Eames & Wood (1985) UK Pre-Post N=24	**Population:** ABI=22, Stroke=1, Other=1; Mean Age=26.8yr; Gender: Male=18, Female=6; Mean GCS Score=7.8; Mean Time Post Injury=44.7mo. **Intervention:** Patients were on a specialized TBI unit that used a wide range of physical, occupational, social, cognitive, and behavioural techniques-based token economy. **Outcome Measure:** Patient placement.	1. More than 2/3 of patients had improved placements after treatment; only one person had a substantial improvement. Fewer than 1/3 of patients made no change, and no one was demoted to a worse setting.

Discussion

Westerhof-Evers et al. (2017) compared a program for impairments in social cognition and emotion regulation (T-ScEmo) to computerized cognitive training. The authors found that individuals who received the T-ScEmo program had significant improvements in empathetic behaviour, when compared to those in the cognitive training group (Westerhof-Evers et al., 2017). In an RCT, Carnevale et al. (2006) found significant improvements in social behaviour for participants who received an individualized education and behaviour modification program in the natural community setting compared to those who only received education. In an earlier pre-post study, Eames and Wood (1985) reported that a behaviour modification program based on a token effectively reduced some negative behaviours in participants, and improved relationships and living arrangements.

Conclusions

There is level 1b evidence (Westerhof-Evers et al., 2017), level 2 evidence (Carnevale et al., 2006), and level 4 evidence (Eames & Wood, 1985) that behavioural modification programs may improve social behaviour and empathy post ABI.

KEY POINTS

- Behavioural modification programs may improve social behaviour and empathy in individuals with ABI.

Cognitive Rehabilitation

Cognitive rehabilitation aims to help individual with ABI to regain cognitive function or to compensate for cognitive deficits, and it can be implemented using technologies such as computer-based cognitive tools and virtual reality (De Luca et al., 2018).

TABLE 97 | Cognitive Rehabilitation for Social Behaviour Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Salazar et al. (2000) USA RCT PEDro=6 $N_{Initial}$=120, N_{Final}=107	**Population:** TBI; *Hospital rehabilitation* (n=67): Mean age=25yr; Gender: Male=62, Female=5; Mean Time post-injury=38d; Mean GCS=9.4; *Home rehabilitation* (n=53): Mean age=26yr; Gender: Male=51, Female=2; Mean Time post-injury=39d. Mean GCS=9.5. **Intervention:** Patients were randomly assigned to either an intensive, standardized, 8wk, in-hospital cognitive rehabilitation program or a limited home rehabilitation program with weekly telephone support from a psychiatric nurse. Outcomes were assessed at baseline and at the 1yr follow-up. **Outcomes:** Katz Adjustment scale (KAS), Halstead-Reitan Neuropsychological Battery, Buschke Selective Reminding Test (SRT), Continuous Visual Memory Test (CVMT), Paced Auditory Serial Addition Test (PASAT), Wisconsin Card Sorting Test (WCST), Wechsler Memory Scale Revised (WMS-R), Auditory Consonant Trigrams (ACT).	1. There were no significant differences between treatment groups reported at 1 year in measures of belligerence (p=0.19), social irresponsibility (p=0.99), antisocial behaviour (p=0.24), social withdrawal (p=0.40), and apathy (p=0.21). 2. At 1 year after randomization, no significant differences were found for verbal or physical aggression (p=0.82). 3. No significant differences were found at 1 year for major depression (p=0.26) and generalized anxiety (p=0.33), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Discussion

In an RCT Salazar et al. (2000) randomly assigned patients to either an intensive, standardized, in-hospital cognitive rehabilitation program or a limited home rehabilitation program with telephone support every week from a psychiatric nurse. The authors found no differences between the groups in social behaviour such as belligerence, social irresponsibility, antisocial behaviour, social withdrawal, and apathy.

Conclusions

There is level 1b evidence (Salazar et al., 2000) that in-hospital cognitive rehabilitation may not be more effective than home rehabilitation with telephone support for social behaviour post TBI.

KEY POINTS

- In-hospital cognitive rehabilitation may not be different than a home rehabilitation program with telephone support for social behaviour in individuals with moderate to severe TBI.

Emotion Recognition

Emotion recognition is an essential aspect of social cognition that mediates affiliative behaviours and social interactions with others (Ferretti & Papaleo, 2019).

TABLE 98| Emotion Recognition for Social Behaviour Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Babbage et al. (2018) USA RCT PEDro=8 $N_{Initial}$=71, N_{Final}=57	**Population:** Moderate-Severe TBI; Mean time post-injury > 1yr; *Stories intervention* (n=23): Male=18, Female=5 *Active control* (n=24): Male=16, Female=8. **Intervention:** Participants were randomly assigned to a one-on-one computer-assisted treatment for either Stories intervention that taught participants to infer emotions from contextual information or to a sham control for 9 sessions, 1hr/2-3 times per wk. Outcomes were assessed at baseline, post-intervention, 3-, and 6-mo follow-up. **Outcome Measures:** Diagnostic Assessment of Nonverbal Accuracy2- Adult Faces (DANVA2-AF), Emotional Inference from Stories Test (EIST).	1. The Stories group showed a significant treatment effect on the DANVA2-AF (p=0.038) and EIST (p=0.001). 2. In terms of sex differences, a significant treatment effect was observed for the Stories intervention for women, who demonstrated and maintained improved facial affect recognition. 3. In contrast, males in our sample did not benefit from the Stories intervention.

Author Year Country Study Design Sample Size	Methods	Outcome
McDonald et al. (2013) Australia RCT PEDro=6 N=20	**Population:** Severe TBI=16, CVA=3, Other=1; Mean Age=45.62yr; Gender: Male=15, Female=5; Mean Time Post Injury=9.41yr. **Intervention:** Participants were assigned to either a treatment group (n=10) or a control group (n=10). Participants received treatment 2hr/wk for 3 wk. The program focused on assisting individuals with the identification of prosodic cues that may be seen in expressions of emotions and interactions with others. **Outcome Measures:** The Awareness of Social Inference Test (TASIT), Prosodic Emotion Labelling Task, Self-Communication Questionnaire, Relative Communication Questionnaire. Self-report questionnaire for everyday behaviour.	1. There were no significant differences between groups. The treatment did not perform better than the waitlist control.
Bornhofen & McDonald (2008a) Australia RCT PEDro=6 $N_{Initial}$=18, N_{Final}=13	**Population:** Severe TBI; Male=17, Female=1; *Errorless learning (EL) intervention* (n=4): Mean age=43.75y; Mean time post-injury=60mo. *Self-instruction training (SIT) intervention* (n=5): Mean age=35.4y; Mean time post-injury=79.6mo. *Waitlist (WL) Intervention* (n=5): Mean age=31.2; Mean time post-injury=148.2mo. **Intervention:** Participants were randomly assigned to receive 25hr of either EL or SIT over 10wk or were placed in the WL intervention (control). **Outcome Measures:** Wechsler Test of Adult Reading (WTAR), Wechsler Memory Scale—Third Edition (WMS-III), Wechsler Adult Intelligence Scale—Third Edition (WAIS-III), Benton Facial Recognition Test (BFRT) Short Form (27-item), The Facial Expression Same/Different Task, The Facial Expression Naming Task, The Facial Expression Matching Task, The Awareness of Social Inference Test (TASIT), Sydney Psychosocial Reintegration Scale (SPRS), Depression Anxiety Stress Scales (DASS), Katz Adjustment Scale, Social Performance Survey Schedule (SPSS).	1. Both the EL and SIT groups demonstrated a positive treatment effect on the Facial Expression Matching Task ($p<0.01$). These effects were lost at the 6-month follow-up. 2. Relatives of those in the EL group observed a significant increase in socially favorable behaviors (SPSS). No other significant results were observed. 3. No other significant results were observed.
Bornhofen & McDonald (2008b) Australia RCT PEDro=4 $N_{Initial}$=12, N_{Final}=11	**Population:** Severe TBI; Mean age=35.8y; Male=11, Female=1; Mean time post-injury=93.58mos **Intervention:** Participant were randomly allocated to an emotional perception treatment or waitlist group. Those in the treatment group received 25 hours of therapy over 8 weeks. **Outcome Measures:** The Facial Expression Naming Task, The Facial Expression Matching Task, The Awareness of Social Inference Test, The Sydney Psychosocial Reintegration Scale.	1. The Sydney Psychosocial Reintegration Scale scores of the treatment group in set B were significantly lower than the waitlist group ($p<0.01$). 2. There was a significant treatment effect for TASIT part 3 Form A. 3. No other significant treatment effects were observed.

Discussion

In one RCT, MacDonald et al. (2013) examined an intervention to improve emotion recognition in prosody post-severe ABI, including recognizing emotions and associated behaviours. Interactions with others were assessed with communication questionnaires and an assessment of every day behaviour; however, no differences were found between the intervention group and the waitlist control (McDonald et al., 2013). In an RCT by Babbage et al. (2018), a 'Stories' intervention that aimed to teach participants to infer emotion from contextual information resulted in a significant treatment effect for emotion recognition; additionally, women seemed to benefit more from the intervention than men.

In an RCT, Bornhofen and McDonald (2008a) participants received emotion perception training and were allocated to the errorless learning group or self-instruction learning group. Errorless learning (EL) included identifying patterns associated with emotions, from exaggerated cues to more subtler cues, and constantly reminding individuals not to guess. Self-instruction learning followed a problem-solving process to approach each emotion identification task in the program. While individuals from the EL group showed a significant increase in socially favorable behaviours, as reported by their family members, no significant effects were found for social functioning. In another RCT, Bornhofen and McDonald (2008b) examined an intervention designed to address emotion perception. The intervention aimed to promote appropriate social behaviours by improving participants' ability to make social inferences and judge basic emotional stimuli. While participants showed improved accuracy in judging emotional cues, the authors found no significant effects on psychosocial functioning (Bornhofen & McDonald, 2008b).

Conclusions

There is level 1b evidence (Babbage et al., 2018) that women may show greater benefit from an intervention to recognize emotions from context, compared to men.

There is level 1b evidence (McDonald et al., 2013) that an intervention for the identification of emotional prosody may not improve social behaviour or interactions with others post severe ABI.

There is level 1b evidence (Bornhofen & McDonald, 2008a) and level 2 evidence (Bornhofen & McDonald, 2008b) that emotion perception training may not improve social behaviour and psychosocial functioning post TBI.

KEY POINTS

- Emotion perception training may not improve psychosocial functioning and everyday behaviours in individuals with moderate to severe ABI.
- Women may benefit more from an intervention to infer emotions from context, compared to men.

Social Skills Training

Initially developed for individuals with autism, social skills training is an intervention often delivered in groups that involves goal setting, role modeling, behavioral rehearsal and other behavioral strategies to help individuals improve social function (Dubreucq et al., 2022).

TABLE 99 | Social Skills Training for Social Behaviour Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
McDonald et al. (2008) Australia RCT PEDro=6 N=39	**Population:** TBI; Gender: Male=28, Female=11. *Treatment Group (n=13)*: Mean Age=35.5yr; Mean Time Post Injury=4.0yr. *Social Group (n=13)*: Mean Age=34.3yr; Mean Time Post Injury=4.3yr. *Waitlist Group (n=13)*: Mean Age=35.3yr; Mean Time Post Injury=3.5yr. **Intervention:** Participants were randomly allocated to waitlist (deferred treatment group; n=13), control (non-therapeutic social group; n=13), or the social skills group (treatment group; n=13). Participants in the skills training group attended 12wk program of group and individual sessions totaling 4 hr/wk. Control group received 4 hr/wk of social activities only for 12wk. **Outcome Measure:** Behaviorally Referenced Rating System of Intermediary Social Skills Revised (BRISS-R), The Awareness of Social Inference Test (TASIT), Depression Anxiety Stress Scale (DASS), Katz Adjustment Scale (KAS-R1), Social Performance Survey Schedule (SPSS), La Trobe Communication Questionnaire (LCQ), SPRS, Katz adjustment scale-R1 (KAS), the Social Performance Survey Schedule (SPSS), La Trobe Communication Questionnaire (LTCQ), Sydney Psychosocial Reintegration Scale (SPRS).	1. The social skills training group made significant improvement on the PDBS compared to the placebo and waitlist group ($p<0.004$). 2. Results indicate no effects for the social group relative to the waitlist group. 3. Changes were not noted for any group when looking at social functioning and social participation post treatment. 4. Treatment effects were found to be modest at best and limited to direct measures of social behaviour.
Brotherton et al. (1988) USA Case Series N=4	**Population:** TBI; Mean Age=23.5yr; Gender: Male=3, Female=1; Mean Time Post Injury=5.75yr. **Intervention:** Social skills training program comprised of education, instruction, manipulation, feedback, and reinforcement. **Outcome Measure:** Behavioural changes.	1. Intervention was effective in 3 of 4 patients treated, but not all behaviours were equally amenable to treatment. 2. Behaviours showing clear training effects also showed good maintenance 1yr after training.

Discussion

In a multicenter RCT, McDonald et al. (2008) compared social skills training, social activity, and a waitlist control group. The social skills group showed a significant improvement in behaviour compared to the other interventions, but there was only a modest treatment effect. In an earlier case series study, Brotherthon et al. (1988) found that social skills training was effective for some behaviours in three out

of four participants; some improvements were maintained up to one year after treatment (Brotherton et al., 1988).

Conclusions

There is level 1b evidence (McDonald et al., 2008), and level 4 evidence (Brotherton et al., 1988) that a social skills training programs may improve social behaviour post TBI.

KEY POINTS

- Social skills training may be effective in improving social behaviour in individuals with TBI.

Music Therapy

Music therapy has a positive influence on emotion and social integration, and it been used in the rehabilitation of individuals with a variety of neurological condition, including TBI (Mishra et al., 2021). There is limited evidence on the use of music therapy for social behaviour and behavioral regulation in individuals with brain injuries.

TABLE 100 | Music Therapy for Social Behaviour Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Siponkoski et al. (2022) RCT Crossover PEDro=5 N=38	**Population:** *TBI: Moderate-Severe; AB Group (n=20):* Mean Age=41.6yr; Gender: Male=10, Female=10; Mean Time Post Injury=8.6mo. *BA Group (n=18):* Mean Age=41.8yr; Gender: Male=12, Female=6; Mean Time Post Injury=9.8mo. Caregivers of the patients=33. **Intervention:** Participants were randomized into two groups (AB and BA). For the duration of the first 3 months, the AB group received neurological music therapy in addition to standard care, whereas the BA group received only standard care. Both groups received treatment for 60 min/day, 2days/week and switched halfway through the study period after 3 months. Outcome measures were assessed at 3-mnth, 6-month, and 18-month stages. **Outcome Measures:** Behaviour Rating Inventory of Executive Function- Adult version (BRIEF-A), Quality of Life after Brain Injury (QOLIBRI), Global Executive Composite Index (GECI), Beck Depression Inventory II (BDI-II).	1. The AB group showed a significant improvement in self-reported BRIEF-A Behaviour Regulation Index (BRI), as indicated by lowering of the BRI score compared to the BA group between time baseline and at 3 months. The change within the BA group did not reach significance (p=0.275). 2. No significant interactions were found in the other BRIEF-A indices or in the other questionnaires (BDI-II, QOLIBRI). 3. The only domain in which the numeric ratings of the persons with TBI and the caregivers differed significantly was Motor: participants with TBI experienced more benefits in motor functioning than the caregivers (p=0.008). 4. Participant feedback revealed that many participants experienced the intervention as

Author Year Country Study Design Sample Size	Methods	Outcome
		helpful in terms of emotional well-being and activity.

Discussion

In an RCT crossover, Siponkoski et al. (2022) examined the effects of a music therapy intervention for individuals with TBI compared to a standard care control. The authors reported that the group that received the music therapy intervention first, followed by the standard care control showed a significant improvement in behavioural regulation, as measured by the Behaviour Rating Inventory of Executive Function – Adult Version (BRIEF-A) scores, whereas those who received the standard care control before the music therapy intervention had BRIEF-A scores that did not reach significant improvements.

Conclusions

There is level 2 evidence (Siponkoski et al., 2022) that music therapy may improve behavioral regulation in individuals with TBI; however, further research is needed.

KEY POINTS

- Music therapy may improve behavioural regulation in individuals with TBI; however, additional research is needed.

Compassionate Imagery

Empathy is an essential pro-social behaviour for the functioning of society and it encompasses the ability to understand the experiences and feelings of others, facilitating compassion (Stevens & Taber, 2021). Compassionate therapy is a therapeutic approach that involves techniques such as breathing and compassionate imagery to help the individual acquire compassionate attributes and skills (Maner et al., 2023).

TABLE 101 | Compassionate Imagery for Social Behaviour Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
O'Neill & McMillan (2012) UK RCT PEDro=6 N=24	**Population:** Severe TBI. *Compassionate imagery* (n=12): Male=10, Female=2; Mean age=45.33y; Median time post-injury=57.5mo. *Relaxation* (n=12): Male=11, Female=1; Mean age=39.08y; Median time post-injury=124.5mo. **Intervention:** Patients were randomly allocated to a single treatment session of compassionate imagery or a control relaxation condition. Outcomes were measured at baseline and post-intervention. **Outcome Measures:** The Self-Compassion Scale, The Empathy Quotient	1. There were no significant differences in empathy observed in the compassionate injury group when compared to the relaxation group (p>0.05), as measured by the self-compassion scale or empathy quotient.

Discussion

In an RCT, O'Neill and McMillan (2012) compared compassionate imagery to a relaxation control condition and examined empathy among individuals with severe TBI. The majority of participants had low empathy (55%). While there was a trend towards an increase in compassion after one session, the authors found no significant group effect of compassionate imagery on empathy.

Conclusions

There is level 1b evidence (O'Neill & McMillan, 2012) that compassionate imagery may not improve empathy post severe TBI, compared to relaxation only.

KEY POINTS

- Compassionate Imagery may not be effective for empathy in individuals with severe TBI.

Pharmacological Interventions

Methylphenidate

Methylphenidate is a stimulant that has been used for the treatment of behavioural disorders associated with attention deficit hyperactivity disorder (ADHD) (Britton, 2012). There is limited research on using methylphenidate for social behaviour post-TBI.

TABLE 102 | Methylphenidate for Social Behaviour Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Speech et al. (1993) USA RCT Crossover PEDro=7 N=12	**Population:** TBI; Mean Age=27.6yr; Gender: Male=5, Female=7; Mean Time Post Injury=48.5 mo; Mean length of PTA=81.8d. **Intervention:** In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate, 2×/day, for 1 wk, followed by 1wk of placebo, or receive the treatment in a reverse order. **Outcome Measures:** Gordon Diagnostic System, Digit Symbol and Digit Span subtests of the Wechsler Adult Intelligence Scale-Revised, Stroop Interference Task, Sternberg High Speed Scanning Task, Selective Reminding Test, Serial Digit Test, and Katz Adjustment Scale.	1. No significant differences were found between methylphenidate and placebo condition in any of the outcome measures studied.

Discussion

Only one RCT (Speech et al., 1993) addressed social behaviour in individuals who had received methylphenidate, compared to placebo. The authors found no significant results on social behaviour and personality functioning, such as the use of inappropriate language and stubbornness, as measured by the Katz Adjustment Scale (KAS); however, given that social behaviour was rated by family members and close friends of the individual with TBI, results need to be interpreted with caution. More research is needed to determine the effects of methylphenidate on social behaviour post TBI.

Conclusion

There is level 1a evidence (Speech et al., 1993) that methylphenidate may not improve social behaviour post TBI. However, further research is needed.

KEY POINTS

- Further research is needed to determine whether or not methylphenidate may improve social behaviour in individuals with moderate to severe TBI.

Conclusion

Mental health, behaviour and substance misuse post-ABI may be challenging area of rehabilitation. Brain injuries have been associated with elevated psychological distress that can also impact physical symptoms; for instance, depression may exacerbate fatigue, headaches and pain, and vice versa (Chan et al., 2022). In addition, damage to the frontal areas of the brain may result in difficulties with cognition and executive functioning, resulting in behavioural problems that may hinder rehabilitation (Corrigan, 2021).

The needs of a diverse population also need to be considered. For instance, individuals with TBI who served in the military have a higher risk of developing major depressive disorder, PTSD and suicidal ideation (Howlett et al., 2022). Military personnel may also be at higher risk of developing substance use disorders, including alcohol consumption, use of illegal drugs and prescription medication misuse (Inoue et al., 2023). Age is another important factor to consider. Individuals who sustained a TBI at a young age may be at risk of alcohol and substance abuse, behaviour disorders and difficulties with social functioning, as well as poor mental health (Maresca et al., 2023). For those who have sustained a head injury in older age, comorbidities and greater risk of secondary complications need to be taken into account (Thompson et al., 2006). Additionally, older adults are at risk of depression in late life due to age-related stressful events, such as the presence of cognitive impairment, bereavement, reduction in activities, new physical illness or disability, and limited social support (Fiske et al., 2009).

Special consideration should be given to the stigma associated with brain injury and mental health, as it may result in discrimination, exacerbated caregiver strain, social isolation, depression and anxiety, affecting not only the individual but also families and communities (Phelan et al., 2011). Finally, it is critical to address social function, such as social network deficits, isolation and loneliness in individuals with brain injuries (Rigon et al., 2019).

References

Aboulafia-Brakha, T., Greber Buschbeck, C., Rochat, L., & Annoni, J. M. (2013). Feasibility and initial efficacy of a cognitive-behavioural group programme for managing anger and aggressiveness after traumatic brain injury [Research Support, Non-U.S. Gov't]. *Neuropsychol Rehabil, 23*(2), 216-233. https://doi.org/http://dx.doi.org/10.1080/09602011.2012.747443

Aboulafia-Brakha, T., & Ptak, R. (2016). Effects of group psychotherapy on anger management following acquired brain injury. *Brain Inj, 30*(9), 1121-1130. https://doi.org/10.1080/02699052.2016.1174784

Afsar, M., Shukla, D., Bhaskarapillai, B., & Rajeswaran, J. (2021). Cognitive Retraining in Traumatic Brain Injury: Experience from Tertiary Care Center in Southern India. *Journal of Neurosciences in Rural Practice, 12*(2), 295-301. https://doi.org/https://dx.doi.org/10.1055/s-0041-1722817

Ahmedani, B. K., Peterson, E. L., Hu, Y., Rossom, R. C., Lynch, F., Lu, C. Y., Waitzfelder, B. E., Owen-Smith, A. A., Hubley, S., Prabhakar, D., Williams, L. K., Zeld, N., Mutter, E., Beck, A., Tolsma, D., & Simon, G. E. (2017, 2017-12-14). Major physical health conditions and risk of suicide. *American Journal of Preventive Medicine, 53*(3), 308-315. https://doi.org/http://dx.doi.org/10.1016/j.amepre.2017.04.001

Al-Majed, A. A., Bakheit, A. H. H., Abdel Aziz, H. A., Alajmi, F. M., & AlRabiah, H. (2017). Propranolol. *Profiles Drug Subst Excip Relat Methodol, 42*, 287-338. https://doi.org/10.1016/bs.podrm.2017.02.006

Al-Ozairi, A., McCullagh, S., & Feinstein, A. (2014). Predicting posttraumatic stress symptoms following mild, moderate, and severe traumatic brain injury: The role of posttraumatic amnesia. *Journal of Head Trauma Rehabilitation*. https://doi.org/10.1097/HTR.0000000000000043

Alexander, S., Kerr, M. E., Yonas, H., & Marion, D. W. (2004). The effects of admission alcohol level on cerebral blood flow and outcomes after severe traumatic brain injury. *J Neurotrauma, 21*(5), 575-583.

Alway, Y., Gould, K. R., Johnston, L., McKenzie, D., & Ponsford, J. (2016, Apr). A prospective examination of Axis I psychiatric disorders in the first 5 years following moderate to severe traumatic brain injury. *Psychol Med, 46*(6), 1331-1341. https://doi.org/10.1017/s0033291715002986

Alway, Y., McKay, A., Ponsford, J., & Schönberger, M. (2012, 2013-02-20). Expressed emotion and its relationship to anxiety and depression after traumatic brain injury. *Neuropsychol Rehabil, 22*(3), 374-390. https://doi.org/http://dx.doi.org/10.1080/09602011.2011.648757

American Nurses Association. (2012). *Postion statement: Reduction of patient restraint and seclusion in health care settings*. http://www.nursingworld.org/restraintposition

Andelic, N., Jerstad, T., Sigurdardottir, S., Schanke, A. K., Sandvik, L., & Roe, C. (2010). Effects of acute substance use and pre-injury substance abuse on traumatic brain injury severity in adults admitted to a trauma centre. *J Trauma Manag Outcomes, 4*, 6. https://doi.org/10.1186/1752-2897-4-6

Andrewes, H. E., Walker, V., & O'Neill, B. (2014). Exploring the use of positive psychology interventions in brain injury survivors with challenging behaviour. *Brain Injury, 28*(7), 965-971. https://doi.org/http://dx.doi.org/10.3109/02699052.2014.888764

Anke, A., Andelic, N., Skandsen, T., Knoph, R., Ader, T., Manskow, U., Sigurdardottir, S., & Roe, C. (2015, 30 Jul). Functional Recovery and Life Satisfaction in the First Year after Severe Traumatic Brain Injury: A Prospective Multicenter Study of a Norwegian National Cohort [Review]. *Journal of Head Trauma Rehabilitation, 30*(4), E38-E49. https://doi.org/http://dx.doi.org/10.1097/HTR.0000000000000080

Anson, K., & Ponsford, J. (2006, Jan). Who benefits? Outcome following a coping skills group intervention for traumatically brain injured individuals. *Brain Inj, 20*(1), 1-13. https://doi.org/10.1080/02699050500309791

Arundine, A., Bradbury, C. L., Dupuis, K., Dawson, D. R., Ruttan, L. A., & Green, R. E. A. (2012). Cognitive behavior therapy after acquired brain injury: Maintenance of therapeutic benefits at 6 months posttreatment. *Journal of Head Trauma Rehabilitation, 27*(2), 104-112. http://www.scopus.com/inward/record.url?eid=2-s2.0-84858129657&partnerID=40&md5=bdbca733430ca1568bd97246027949e9

Ashman, T., Cantor, J. B., Tsaousides, T., Spielman, L., & Gordon, W. (2014, 10 Dec). Comparison of cognitive behavioral therapy and supportive psychotherapy for the treatment of depression following traumatic brain injury: A randomized controlled trial. *Journal of Head Trauma Rehabilitation, 29*(6), 467-478. https://doi.org/http://dx.doi.org/10.1097/HTR.0000000000000098

Ashman, T. A., Cantor, J. B., Gordon, W. A., Spielman, L., Flanagan, S., Ginsberg, A., Engmann, C., Egan, M., Ambrose, F., & Greenwald, B. (2009). A Randomized Controlled Trial of Sertraline for the Treatment of Depression in Persons With Traumatic Brain Injury. *Archives of Physical Medicine and Rehabilitation, 90*(5), 733-740.

Ashworth, F., Clarke, A., Jones, L., Jennings, C., & Longworth, C. (2015, Jun). An exploration of compassion focused therapy following acquired brain injury [Clinical Trial]. *Psychology & Psychotherapy: Theory, Research & Practice, 88*(2), 143-162. https://doi.org/http://dx.doi.org/10.1111/papt.12037

Assonov, D. (2021). Two-step resilience-oriented intervention for veterans with traumatic brain injury: A pilot randomized controlled trial. *Clinical Neuropsychiatry: Journal of Treatment Evaluation, 18*(5), 247-259.

Azouvi, P., Jokic, C., Attal, N., Denys, P., Markabi, S., & Bussel, B. (1999). Carbamazepine in agitation and aggressive behaviour following severe closed-head injury: Results of an open trial. *Brain Injury, 13*(10), 797-804.

Babbage, D. R., Zupan, B., Neumann, D., & Willer, B. (2018). Sex differences in response to emotion recognition training after traumatic brain injury. *Brain Injury, 32*(12), 1492-1499. https://doi.org/http://dx.doi.org/10.1080/02699052.2018.1497811

Baguley, I. J., Cooper, J., & Felmingham, K. (2006). Aggressive behavior following traumatic brain injury: How common is common? *Journal of Head Trauma Rehabilitation, 21*(1), 45-56.

Bahraini, N. H., Simpson, G. K., Brenner, L. A., Hoffberg, A. S., & Schneider, A. L. (2013, May). Suicidal ideation and behaviours after traumatic brain injury: A systematic review [Review]. *Brain Impairment, 14*(1), 92-112. https://doi.org/http://dx.doi.org/10.1017/BrImp.2013.11

Bakchine, S., Lacomblez, L., Benoit, N., Parisot, D., Chain, F., & Lhermitte, F. (1989). Manic-like state after bilateral orbitofrontal and right temporoparietal injury: Efficacy of clonidine. *Neurology, 39*(6), 777-781. http://www.scopus.com/inward/record.url?eid=2-s2.0-0024340337&partnerID=40&md5=e631b49f9a9b370c14c5c27fea2f8deb

Balba, N. M., Elliott, J. E., Weymann, K. B., Opel, R. A., Duke, J. W., Oken, B. S., Morasco, B. J., Heinricher, M. M., & Lim, M. M. (2018, Nov 15). Increased Sleep Disturbances and Pain in Veterans With Comorbid Traumatic Brain Injury and Posttraumatic Stress Disorder. *J Clin Sleep Med, 14*(11), 1865-1878. https://doi.org/10.5664/jcsm.7482

Banos, J. H., Novack, T. A., Brunner, R., Renfroe, S., Lin, H. Y., & Meythaler, J. (2010, Sep-Oct). Impact of early administration of sertraline on cognitive and behavioral recovery in the first year after moderate to severe traumatic brain injury. *J Head Trauma Rehabil, 25*(5), 357-361. https://doi.org/10.1097/HTR.0b013e3181d6c715

Barker-Collo, S., Theadom, A., Ameratunga, S., Jones, K., Jones, A., Starkey, N., & Feigin, V. L. (2013). Prevalence and predictors of post-traumatic stress disorder in adults one year following traumatic brain injury: A population-based study. *Brain Impairment, 14*(3), 425-435. https://doi.org/10.1017/BrImp.2013.27

Barnes, S. M., Monteith, L. L., Gerard, G. R., Hoffberg, A. S., Homaifar, B. Y., & Brenner, L. A. (2017, Nov 2017). Problem-solving therapy for suicide prevention in veterans with moderate-to-severe traumatic brain injury. *Rehabil Psychol, 62*(4), 600-608. https://doi.org/http://dx.doi.org/10.1037/rep0000154

Barua, U., Ahrens, J., Shao, R., McKenzie, H., Wolfe, D., Sequeira, K., Teasell, R., Loh, E., & Mehta, S. (2024, Feb 6). Cognitive behavioral therapy for managing depressive and anxiety symptoms after brain injury: a meta-analysis. *Brain Inj*, 1-14. https://doi.org/10.1080/02699052.2024.2309264

Bateman, A., Culpan, F. J., Pickering, A. D., Powell, J. H., Scott, O. M., & Greenwood, R. J. (2001, Feb). The effect of aerobic training on rehabilitation outcomes after recent severe brain injury: a randomized controlled evaluation. *Arch Phys Med Rehabil, 82*(2), 174-182. https://doi.org/10.1053/apmr.2001.19744

Bay, E., & Covassin, T. (2012). Chronic Stress, Somatic and Depressive Symptoms Following Mild to Moderate Traumatic Brain Injury. *Archives of Psychiatric Nursing, 26*(6), 477-486. https://doi.org/10.1016/j.apnu.2012.06.002

Bedard, M., Felteau, M., Mazmanian, D., Fedyk, K., Klein, R., Richardson, J., Parkinson, W., & Minthorn-Biggs, M.-B. (2003). Pilot evaluation of a mindfulness-based intervention to improve quality of life among individuals who sustained traumatic brain injuries. *Disability & Rehabilitation, 25*(13), 722-731. https://doi.org/10.1080/0963828031000090489

Bell, K. R., Brockway, J. A., Hart, T., Whyte, J., Sherer, M., Fraser, R. T., Temkin, N. R., & Dikmen, S. S. (2011, Oct). Scheduled telephone intervention for traumatic brain injury: a multicenter randomized controlled trial. *Arch Phys Med Rehabil, 92*(10), 1552-1560. https://doi.org/10.1016/j.apmr.2011.05.018

Bell, K. R., Fogelberg, D., Barber, J., Nakase-Richardson, R., Zumsteg, J. M., Dubiel, R., Dams-O'Connor, K., & Hoffman, J. M. (2021). The effect of phototherapy on sleep during acute rehabilitation after traumatic brain injury: a randomized controlled trial. *Brain Injury, 35*(2), 180-188. https://doi.org/https://dx.doi.org/10.1080/02699052.2021.1871952

Bellon, K., Kolakowsky-Hayner, S., Wright, J., Huie, H., Toda, K., Bushnik, T., & Englander, J. (2015, 01 Mar). A home-based walking study to ameliorate perceived stress and depressive symptoms in people with a traumatic brain injury. *Brain Injury, 29*(3), 313-319. https://doi.org/http://dx.doi.org/10.3109/02699052.2014.974670

Bergquist, T., Gehl, C., Mandrekar, J., Lepore, S., Hanna, S., Osten, A., & Beaulieu, W. (2009). The effect of internet-based cognitive rehabilitation in persons with memory impairments after severe traumatic brain injury. *Brain Injury, 23*(10), 790-799. https://doi.org/http://dx.doi.org/10.1080/02699050903196688

Berry, C., Salim, A., Alban, R., Mirocha, J., Margulies, D. R., & Ley, E. J. (2010). Serum ethanol levels in patients with moderate to severe traumatic brain injury influence outcomes: A surprising finding. *American Surgeon, 76*(10), 1067-1070.

Berthier, M. L., Kulisevsky, J., Gironell, A., & López, O. L. (2001). Obsessive-compulsive disorder and traumatic brain injury: Behavioral, cognitive, and neuroimaging findings. *Neuropsychiatry, Neuropsychology and Behavioral Neurology, 14*(1), 23-31. http://www.scopus.com/inward/record.url?eid=2-s2.0-0034745793&partnerID=40&md5=cbd93f230e5c9c59ad7d908350227ec7

Bertisch, H. C., Long, C., Langenbahn, D. M., Rath, J. F., Diller, L., & Ashman, T. (2013, Nov). Anxiety as a primary predictor of functional impairment after acquired brain injury: a brief report. *Rehabil Psychol, 58*(4), 429-435. https://doi.org/10.1037/a0034554

Besson, M., & Schon, D. (2001, Jun). Comparison between language and music. *Ann N Y Acad Sci, 930*, 232-258.

Betchel, N. T., Fariba, K. A., & Saadabadi, A. (2023). *Lamotrigine*. StatPearls Publishing.

Bhugra, D., Till, A., & Sartorius, N. (2013). *What is mental health?* (0020-7640).

Bilodeau, V., Saavedra-Mitjans, M., Frenette, A. J., Burry, L., Albert, M., Bernard, F., & Williamson, D. R. (2021). Safety of dexmedetomidine for the control of agitation in critically ill traumatic brain injury patients: a descriptive study. *Journal of clinical pharmacy and therapeutics, 46*(4), 1020-1026. https://doi.org/https://dx.doi.org/10.1111/jcpt.13389

Birks, J. S., & Evans, J. G. (2015). Rivastigmine for Alzheimer's disease. *Cochrane Database of systematic reviews*(4).

Bjork, J. M., & Grant, S. J. (2009). Does traumatic brain injury increase risk for substance abuse? *J Neurotrauma, 26*(7), 1077-1082.

Blake, H., & Batson, M. (2009). Exercise intervention in brain injury: A pilot randomized study of Tai Chi Qigong. *Clinical Rehabilitation, 23*(7), 589-598.

Blick, S. K., & Keating, G. M. (2007). Lisdexamfetamine. *Paediatr Drugs, 9*(2), 129-135; discussion 136-128. https://doi.org/10.2165/00148581-200709020-00007

Blin, O., Azorin, J. M., & Bouhours, P. (1996, Feb). Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. *J Clin Psychopharmacol, 16*(1), 38-44. https://doi.org/10.1097/00004714-199602000-00007

Bogner, J., Barrett, R. S., Hammond, F. M., Horn, S. D., Corrigan, J. D., Rosenthal, J., Beaulieu, C. L., Waszkiewicz, M., Shea, T., Reddin, C. J., Cullen, N., Giuffrida, C. G., Young, J., & Garmoe, W. (2015, Aug). Predictors of Agitated Behavior During Inpatient Rehabilitation for Traumatic Brain Injury. *Arch Phys Med Rehabil, 96*(8 Suppl), S274-281.e274. https://doi.org/10.1016/j.apmr.2015.04.020

Bogner, J., Corrigan, J. D., Peng, J., Kane, C., & Coxe, K. (2021). Comparative effectiveness of a brief intervention for alcohol misuse following traumatic brain injury: A randomized controlled trial. *Rehabil*

Psychol((Bogner, Corrigan, Kane) Department of Physical Medicine and Rehabilitation(Peng) Center for Biostatistics(Coxe) College of Social Work). https://doi.org/https://dx.doi.org/10.1037/rep0000405

Bogner, J. A., Corrigan, J. D., Spafford, D. E., & Lamb-Hart, G. L. (1997). Integrating substance abuse treatment and vocational rehabilitation after traumatic brain injury. *Journal of Head Trauma Rehabilitation, 12*(5), 57-71. http://www.scopus.com/inward/record.url?eid=2-s2.0-0030662507&partnerID=40&md5=2e90b13add503c9f42872b7e6a974975

Bombardier, C. H., Bell, K. R., Temkin, N. R., Fann, J. R., Hoffman, J., & Dikmen, S. (2009, Jul-Aug). The efficacy of a scheduled telephone intervention for ameliorating depressive symptoms during the first year after traumatic brain injury. *J Head Trauma Rehabil, 24*(4), 230-238. https://doi.org/10.1097/HTR.0b013e3181ad65f0

Bombardier, C. H., Hoekstra, T., Dikmen, S., & Fann, J. R. (2016). Depression trajectories during the first year after traumatic brain injury. *J Neurotrauma, 33*(23), 2115-2124. https://doi.org/http://dx.doi.org/10.1089/neu.2015.4349

Bombardier, C. H., Rimmele, C. T., & Zintel, H. (2002). The magnitude and correlates of alcohol and drug use before traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 83*(12), 1765-1773.

Bombardier, C. H., Temkin, N. R., Machamer, J., & Dikmen, S. S. (2003). The natural history of drinking and alcohol-related problems after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 84*(2), 185-191.

Bombardier, C. H., & Thurber, C. A. (1998). Blood alcohol level and early cognitive status after traumatic brain injury. *Brain Injury, 12*(9), 725-734.

Bond, D. J., Lam, R. W., & Yatham, L. N. (2010, Aug). Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J Affect Disord, 124*(3), 228-234. https://doi.org/10.1016/j.jad.2009.11.008

Borgen, I. M. H., Lovstad, M., Hauger, S. L., Forslund, M. V., Kleffelgard, I., Andelic, N., Sveen, U., Soberg, H. L., Sigurdardottir, S., Winter, L., Lindstad, M. O., Brunborg, C., & Roe, C. (2023). Effect of an Individually

Tailored and Home-Based Intervention in the Chronic Phase of Traumatic Brain Injury: A Randomized Clinical Trial. *JAMA network open, 6*(5), e2310821. https://doi.org/https://dx.doi.org/10.1001/jamanetworkopen.2023.10821

Bornhofen, C., & McDonald, S. (2008a, Mar-Apr). Comparing strategies for treating emotion perception deficits in traumatic brain injury. *J Head Trauma Rehabil, 23*(2), 103-115. https://doi.org/10.1097/01.Htr.0000314529.22777.43

Bornhofen, C., & McDonald, S. (2008b, Jan). Treating deficits in emotion perception following traumatic brain injury. *Neuropsychol Rehabil, 18*(1), 22-44. https://doi.org/10.1080/09602010601061213

Bosma, C. M., Mansoor, N., & Haller, C. S. (2018, Aug). Association of Posttraumatic Stress Symptom Severity With Health-Related Quality of Life and Self-Reported Functioning Across 12 Months After Severe Traumatic Brain Injury. *Arch Phys Med Rehabil, 99*(8), 1576-1583. https://doi.org/10.1016/j.apmr.2018.02.008

Bradbury, C. L., Christensen, B. K., Lau, M. A., Ruttan, L. A., Arundine, A. L., & Green, R. E. (2008, Dec). The efficacy of cognitive behavior therapy in the treatment of emotional distress after acquired brain injury. *Arch Phys Med Rehabil, 89*(12 Suppl), S61-68. https://doi.org/10.1016/j.apmr.2008.08.210

Brasure, M., Lamberty, G. J., Sayer, N. A., Nelson, N. W., MacDonald, R., Ouellette, J., & Wilt, T. J. (2013). Participation after multidisciplinary rehabilitation for moderate to severe traumatic brain injury in adults: a systematic review. *Archives of Physical Medicine and Rehabilitation, 94*(7), 1398-1420.

Brenner, L. A., Forster, J. E., Hoffberg, A. S., Matarazzo, B. B., Hostetter, T. A., Signoracci, G., & Simpson, G. K. (2018, Oct 27). Window to Hope: A Randomized Controlled Trial of a Psychological Intervention for the Treatment of Hopelessness Among Veterans With Moderate to Severe Traumatic Brain Injury. *J Head Trauma Rehabil*. https://doi.org/10.1097/htr.0000000000000351

Britton, G. B. (2012). Cognitive and emotional behavioural changes associated with methylphenidate treatment: a review of preclinical studies. *The The International Journal of Neuropsychopharmacology, 15*(1), 41-53.

Brooke, M. M., Patterson, D. R., Questad, K. A., Cardenas, D., & Farrel-Roberts, L. (1992). The treatment of agitation during initial hospitalization after traumatic brain injury. *Archives of Physical Medicine and*

Rehabilitation, 73(10), 917-921. http://www.scopus.com/inward/record.url?eid=2-s2.0-0026775946&partnerID=40&md5=e67d805a29d0d80b4a6808bee4b12f20

Brotherton, F. A., Thomas, L. L., Wisotzek, I. E., & Milan, M. A. (1988). Social skills training in the rehabilitation of patients with traumatic closed head injury. *Archives of Physical Medicine and Rehabilitation, 69*(10), 827-832. http://www.scopus.com/inward/record.url?eid=2-s2.0-0023815427&partnerID=40&md5=72ced045dbd6a666986a57aea2277fe4

Brown, A. P., Marquis, A., & Guiffrida, D. A. (2013). Mindfulness-Based Interventions in Counseling. *Journal of Counseling & Development 91*(1), 96-104.

Brunoni, A. R., Chaimani, A., Moffa, A. H., Razza, L. B., Gattaz, W. F., Daskalakis, Z. J., & Carvalho, A. F. (2017, Feb 1). Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. *JAMA Psychiatry, 74*(2), 143-152. https://doi.org/10.1001/jamapsychiatry.2016.3644

Bryant, R. (2011). Post-traumatic stress disorder vs traumatic brain injury. *Dialogues in clinical neuroscience*.

Bryant, R. A., Marosszeky, J. E., Crooks, J., Baguley, I. J., & Gurka, J. A. (2001, 2012-09-10). Posttraumatic stress disorder and psychosocial functioning after severe traumatic brain injury. *Journal of Nervous and Mental Disease, 189*(2), 109-113. https://doi.org/http://dx.doi.org/10.1097/00005053-200102000-00006

Bugg, A., Turpin, G., Mason, S., & Scholes, C. (2009). A randomised controlled trial of the effectiveness of writing as a self-help intervention for traumatic injury patients at risk of developing post-traumatic stress disorder. *Behaviour Research and Therapy, 47*(1), 6-12. https://doi.org/http://dx.doi.org/10.1016/j.brat.2008.10.006

Burke, W. H., Wesolowski, M. D., & Lane, I. (1988). A positive approach to the treatment of aggressive brain injured clients. *International Journal of Rehabilitation Research, 11*(3), 235-241. http://www.scopus.com/inward/record.url?eid=2-s2.0-0024153816&partnerID=40&md5=263d99d9280257369f36889ffe395ac5

Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006, Jan). The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev, 26*(1), 17-31. https://doi.org/10.1016/j.cpr.2005.07.003

Byrne, A., & Byrne, D. G. (1993, Sep). The effect of exercise on depression, anxiety and other mood states: a review. *J Psychosom Res, 37*(6), 565-574.

Byrne, C., & Coetzer, R. (2016, Jun 30). The effectiveness of psychological interventions for aggressive behavior following acquired brain injury: A meta-analysis and systematic review. *NeuroRehabilitation, 39*(2), 205-221. https://doi.org/10.3233/nre-161352

Cadet, J. L., Bisagno, V., & Milroy, C. M. (2014). Neuropathology of substance use disorders. *Acta neuropathologica, 127*, 91-107.

Campbell, I. N., Gallagher, M., McLeod, H. J., O'Neill, B., & McMillan, T. M. (2019, Jul). Brief compassion focused imagery for treatment of severe head injury. *Neuropsychol Rehabil, 29*(6), 917-927. https://doi.org/10.1080/09602011.2017.1342663

Campbell, M. (2000). *Rehabilitation for traumatic brain injury: physical therapy practice in context* (2 ed.). Churchill Livingstone

Cantor, J., Ashman, T., Dams-O'Connor, K., Dijkers, M. P., Gordon, W., Spielman, L., Tsaousides, T., Allen, H., Nguyen, M., & Oswald, J. (2014, Jan). Evaluation of the short-term executive plus intervention for executive dysfunction after traumatic brain injury: a randomized controlled trial with minimization. *Arch Phys Med Rehabil, 95*(1), 1-9.e3. https://doi.org/10.1016/j.apmr.2013.08.005

Carnevale, G. J., Anselmi, V., Johnston, M. V., Busichio, K., & Walsh, V. (2006). A Natural Setting Behavior Management Program for Persons With Acquired Brain Injury: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation, 87*(10), 1289-1297.

Carrier, S. L., Hicks, A. J., Ponsford, J., & McKay, A. (2021, Sep). Managing agitation during early recovery in adults with traumatic brain injury: An international survey. *Ann Phys Rehabil Med, 64*(5), 101532. https://doi.org/10.1016/j.rehab.2021.101532

Casañas, R., Catalán, R., del Val, J. L., Real, J., Valero, S., & Casas, M. (2012, Dec 18). Effectiveness of a psycho-educational group program for major depression in primary care: a randomized controlled trial. *BMC Psychiatry, 12*, 230. https://doi.org/10.1186/1471-244x-12-230

Chahine, L. M., & Chemali, Z. (2006). Du rire aux larmes: Pathological laughing and crying in patients with traumatic brain injury and treatment with lamotrigine. *Epilepsy and Behavior, 8*(3), 610-615. http://www.scopus.com/inward/record.url?eid=2-s2.0-33646112388&partnerID=40&md5=19c62471413575eb066ee8dcfc68304e

http://www.sciencedirect.com/science/article/pii/S152550500600028X

Chan, V., Toccalino, D., Omar, S., Shah, R., & Colantonio, A. (2022). A systematic review on integrated care for traumatic brain injury, mental health, and substance use. *PLoS One, 17*(3), e0264116. https://doi.org/10.1371/journal.pone.0264116

Chand, S. P., Arif, H., & Kutlenios, R. M. (2021). *Depression (nursing)*. StatPearls Publishing.

Chand, S. P., Kuckel, D. P., & Huecker, M. R. (2022). Cognitive behavior therapy. In *StatPearls [Internet]*. StatPearls Publishing.

Chand, S. P., Marwaha, R., & Bender, R. M. (2021). *Anxiety (nursing)*. StatPearls Publishing.

Chang, C., & Ramphul, K. (2018). *Amantadine*. StatPearls Publisher.

Chatham Showalter, P. E., & Kimmel, D. N. (2000, Summer). Agitated symptom response to divalproex following acute brain injury. *J Neuropsychiatry Clin Neurosci, 12*(3), 395-397.

Chiaravalloti, N. D., Sandry, J., Moore, N. B., & Deluca, J. (2016, 01 Jul). An RCT to Treat Learning Impairment in Traumatic Brain Injury. *Neurorehabil Neural Repair, 30*(6), 539-550.

Chin, L. M., Keyser, R. E., Dsurney, J., & Chan, L. (2015, Apr). Improved cognitive performance following aerobic exercise training in people with traumatic brain injury. *Arch Phys Med Rehabil, 96*(4), 754-759. https://doi.org/10.1016/j.apmr.2014.11.009

Chokhawala, K., Lee, S., & Saadabadi, A. (2023). Lithium. In *StatPearls*. StatPearls Publishing.

Clay, C. J., Bloom, S. E., & Lambert, J. M. (2018). Behavioral interventions for inappropriate sexual behavior in individuals with developmental disabilities and acquired brain injury: A review. *American Journal on Intellectual and Developmental Disabilities, 123*(3), 254-282. https://doi.org/http://dx.doi.org/10.1352/1944-7558-123.3.254

Cnossen, M. C., Scholten, A. C., Lingsma, H. F., Haagsma, J., & Polinder, S. (2016). Predicting major depression and posttraumatic stress disorder after traumatic brain injury: A systematic review. *Brain Injury, 30*(5-6), 517. https://doi.org/http://dx.doi.org/10.3109/02699052.2016.1162060 (11th World Congress on Brain Injury of the International Brain Injury Association. Netherlands.)

College of Nurses of Ontario. (2009). *The Standard of Care-Practice Standard*. http://www.cno.org

Combs, M. A., Critchfield, E. A., & Soble, J. R. (2018, May). Relax while you rehabilitate: A pilot study integrating a novel, yoga-based mindfulness group intervention into a residential military brain injury rehabilitation program. *Rehabil Psychol, 63*(2), 182-193. https://doi.org/10.1037/rep0000179

Connolly, L. J., Rajaratnam, S. M. W., Murray, J. M., Spitz, G., Lockley, S. W., & Ponsford, J. L. (2021). Home-based light therapy for fatigue following acquired brain injury: a pilot randomized controlled trial. *BMC neurology, 21*(1), 262. https://doi.org/https://dx.doi.org/10.1186/s12883-021-02292-8

Corallo, F., Maresca, G., Formica, C., Bonanno, L., Bramanti, A., Parasporo, N., Giambo, F. M., De Cola, M. C., & Lo Buono, V. (2022). Humanoid Robot Use in Cognitive Rehabilitation of Patients with Severe Brain Injury: A Pilot Study. *Journal of Clinical Medicine, 11*(10), 2940. https://doi.org/https://dx.doi.org/10.3390/jcm11102940

Corrigan, J. D. (2021, Sep 1). Traumatic Brain Injury and Treatment of Behavioral Health Conditions. *Psychiatr Serv, 72*(9), 1057-1064. https://doi.org/10.1176/appi.ps.201900561

De Luca, R., Bonanno, M., Marra, A., Rifici, C., Pollicino, P., Caminiti, A., Castorina, M. V., Santamato, A., Quartarone, A., & Calabro, R. S. (2023). Can Virtual Reality Cognitive Rehabilitation Improve Executive Functioning and Coping Strategies in Traumatic Brain Injury? A Pilot Study. *Brain Sciences, 13*(4), 578. https://doi.org/https://dx.doi.org/10.3390/brainsci13040578

De Luca, R., Calabrò, R. S., & Bramanti, P. (2018, Sep). Cognitive rehabilitation after severe acquired brain injury: current evidence and future directions. *Neuropsychol Rehabil, 28*(6), 879-898. https://doi.org/10.1080/09602011.2016.1211937

Deb, S., Aimola, L., Leeson, V., Bodani, M., Li, L., Weaver, T., Sharp, D., Bassett, P., & Crawford, M. (2020, Sep 10). Risperidone versus placebo for aggression following traumatic brain injury: a feasibility randomised controlled trial. *BMJ Open, 10*(9), e036300. https://doi.org/10.1136/bmjopen-2019-036300

Deb, S., Lyons, I., Koutzoukis, C., Ali, I., & McCarthy, G. (1999). Rate of psychiatric illness 1 year after traumatic brain injury. *American Journal of Psychiatry, 156*(3), 374-378.

DeLambo, D. A., Chandras, K. V., Homa, D., & Chandras, S. V. (2008). Psychiatric disabilities and substance abuse: Applications for rehabilitation professionals. *Compelling counseling intervention: Celebrating VISTAS'fifth anniversary*, 149-159.

Demark, J., & Gemeinhardt, M. (2002, Feb). Anger and it's management for survivors of acquired brain injury. *Brain Inj, 16*(2), 91-108. https://doi.org/10.1080/02699050110102059

Dikmen, S. S., Bombardier, C. H., MacHamer, J. E., Fann, J. R., & Temkin, N. R. (2004). Natural history of depression in traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 85*(9), 1457-1464. http://www.scopus.com/inward/record.url?eid=2-s2.0-4544237514&partnerID=40&md5=62747d7dcb0e925bc36d5840ec18954f

http://www.sciencedirect.com/science/article/pii/S0003999304002850

Dikmen, S. S., Machamer, J. E., Powell, J. M., & Temkin, N. R. (2003). Outcome 3 to 5 years after moderate to severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 84*(10), 1449-1457.

Dikmen, S. S., Temkin, N. R., Miller, B., Machamer, J., & Winn, H. R. (1991). Neurobehavioral Effects of Phenytoin Prophylaxis of Posttraumatic Seizures [Article]. *JAMA: The Journal of the American Medical Association, 265*(10), 1271-1277. https://doi.org/10.1001/jama.1991.03460100073027

DiVita, A., Procacci, M. A., Bellagamba, M., Jacomini, M., Massicci, R., & Ciurli, M. P. (2022). Psychotherapy and Art Therapy: A pilot study of group treatment for patients with traumatic brain injury. *Journal of Health Psychology, 27*(4), 836-846. https://doi.org/10.1177/1359105320967099

Dubiel, R., Callender, L., Dunklin, C., Harper, C., Bennett, M., Kreber, L., Auchus, R., & Diaz-Arrastia, R. (2018, 10 Sep). Phase 2 randomized, placebo-controlled clinical trial of recombinant human growth hormone (rhGH) during rehabilitation from traumatic brain injury. *Frontiers in Endocrinology, 9 (SEP) (no pagination)*(520).

Dubreucq, J., Haesebaert, F., Plasse, J., Dubreucq, M., & Franck, N. (2022, Apr). A Systematic Review and Meta-analysis of Social Skills Training for Adults with Autism Spectrum Disorder. *J Autism Dev Disord, 52*(4), 1598-1609. https://doi.org/10.1007/s10803-021-05058-w

Dundon, N. M., Dockree, S. P., Buckley, V., Merriman, N., Carton, M., Clarke, S., Roche, R. A., Lalor, E. C., Robertson, I. H., & Dockree, P. M. (2015, Aug). Impaired auditory selective attention ameliorated by cognitive training with graded exposure to noise in patients with traumatic brain injury. *Neuropsychologia, 75*, 74-87. https://doi.org/10.1016/j.neuropsychologia.2015.05.012

Duxbury, J., & Wright, K. (2011). Should nurses restrain violent and aggressive patients? *Nursing times, 107*(9), 22-25. http://www.scopus.com/inward/record.url?eid=2-s2.0-79959774077&partnerID=40&md5=127abad7e96c5859459e385df4dbe4b4

Eames, P., & Wood, R. (1985). Rehabilitation after severe brain injury: A follow-up study of a behaviour modification approach. *Journal of Neurology Neurosurgery and Psychiatry, 48*(7), 613-619. http://www.scopus.com/inward/record.url?eid=2-s2.0-0021808419&partnerID=40&md5=bbe270e8445a2a85a9558653ec37e3f6

Eisenberg, M. E., Im, B., Swift, P., & Flanagan, S. R. (2009, 2009-12-01). Management of Traumatic Brain Injury-Related Agitation. *21*(3-4), 215-229. https://doi.org/10.1615/CritRevPhysRehabilMed.v21.i3-4.20

Ekers, D., Webster, L., Van Straten, A., Cuijpers, P., Richards, D., & Gilbody, S. (2014). Behavioural activation for depression; an update of meta-analysis of effectiveness and sub group analysis. *PLoS One, 9*(6), e100100.

Elbogen, E. B., Alsobrooks, A., Battles, S., Molloy, K., Dennis, P. A., Beckham, J. C., McLean, S. A., Keith, J. R., & Russoniello, C. (2021). Mobile Neurofeedback for Pain Management in Veterans with TBI and PTSD. *Pain Medicine (United States), 22*(2), 329-337. https://doi.org/https://dx.doi.org/10.1093/pm/pnz269

Elbogen, E. B., Dennis, P. A., Van Voorhees, E. E., Blakey, S. M., Johnson, J. L., Johnson, S. C., Wagner, H. R., Hamer, R. M., Beckham, J. C., Manly, T., & Belger, A. (2019, Jan/Feb). Cognitive Rehabilitation With Mobile Technology and Social Support for Veterans With TBI and PTSD: A Randomized Clinical Trial. *J Head Trauma Rehabil, 34*(1), 1-10. https://doi.org/10.1097/htr.0000000000000435

Emory, L. E., Cole, C. M., & Meyer, W. J. (1995). Use of Depo-Provera to control sexual aggression in persons with traumatic brain injury. *Journal of Head Trauma Rehabilitation, 10*(3), 47-58. http://www.scopus.com/inward/record.url?eid=2-s2.0-0028869012&partnerID=40&md5=fb9b1e6d03314fee4ac70de2a38793c2

Evans, D., & FitzGerald, M. (2002). Reasons for physically restraining patients and residents: A systematic review and content analysis. *International Journal of Nursing Studies, 39*(7), 735-743. http://www.scopus.com/inward/record.url?eid=2-s2.0-0036730042&partnerID=40&md5=8e995cb94f7cac4536b9ae332f7a0722

http://www.sciencedirect.com/science/article/pii/S0020748902000159

Evans, J. J. (2011). Positive Psychology and Brain Injury Rehabilitation. *Brain Impairment, 12*(2), 117-127.

Fann, J. R., Bombardier, C. H., Temkin, N., Esselman, P., Warms, C., Barber, J., & Dikmen, S. (2017, Sep/Oct). Sertraline for Major Depression During the Year Following Traumatic Brain Injury: A Randomized Controlled Trial. *J Head Trauma Rehabil, 32*(5), 332-342. https://doi.org/10.1097/htr.0000000000000322

Fann, J. R., Bombardier, C. H., Vannoy, S., Dyer, J., Ludman, E., Dikmen, S., Marshall, K., Barber, J., & Temkin, N. (2015, 01 Jan). Telephone and in-person cognitive behavioral therapy for major depression after traumatic brain injury: A randomized controlled trial. *J Neurotrauma, 32*(1), 45-57. https://doi.org/http://dx.doi.org/10.1089/neu.2014.3423

Fann, J. R., Hart, T., & Schomer, K. G. (2009, Dec). Treatment for depression after traumatic brain injury: a systematic review. *J Neurotrauma, 26*(12), 2383-2402. https://doi.org/10.1089/neu.2009.1091

Fann, J. R., Katon, W. J., Uomoto, J. M., & Esselman, P. C. (1995). Psychiatric disorders and functional disability in outpatients with traumatic brain injuries. *American Journal of Psychiatry, 152*(10), 1493-1499. http://www.scopus.com/inward/record.url?eid=2-s2.0-0029098920&partnerID=40&md5=1053b16ee1c39ac8c5c7e991bdfe5c1b

http://psychiatryonline.org/data/Journals/AJP/3650/1493.pdf

Farlow, M. R. (2003, Sep). Update on rivastigmine. *Neurologist, 9*(5), 230-234. https://doi.org/10.1097/01.nrl.0000087724.73783.5f

Fasotti, L., Kovacs, F., Eling, P. A. T. M., & Brouwer, W. H. (2000). Time pressure management as a compensatory strategy training after closed head injury. *Neuropsychol Rehabil, 10*(1), 47-65. https://doi.org/http://dx.doi.org/10.1080/096020100389291

Fedder, D., Patel, H., & Saadabadi, A. (2023). Atomoxetine. In *StatPearls*. StatPearls Publishing.

Feeney, T. J., & Ylvisaker, M. (1995). Choice and routine: Antecedent behavioral interventions for adolescents with severe traumatic brain injury. *Journal of Head Trauma Rehabilitation, 10*(3), 67-86. http://www.scopus.com/inward/record.url?eid=2-s2.0-0028790413&partnerID=40&md5=2f918fd1b9878e42ec7a85b2bd8e3a33

Feiger, J. A., Snell, J., & Chiou, K. S. (2023). Neuropsychological functioning predicts psychosocial adjustment after postacute rehabilitation for traumatic brain injury. *Journal of the International Neuropsychological Society, 29*(4), 410-414. https://doi.org/https://dx.doi.org/10.1017/S1355617722000352

Feng, X., Zhao, B., & Wang, Y. (2022). Effect Evaluation of Dexmedetomidine Intravenous Anesthesia on Postoperative Agitation in Patients with Craniocerebral Injury by Magnetic Resonance Imaging Based on Sparse Reconstruction Algorithm. *Contrast Media and Molecular Imaging, 2022*((Feng, Zhao) Department of Anesthesia Surgery, First Affiliated Hospital, Heilongjiang University of Traditional Chinese Medicine, Heilongjiang, Harbin 150040, China(Wang) Department of Outpatient, Harbin Red Cross Central Hospital, Heilongjiang, Harbin 1), 5161703. https://doi.org/https://dx.doi.org/10.1155/2022/5161703

Ferretti, V., & Papaleo, F. (2019). Understanding others: emotion recognition in humans and other animals. *Genes, Brain and Behavior, 18*(1), e12544.

Finch, E., Copley, A., Cornwell, P., & Kelly, C. (2016, Aug). Systematic Review of Behavioral Interventions Targeting Social Communication Difficulties After Traumatic Brain Injury. *Arch Phys Med Rehabil, 97*(8), 1352-1365. https://doi.org/10.1016/j.apmr.2015.11.005

Fisher, L. B., Pedrelli, P., Iverson, G. L., Bergquist, T. F., Bombardier, C. H., Hammond, F. M., Hart, T., Ketchum, J. M., Giacino, J., & Zafonte, R. (2016, 21 Aug). Prevalence of suicidal behaviour following traumatic brain injury: Longitudinal follow-up data from the NIDRR Traumatic Brain Injury Model Systems [In Press]. *Brain Injury*, 1-8. https://doi.org/http://dx.doi.org/10.1080/02699052.2016.1195517

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in older adults. *Annual review of clinical psychology, 5*, 363-389.

Fleminger, S., Greenwood, R. J., & Oliver, D. L. (2006, Oct 18). Pharmacological management for agitation and aggression in people with acquired brain injury. *Cochrane Database Syst Rev*(4), Cd003299. https://doi.org/10.1002/14651858.CD003299.pub2

Fleminger, S., Oliver, D. L., Williams, W. H., & Evans, J. (2003, Jan-Mar). The neuropsychiatry of depression after brain injury. *Neuropsychol Rehabil, 13*(1-2), 65-87. https://doi.org/10.1080/09602010244000354

Force, D. V. T. B. I. T. (2008). *Report to the Surgeon General: Traumatic Brain Injury Task Force*.

Formisano, R., Vinicola, V., Penta, F., Matteis, M., Brunelli, S., & Weckel, J. W. (2001). Active music therapy in the rehabilitation of severe brain injured patients during coma recovery. *Annali dell'Istituto Superiore di Sanita, 37*(4), 627-630. http://www.scopus.com/inward/record.url?eid=2-s2.0-0035527518&partnerID=40&md5=fecf6d3d41cd0d2d1c14b3dc03a151a9

Fraser, E. E., Downing, M. G., Haines, K., Bennett, L., Olver, J., & Ponsford, J. L. (2022). Evaluating a Novel Treatment Adapting a Cognitive Behaviour Therapy Approach for Sexuality Problems after Traumatic Brain Injury: A Single Case Design with Nonconcurrent Multiple Baselines. *Journal of Clinical Medicine, 11*(12), 3525. https://doi.org/https://dx.doi.org/10.3390/jcm11123525

Galimberti, A., Tik, M., Pellegrino, G., & Schuler, A.-L. (2023). Effectiveness of rTMS and tDCS treatment for chronic TBI symptoms: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 110863.

Gilbert, P. (2009). Introducing compassion-focused therapy. *Advances in Psychiatric Treatment, 15*, 199-208.

Gilbert, P. (2014, Mar). Compassion-focused therapy: Preface and introduction for special section. *Br J Clin Psychol, 53*(1), 1-5. https://doi.org/10.1111/bjc.12045

Glenn, M. B., Wroblewski, B., Parziale, J., Levine, L., Whyte, J., & Rosenthal, M. (1989). Lithium carbonate for aggressive behavior or affective instability in ten brain-injured patients. *American Journal of Physical Medicine and Rehabilitation, 68*(5), 221-226. http://www.scopus.com/inward/record.url?eid=2-s2.0-0024374407&partnerID=40&md5=8752ac5a0a88bf5c998fed4630fbe0ff

Goessl, V. C., Curtiss, J. E., & Hofmann, S. G. (2017, Nov). The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. *Psychol Med, 47*(15), 2578-2586. https://doi.org/10.1017/s0033291717001003

Gordon, W. A., Sliwinski, M., Echo, J., McLoughlin, M., Sheerer, M., & Meili, T. E. (1998). The benefits of exercise in individuals with traumatic brain injury: A retrospective study. *Journal of Head Trauma Rehabilitation, 13*(4), 58-67. http://www.scopus.com/inward/record.url?eid=2-s2.0-0031657401&partnerID=40&md5=53eaa2ba954b0d28accdfb11940587cd

Gould, K. R., Ponsford, J. L., Johnston, L., & Schonberger, M. (2011, Oct). The nature, frequency and course of psychiatric disorders in the first year after traumatic brain injury: a prospective study. *Psychol Med, 41*(10), 2099-2109. https://doi.org/10.1017/s003329171100033x

Gould, K. R., Ponsford, J. L., & Spitz, G. (2014). Association between cognitive impairments and anxiety disorders following traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology, 36*(1), 1-14. http://www.scopus.com/inward/record.url?eid=2-s2.0-84893865920&partnerID=40&md5=6ef33a37954119930dab0c9b1f6fbd67

http://www.tandfonline.com/doi/abs/10.1080/13803395.2013.863832?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Graham, C. D., Gouick, J., Krahé, C., & Gillanders, D. (2016). A systematic review of the use of Acceptance and Commitment Therapy (ACT) in chronic disease and long-term conditions. *Clin Psychol Rev, 46*, 46–58.

Grauwmeijer, E., Heijenbrok-Kal, M. H., Peppel, L. D., Hartjes, C. J., Haitsma, I. K., de Koning, I., & Ribbers, G. M. (2018, 2018 Jul 01

2019-02-14). Cognition, health-related quality of life, and depression ten years after moderate to severe traumatic brain injury: A prospective cohort study. *J Neurotrauma, 35*(13), 1543-1551. https://doi.org/http://dx.doi.org/10.1089/neu.2017.5404

Greenberg, P. E., Fournier, A.-A., Sisitsky, T., Pike, C. T., & Kessler, R. C. (2015). The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *The Journal of clinical psychiatry, 76*(2), 5356.

Greenblatt, K., & Adams, N. (2018). *Modafinil*. StatPearls Publishing.

Grima, N. A., Rajaratnam, S. M. W., Mansfield, D., Sletten, T. L., Spitz, G., & Ponsford, J. L. (2018, Jan 19). Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. *BMC Med, 16*(1), 8. https://doi.org/10.1186/s12916-017-0995-1

Gualtieri, C. T., & Evans, R. W. (1988, Oct-Dec). Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. *Brain Inj, 2*(4), 273-290.

Guétin, S., Soua, B., Voiriot, G., Picot, M. C., & Hérisson, C. (2009). The effect of music therapy on mood and anxiety-depression: An observational study in institutionalised patients with traumatic brain injury. *Ann Phys Rehabil Med, 52*(1), 30-40. http://www.scopus.com/inward/record.url?eid=2-s2.0-61749095580&partnerID=40&md5=6e30b654927a2721be494fa81e3eba56

Gupta, M., & Tripp, J. (2019). *Phenytoin*. Stat Pearls.

Gutierrez, P. M., Brenner, L. A., & Huggins, J. A. (2008, October). A preliminary investigation of suicidality in psychiatrically hospitalized veterans with traumatic brain injury. *Archives of Suicide Research, 12*(4), 336-343. https://doi.org/http://dx.doi.org/10.1080/13811110802324961

Haertl, K. L., & Ero-Phillips, A. M. (2019). The healing properties of writing for persons with mental health conditions. *Arts & Health, 11*(1), 15-25.

Hammond, D. C. (2005, Jan). Neurofeedback with anxiety and affective disorders. *Child Adolesc Psychiatr Clin N Am, 14*(1), 105-123, vii. https://doi.org/10.1016/j.chc.2004.07.008

Hammond, F. M., Bickett, A. K., Norton, J. H., & Pershad, R. (2014, 01 Sep). Effectiveness of amantadine hydrochloride in the reduction of chronic traumatic brain injury irritability and aggression. *Journal of Head Trauma Rehabilitation, 29*(5), 391-399. https://doi.org/http://dx.doi.org/10.1097/01.HTR.0000438116.56228.de

Hammond, F. M., Malec, J. F., Zafonte, R. D., Sherer, M., Bogner, J., Dikmen, S., Whitney, M. P., Bell, K. R., Perkins, S. M., & Moser, E. A. (2017, Sep/Oct). Potential Impact of Amantadine on Aggression in Chronic Traumatic Brain Injury. *J Head Trauma Rehabil, 32*(5), 308-318. https://doi.org/10.1097/htr.0000000000000342

Hammond, F. M., Sherer, M., Malec, J. F., Zafonte, R. D., Whitney, M., Bell, K., Dikmen, S., Bogner, J., Mysiw, J., Pershad, R., & Amantadine Irritability Multisite Study, G. (2015, Aug 15). Amantadine Effect on Perceptions of Irritability after Traumatic Brain Injury: Results of the Amantadine Irritability Multisite Study. *J Neurotrauma, 32*(16), 1230-1238. https://doi.org/http://dx.doi.org/10.1089/neu.2014.3803

Hanks, R. A., Rapport, L. J., Wertheimer, J., & Koviak, C. (2012, Aug). Randomized controlled trial of peer mentoring for individuals with traumatic brain injury and their significant others. *Arch Phys Med Rehabil, 93*(8), 1297-1304. https://doi.org/10.1016/j.apmr.2012.04.027

Harmer, B., Lee, S., Duong, T., & Saadabadi, A. (2020). Suicidal ideation.

Harris, W. S. (2004, Mar). Fish oil supplementation: evidence for health benefits. *Cleve Clin J Med, 71*(3), 208-210, 212, 215-208 passim. https://doi.org/10.3949/ccjm.71.3.208

Hart, T., Brockway, J. A., Maiuro, R. D., Vaccaro, M., Fann, J. R., Mellick, D., Harrison-Felix, C., Barber, J., & Temkin, N. (2017, Sep/Oct). Anger Self-Management Training for Chronic Moderate to Severe Traumatic Brain Injury: Results of a Randomized Controlled Trial. *J Head Trauma Rehabil, 32*(5), 319-331. https://doi.org/10.1097/htr.0000000000000316

Hart, T., Fann, J. R., Chervoneva, I., Juengst, S. B., Rosenthal, J. A., Krellman, J. W., Dreer, L. E., & Kroenke, K. (2016). Prevalence, Risk Factors, and Correlates of Anxiety at 1 Year after Moderate to Severe Traumatic Brain Injury. *Archives of Physical Medicine and Rehabilitation, 97*(5), 701-707. https://doi.org/http://dx.doi.org/10.1016/j.apmr.2015.08.436

Hart, T., Vaccaro, M., Collier, G., Chervoneva, I., & Fann, J. R. (2020, Sep). Promoting mental health in traumatic brain injury using single-session Behavioural Activation and SMS messaging: A randomized controlled trial. *Neuropsychol Rehabil, 30*(8), 1523-1542. https://doi.org/10.1080/09602011.2019.1592761

Hart, T., & Vaccaro, M. J. (2017). Goal intention reminding in traumatic brain injury: A feasibility study using implementation intentions and text messaging. *Brain Inj, 31*(3), 297-303. https://doi.org/10.1080/02699052.2016.1251612

Hart, T., Vaccaro, M. J., Hays, C., & Maiuro, R. D. (2012). Anger self-management training for people with traumatic brain injury: A preliminary investigation. *Journal of Head Trauma Rehabilitation, 27*(2), 113-122. http://www.scopus.com/inward/record.url?eid=2-s2.0-84858155824&partnerID=40&md5=df887d08ae6e2a350b108cb3206e3882

http://graphics.tx.ovid.com/ovftpdfs/FPDDNCLBEHDGJD00/fs046/ovft/live/gv023/00001199/00001199-201203000-00005.pdf

Hart, T., Whyte, J., Watanabe, T., & Chervoneva, I. (2018, Apr). Effects of dextroamphetamine in subacute traumatic brain injury: A randomized, placebo-controlled pilot study. *J Neurosci Res, 96*(4), 702-710. https://doi.org/10.1002/jnr.24102

Hassett, L. M., Moseley, A. M., Tate, R. L., Harmer, A. R., Fairbairn, T. J., & Leung, J. (2009, Mar). Efficacy of a fitness centre-based exercise programme compared with a home-based exercise programme in traumatic brain injury: a randomized controlled trial. *J Rehabil Med, 41*(4), 247-255. https://doi.org/10.2340/16501977-0316

Hibbard, M. R., Uysal, S., Kepler, K., Bogdany, J., & Silver, J. (1998). Axis I psychopathology in individuals with traumatic brain injury. *Journal of Head Trauma Rehabilitation, 13*(4), 24-39. http://www.scopus.com/inward/record.url?eid=2-s2.0-0031691210&partnerID=40&md5=440acf99a39d005aa1e0f6f77107d6f0

High, W. M., Jr., Briones-Galang, M., Clark, J. A., Gilkison, C., Mossberg, K. A., Zgaljardic, D. J., Masel, B. E., & Urban, R. J. (2010, Sep). Effect of growth hormone replacement therapy on cognition after traumatic brain injury. *J Neurotrauma, 27*(9), 1565-1575. https://doi.org/10.1089/neu.2009.1253

Hoffman, J. M., Bell, K. R., Powell, J. M., Behr, J., Dunn, E. C., Dikmen, S., & Bombardier, C. H. (2010). A randomized controlled trial of exercise to improve mood after traumatic brain injury. *PM and R, 2*(10), 911-919. http://www.scopus.com/inward/record.url?eid=2-s2.0-77958183025&partnerID=40&md5=1ae700bc01674aeea64f09e5f1ea7546

http://www.sciencedirect.com/science/article/pii/S1934148210005095

Howlett, J. R., Nelson, L. D., & Stein, M. B. (2022, Mar 1). Mental Health Consequences of Traumatic Brain Injury. *Biol Psychiatry, 91*(5), 413-420. https://doi.org/10.1016/j.biopsych.2021.09.024

Hsieh, M. Y., Ponsford, J., Wong, D., & McKay, A. (2012). Exploring variables associated with change in cognitive behaviour therapy (CBT) for anxiety following traumatic brain injury. *Disability and Rehabilitation, 34*(5), 408-415. http://www.scopus.com/inward/record.url?eid=2-s2.0-84855928249&partnerID=40&md5=2de1ef68b4d23f72c351a0a6750dfd45

http://informahealthcare.com/doi/pdfplus/10.3109/09638288.2011.607219

Hsieh, M. Y., Ponsford, J., Wong, D., Schonberger, M., Taffe, J., & McKay, A. (2012). Motivational interviewing and cognitive behaviour therapy for anxiety following traumatic brain injury: a pilot randomised controlled trial. *Neuropsychol Rehabil, 22*(4), 585-608. https://doi.org/10.1080/09602011.2012.678860

Hudak, A. M., Hynan, L. S., Harper, C. R., & Diaz-Arrastia, R. (2012, Mar-Apr). Association of depressive symptoms with functional outcome after traumatic brain injury. *J Head Trauma Rehabil, 27*(2), 87-98. https://doi.org/10.1097/HTR.0b013e3182114efd

Hughes, R., Fleming, P., & Henshall, L. (2020, Jun 6). Peer support groups after acquired brain injury: a systematic review. *Brain Inj, 34*(7), 847-856. https://doi.org/10.1080/02699052.2020.1762002

Igoe, A., Twomey, D. M., Allen, N., Carton, S., Brady, N., & O'Keeffe, F. (2023, Apr 6). A longitudinal analysis of factors associated with post traumatic growth after acquired brain injury. *Neuropsychol Rehabil*, 1-23. https://doi.org/10.1080/09602011.2023.2195190

Iguina, M. M., & Kashan, S. (2019). *Art therapy*.

Inoue, C., Shawler, E., Jordan, C. H., Moore, M. J., & Jackson, C. A. (2023). Veteran and Military Mental Health Issues. In *StatPearls*. StatPearls Publishing.

Jagger, J., Fife, D., Vernberg, K., & Jane, J. A. (1984). Effect of alcohol intoxication on the diagnosis and apparent severity of brain injury. *Neurosurgery, 15*(3), 303-306. http://www.scopus.com/inward/record.url?eid=2-s2.0-0021143336&partnerID=40&md5=fe1700ed96f0ef19d517726680d5c253

Janzen, S., McIntyre, A., Meyer, M., Sequeira, K., & Teasell, R. (2014). The management of agitation among inpatients in a brain injury rehabilitation unit. *Brain Injury, 28*(3), 318-322. https://doi.org/http://dx.doi.org/10.3109/02699052.2013.860478

Jarosz, K., Kojder, K., Andrzejewska, A., Solek-Pastuszka, J., & Jurczak, A. (2023, Mar 17). Cerebrolysin in Patients with TBI: Systematic Review and Meta-Analysis. *Brain Sci, 13*(3). https://doi.org/10.3390/brainsci13030507

Jean-Bay, E. (2000). The biobehavioral correlates of post-traumatic brain injury depression. *The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses, 32*(3), 169-176. http://www.scopus.com/inward/record.url?eid=2-s2.0-0034201589&partnerID=40&md5=0b9284ad56cedc3aecd64cb7690e4dca

Jenkins, P. O., De Simoni, S., Bourke, N. J., Fleminger, J., Scott, G., Towey, D. J., Svensson, W., Khan, S., Patel, M. C., Greenwood, R., Friedland, D., Hampshire, A., Cole, J. H., & Sharp, D. J. (2019, Aug 1). Stratifying drug treatment of cognitive impairments after traumatic brain injury using neuroimaging. *Brain, 142*(8), 2367-2379. https://doi.org/10.1093/brain/awz149

Jha, A., Weintraub, A., Allshouse, A., Morey, C., Cusick, C., Kittelson, J., Harrison-Felix, C., Whiteneck, G., & Gerber, D. (2008, Jan-Feb). A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil, 23*(1), 52-63. https://doi.org/10.1097/01.HTR.0000308721.77911.ea

Jorge, R. E. (2005). Neuropsychiatric consequences of traumatic brain injury: A review of recent findings. *Current Opinion in Psychiatry, 18*(3), 289-299. http://www.scopus.com/inward/record.url?eid=2-s2.0-17844405052&partnerID=40&md5=6b7cba3f46f4745f62e4fa4582d0215e

http://graphics.tx.ovid.com/ovftpdfs/FPDDNCLBEHDGJD00/fs046/ovft/live/gv023/00001504/00001504-200505000-00012.pdf

Kagan, I., Mesilati-Stahy, R., Green, P., & Singer, P. (2021). Effect of Supplemental Enteral Fish Oil on the Development of Psychological Complications in Critically Ill Multiple-Trauma Patients: 6 Months' Follow-Up. *Journal of Parenteral and Enteral Nutrition, 45*(7), 1567-1580. https://doi.org/https://dx.doi.org/10.1002/jpen.2025

Kant, R., Smith-Seemiller, L., & Zeiler, D. (1998). Treatment of aggression and irritability after head injury. *Brain Injury, 12*(8), 661-666. http://www.scopus.com/inward/record.url?eid=2-s2.0-0031846958&partnerID=40&md5=6a4a2921a298cc8e4706066a1a986c6e

http://www.ingentaconnect.com/content/apl/tbin/1998/00000012/00000008/art00003?token=005112bd04383a4b3b2570747b5f243f3853382063212a726e2d2954496f642f466fb07469354ffff

Keller, M. B., Kocsis, J. H., Thase, M. E., Gelenberg, A. J., Rush, A. J., Koran, L., Schatzberg, A., Russell, J., Hirschfeld, R., Klein, D., McCullough, J. P., Fawcett, J. A., Kornstein, S., LaVange, L., & Harrison, W. (1998,

Nov 18). Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *Jama, 280*(19), 1665-1672. https://doi.org/10.1001/jama.280.19.1665

Kelly, M. P., Johnson, C. T., Knoller, N., Drubach, D. A., & Winslow, M. M. (1997, Jun). Substance abuse, traumatic brain injury and neuropsychological outcome. *Brain Inj, 11*(6), 391-402. http://www.ingentaconnect.com/content/apl/tbin/1997/00000011/00000006/art00001?token=004f1a13df55fa2c427e41225f40382d2c7467477677342445495 76b3427656c3c6a333f25666a8

Kemp, S., Biswas, R., Neumann, V., & Coughlan, A. (2004, September). The value of melatonin for sleep disorders occuring post-head injury: A pilot RCT. *Brain Injury, 18*(9), 911-919.

Kim, E. (2002). Agitation, aggression, and disinhibition syndromes after traumatic brain injury. *NeuroRehabilitation, 17*(4), 297-310. http://www.scopus.com/inward/record.url?eid=2-s2.0-0036988932&partnerID=40&md5=3d7ad0f33b70b70cfd29c92f204cbfd4

http://iospress.metapress.com/content/aqq15cxx83fp7mgj/?genre=article&issn=1053-8135&volume=17&issue=4&spage=297

Kim, E., & Humaran, T. J. (2002). Divalproex in the management of neuropsychiatric complications of remote acquired brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences, 14*(2), 202-205. http://www.scopus.com/inward/record.url?eid=2-s2.0-0036265201&partnerID=40&md5=22c3697620c41a5c76954c5d416b09a5

http://psychiatryonline.org/data/Journals/NP/3919/202.pdf

Knoll, A. D., & MacLennan, R. N. (2017). Prevalence and correlates of depression in Canada: Findings from the Canadian Community Health Survey. *Canadian Psychology/Psychologie canadienne, 58*(2), 116-123. https://doi.org/10.1037/cap0000103

Koponen, S., Taiminen, T., Hiekkanen, H., & Tenovuo, O. (2011). Axis I and II psychiatric disorders in patients with traumatic brain injury: a 12-month follow-up study. *Brain Inj, 25*(11), 1029-1034. https://doi.org/10.3109/02699052.2011.607783

Koponen, S., Taiminen, T., Portin, R., Himanen, L., Isoniemi, H., Heinonen, H., Hinkka, S., & Tenovuo, O. (2002, Aug). Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. *Am J Psychiatry, 159*(8), 1315-1321. https://doi.org/10.1176/appi.ajp.159.8.1315

Kow, J. V., & Hogan, D. B. (2000). Use of physical and chemical restraints in medical teaching units. *CMAJ, 162*(3), 339-340. http://www.scopus.com/inward/record.url?eid=2-s2.0-0034620551&partnerID=40&md5=4a228e60bd0ec0ea944439dc4b70bc38

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1231012/pdf/cmaj_162_3_339.pdf

Kraus, J. F., Morgenstern, H., Fife, D., Conroy, C., & Nourjah, P. (1989, Mar). Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *Am J Public Health, 79*(3), 294-299. https://doi.org/10.2105/ajph.79.3.294

Krese, K., Ingraham, B., O'Brien, M. K., Mummidisetty, C. K., McNulty, M., Srdanovic, N., Kocherginsky, M., & Ripley, D. (2020, Jul 2). The impact of a yoga-based physical therapy group for individuals with traumatic brain injury: results from a pilot study. *Brain Inj, 34*(8), 1118-1126. https://doi.org/10.1080/02699052.2020.1776394

Kumar, R. G., Gao, S., Juengst, S. B., Wagner, A. K., & Fabio, A. (2018, Mar 2018

2018-02-27). The effects of post-traumatic depression on cognition, pain, fatigue, and headache after moderate-to-severe traumatic brain injury: A thematic review. *Brain Injury, 32*(4), 383-394. https://doi.org/http://dx.doi.org/10.1080/02699052.2018.1427888

Kvam, S., Kleppe, C. L., Nordhus, I. H., & Hovland, A. (2016, 2016/09/15/). Exercise as a treatment for depression: A meta-analysis. *Journal of Affective Disorders, 202*, 67-86. https://doi.org/https://doi.org/10.1016/j.jad.2016.03.063

Lam, R. W., Wan, D. D., Cohen, N. L., & Kennedy, S. H. (2002, Aug). Combining antidepressants for treatment-resistant depression: a review. *J Clin Psychiatry, 63*(8), 685-693. https://doi.org/10.4088/jcp.v63n0805

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Ziemann, U., Garcia-Larrea, L., & Paulus, W. (2017,

Jan). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol, 128*(1), 56-92. https://doi.org/10.1016/j.clinph.2016.10.087

Levy, B. B., Luong, D., Bayley, M. T., Sweet, S. N., Voth, J., Kastner, M., Nelson, M. L. A., Jaglal, S. B., Salbach, N. M., Wilcock, R., Thoms, C., Shepherd, J., & Munce, S. E. P. (2021, Jun 29). A Pilot Feasibility Randomized Controlled Trial on the Ontario Brain Injury Association Peer Support Program. *J Clin Med, 10*(13). https://doi.org/10.3390/jcm10132913

Levy, M., Berson, A., Cook, T., Bollegala, N., Seto, E., Tursanski, S., Kim, J., Sockalingam, S., Rajput, A., Krishnadev, N., Feng, C., & Bhalerao, S. (2005). Treatment of agitation following traumatic brain injury: A review of the literature. *NeuroRehabilitation, 20*(4), 279-306. http://www.scopus.com/inward/record.url?eid=2-s2.0-29744441218&partnerID=40&md5=66bf1f9b44cc13ebc3fe05fa49b9de09

http://iospress.metapress.com/content/9lpp72uv9fnw4f54/?genre=article&issn=1053-8135&volume=20&issue=4&spage=279

Lizzo, J. M., Waseem, M., & Tatikonda, G. (2021). *Brain Trauma (Nursing)*. Treasure Island (FL): StatPearls Publishing; 2023 Jan.

Loggini, A., Tangonan, R., El Ammar, F., Mansour, A., Goldenberg, F. D., Kramer, C. L., & Lazaridis, C. (2020, Jul). The role of amantadine in cognitive recovery early after traumatic brain injury: A systematic review. *Clin Neurol Neurosurg, 194*, 105815. https://doi.org/10.1016/j.clineuro.2020.105815

Luauté, J., Plantier, D., Wiart, L., & Tell, L. (2016, Feb). Care management of the agitation or aggressiveness crisis in patients with TBI. Systematic review of the literature and practice recommendations. *Ann Phys Rehabil Med, 59*(1), 58-67. https://doi.org/10.1016/j.rehab.2015.11.001

Luo, X., Zhu, D., Li, J., Ren, M., Liu, Y., Si, T., & Chen, Y. (2023, Sep). Selection of the optimal dose of sertraline for depression: A dose-response meta-analysis of randomized controlled trials. *Psychiatry Res, 327*, 115391. https://doi.org/10.1016/j.psychres.2023.115391

Mackelprang, J. L., Bombardier, C. H., Fann, J. R., Temkin, N. R., Barber, J. K., & Dikmen, S. S. (2014, Jul). Rates and predictors of suicidal ideation during the first year after traumatic brain injury. *American journal of public health, 104*(7), e100-107. https://doi.org/http://dx.doi.org/10.2105/AJPH.2013.301794

Madsen, T., Erlangsen, A., Orlovska, S., Mofaddy, R., Nordentoft, M., & Benros, M. E. (2018, Aug 14). Association Between Traumatic Brain Injury and Risk of Suicide. *Jama, 320*(6), 580-588. https://doi.org/10.1001/jama.2018.10211

Maner, S., Morris, P. G., & Flewitt, B. I. (2023, Mar). A systematic review of the effectiveness of compassion focused imagery in improving psychological outcomes in clinical and non-clinical adult populations. *Clin Psychol Psychother, 30*(2), 250-269. https://doi.org/10.1002/cpp.2801

Mania, I., Evcimen, H., & Mathews, M. (2006). Citalopram treatment for inappropriate sexual behavior in a cognitively impaired patient. *Primary Care Companion to the Journal of Clinical Psychiatry, 8*(2), 106-107.

Maresca, G., Lo Buono, V., Anselmo, A., Cardile, D., Formica, C., Latella, D., Quartarone, A., & Corallo, F. (2023, Jul 27). Traumatic Brain Injury and Related Antisocial Behavioral Outcomes: A Systematic Review. *Medicina (Kaunas), 59*(8). https://doi.org/10.3390/medicina59081377

Marmarou, A., Nichols, J., Burgess, J., Newell, D., Troha, J., Burnham, D., & Pitts, L. (1999, Jun). Effects of the bradykinin antagonist Bradycor (deltibant, CP-1027) in severe traumatic brain injury: results of a multi-center, randomized, placebo-controlled trial. American Brain Injury Consortium Study Group. *J Neurotrauma, 16*(6), 431-444. https://doi.org/10.1089/neu.1999.16.431

Martin, D., & Le, J. K. (2020). *Amphetamine*. StatPearls Publishing.

Maryniak, O., Manchanda, R., & Velani, A. (2001). Methotrimeprazine in the treatment of agitation in acquired brain injury patients. *Brain Injury, 15*(2), 167-174. http://www.scopus.com/inward/record.url?eid=2-s2.0-0035138025&partnerID=40&md5=2dd974faab59b2e0c5c0bad1a3f53cd8

http://www.ingentaconnect.com/content/apl/tbin/2001/00000015/00000002/art00008?token=0053165b6f05bf5c5f3b3b474666483f2577706e4a422a5a4f582a2f4876753375686f4956d14b0c529

May, M., Milders, M., Downey, B., Whyte, M., Higgins, V., Wojcik, Z., Amin, S., & O'Rourke, S. (2017, May). Social Behavior and Impairments in Social Cognition Following Traumatic Brain Injury. *J Int Neuropsychol Soc, 23*(5), 400-411. https://doi.org/10.1017/s1355617717000182

Mayou, R., Bryant, B., & Duthie, R. (1993). Psychiatric consequences of road traffic accidents. *British Medical Journal, 307*(6905), 647-651.

McDonald, S., Tate, R., Togher, L., Bornhofen, C., Long, E., Gertler, P., & Bowen, R. (2008). Social Skills Treatment for People With Severe, Chronic Acquired Brain Injuries: A Multicenter Trial. *Archives of Physical Medicine and Rehabilitation, 89*(9), 1648-1659. http://www.scopus.com/inward/record.url?eid=2-s2.0-49949099314&partnerID=40&md5=2ef9f2509015ca6068b9c491fd2393c1

http://ac.els-cdn.com/S0003999308004310/1-s2.0-S0003999308004310-main.pdf?_tid=5dea88ea-a2fd-11e3-a543-00000aacb361&acdnat=1393869663_f5ecd1fa3559405514f58677f0b44b3e

McDonald, S., Togher, L., Tate, R., Randall, R., English, T., & Gowland, A. (2013). A randomised controlled trial evaluating a brief intervention for deficits in recognising emotional prosody following severe ABI. *Neuropsychol Rehabil, 23*(2), 267-286. https://doi.org/10.1080/09602011.2012.751340

McDonald, S., Trimmer, E., Newby, J., Grant, S., Gertler, P., & Simpson, G. K. (2021, Apr). Providing on-line support to families of people with brain injury and challenging behaviour: A feasibility study. *Neuropsychol Rehabil, 31*(3), 392-413. https://doi.org/10.1080/09602011.2019.1696846

McKay, A., Love, J., Trevena-Peters, J., Gracey, J., & Ponsford, J. (2018). The relationship between agitation and impairments of orientation and memory during the pta period after traumatic brain injury. *Neuropsychol Rehabil*. https://doi.org/http://dx.doi.org/10.1080/09602011.2018.1479276

McMillan, T., Robertson, I. H., Brock, D., & Chorlton, L. (2002). Brief mindfulness training for attentional problems after traumatic brain injury: A randomised control treatment trial. *Neuropsychol Rehabil, 12*(2), 117-125.

McNett, M., Sarver, W., & Wilczewski, P. (2012). The prevalence, treatment and outcomes of agitation among patients with brain injury admitted to acute care units. *Brain Injury, 26*(9), 1155-1162. http://www.scopus.com/inward/record.url?eid=2-s2.0-84863693322&partnerID=40&md5=51ac9d7f9623d8bc97be93b66d1d99b6

http://informahealthcare.com/doi/pdfplus/10.3109/02699052.2012.667587

Medd, J., & Tate, R. L. (2000). Evaluation of an anger management therapy programme following acquired brain injury: A preliminary study. *Neuropsychol Rehabil, 10*(2), 185-201. http://www.scopus.com/inward/record.url?eid=2-s2.0-0034050131&partnerID=40&md5=cc71ee1016bcb8a00838b7698c6f5516

Mendes, L., Reis, L. P., & Barbosa, F. (2021). Effectiveness of a holistic neuropsychological rehabilitation program using virtual reality. *PsychTech & Health Journal, 5*(1), 20-41.

Meythaler, J. M., Brunner, R. C., Johnson, A., & Novack, T. A. (2002, Aug). Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. *J Head Trauma Rehabil, 17*(4), 300-313.

Meythaler, J. M., Depalma, L., Devivo, M. J., Guin-Renfroe, S., & Novack, T. A. (2001, Apr). Sertraline to improve arousal and alertness in severe traumatic brain injury secondary to motor vehicle crashes. *Brain Inj, 15*(4), 321-331. https://doi.org/10.1080/026990501750111274

Milders, M. (2019). Relationship between social cognition and social behaviour following traumatic brain injury. *Brain Inj, 33*(1), 62-68. https://doi.org/10.1080/02699052.2018.1531301

Ministry of Health and Long Term Care for the Province of Ontario. (2001). *Patient Restraints Minimization Act*. http://www.e-laws.gov.on.ca/html/source/statues/english/2001

Minnick, A. F., Mion, L. C., Johnson, M. E., Catrambone, C., & Leipzig, R. (2007). Prevalence and variation of physical restraint use in acute care settings in the US: Clinical scholarship. *Journal of Nursing Scholarship, 39*(1), 30-37.

Mion, L. C., Minnick, A., & Palmer, R. (1996). Physical Restraint Use in the Hospital Setting: Unresolved Issues and Directions for Research. *Milbank Quarterly, 74*(3), 411-433. http://www.scopus.com/inward/record.url?eid=2-s2.0-0029692415&partnerID=40&md5=cd44a212080a85f6bf4fe31d256e727e

Mishra, R., Florez-Perdomo, W. A., Shrivatava, A., Chouksey, P., Raj, S., Moscote-Salazar, L. R., Rahman, M. M., Sutar, R., & Agrawal, A. (2021, Feb). Role of Music Therapy in Traumatic Brain Injury: A Systematic Review and Meta-analysis. *World Neurosurg, 146*, 197-204. https://doi.org/10.1016/j.wneu.2020.10.130

Mooney, G. F., & Haas, L. J. (1993). Effect of methylphenidate on brain injury-related anger. *Archives of Physical Medicine and Rehabilitation, 74*(2), 153-160. http://www.scopus.com/inward/record.url?eid=2-s2.0-0027453239&partnerID=40&md5=b1b9ff4bec4b1b978c5e22a6ede27e28

Moseley, A. M., Herbert, R. D., Sherrington, C., & Maher, C. G. (2002). Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). *Aust J Physiother, 48*(1), 43-49. https://doi.org/10.1016/s0004-9514(14)60281-6

Muir-Cochrane, E., Oster, C., Gerace, A., Dawson, S., Damarell, R., & Grimmer, K. (2020, Apr). The effectiveness of chemical restraint in managing acute agitation and aggression: A systematic review of randomized controlled trials. *Int J Ment Health Nurs, 29*(2), 110-126. https://doi.org/10.1111/inm.12654

Muresanu, D. F., Florian, S., Hömberg, V., Matula, C., von Steinbüchel, N., Vos, P. E., von Wild, K., Birle, C., Muresanu, I., Slavoaca, D., Rosu, O. V., Strilciuc, S., & Vester, J. (2020, May). Efficacy and safety of cerebrolysin in neurorecovery after moderate-severe traumatic brain injury: results from the CAPTAIN II trial. *Neurol Sci, 41*(5), 1171-1181. https://doi.org/10.1007/s10072-019-04181-y

Mysiw, W. J., Bogner, J. A., Corrigan, J. D., Fugate, L. P., Clinchot, D. M., & Kadyan, V. (2006, Aug). The impact of acute care medications on rehabilitation outcome after traumatic brain injury. *Brain Inj, 20*(9), 905-911. https://doi.org/10.1080/02699050600743972

Mysiw, W. J., Jackson, R. D., & Corrigan, J. D. (1988). Amitriptyline for post-traumatic agitation. *American Journal of Physical Medicine and Rehabilitation, 67*(1), 29-33. http://www.scopus.com/inward/record.url?eid=2-s2.0-0023894155&partnerID=40&md5=98174f7b661724be5ea234c329c77c09

Nash, R. P., Weinberg, M. S., Laughon, S. L., McCall, R. C., Bateman, J. R., & Rosenstein, D. L. (2018). Acute pharmacological management of behavioral and emotional dysregulation following a traumatic brain injury: A systematic review of the literature. *Psychosomatics: Journal of Consultation and Liaison Psychiatry*. https://doi.org/http://dx.doi.org/10.1016/j.psym.2018.11.009

National Guideline Alliance UK. (2018). *Evidence reviews for psychological, psychosocial and other non-pharmacological interventions for the treatment of PTSD in adults*.

Neumann, D., Babbage, D. R., Zupan, B., & Willer, B. (2015, May-Jun). A randomized controlled trial of emotion recognition training after traumatic brain injury. *J Head Trauma Rehabil, 30*(3), E12-23. https://doi.org/10.1097/htr.0000000000000054

Neumann, D., Juengst, S. B., Bombardier, C. H., Finn, J. A., Miles, S. R., Zhang, Y., Kennedy, R., Rabinowitz, A. R., Thomas, A., & Dreer, L. E. (2022). Anxiety Trajectories the First 10 Years After a Traumatic Brain Injury (TBI): A TBI Model Systems Study. *Archives of Physical Medicine and Rehabilitation, 103*(11), 2105-2113. https://doi.org/https://dx.doi.org/10.1016/j.apmr.2022.07.002

Neumann, D., Malec, J. F., & Hammond, F. M. (2017). Reductions in Alexithymia and Emotion Dysregulation after Training Emotional Self-Awareness Following Traumatic Brain Injury: A Phase i Trial. *Journal of Head Trauma Rehabilitation, 32*(5), 286-295. https://doi.org/http://dx.doi.org/10.1097/HTR.0000000000000277

Neville, I. S., Zaninotto, A. L., Hayashi, C. Y., Rodrigues, P. A., Galhardoni, R., de Andrade, D. C., Brunoni, A. R., Amorim, R. L. O., Teixeira, M. J., & Paiva, W. S. (2019). Repetitive TMS does not improve cognition in patients with TBI: A randomized double-blind trial. *Neurology, 93*(2), e190-e199.

Nguyen, S., McKay, A., Wong, D., Rajaratnam, S. M., Spitz, G., Williams, G., Mansfield, D., & Ponsford, J. L. (2017, Aug). Cognitive Behavior Therapy to Treat Sleep Disturbance and Fatigue After Traumatic Brain Injury: A Pilot Randomized Controlled Trial. *Arch Phys Med Rehabil, 98*(8), 1508-1517.e1502. https://doi.org/10.1016/j.apmr.2017.02.031

Noé, E., Ferri, J., Trénor, C., & Chirivella, J. (2007). Efficacy of ziprasidone in controlling agitation during post-traumatic amnesia. *Behavioural Neurology, 18*(1), 7-11. http://www.scopus.com/inward/record.url?eid=2-s2.0-33847375164&partnerID=40&md5=92f16c15976f82b869948a3440b73d6d

http://iospress.metapress.com/content/8kk9bk58kqg5l34v/?genre=article&issn=0953-4180&volume=18&issue=1&spage=7

Nott, M. T., Chapparo, C., & Baguley, I. J. (2006, Oct). Agitation following traumatic brain injury: an Australian sample. *Brain Inj, 20*(11), 1175-1182. https://doi.org/10.1080/02699050601049114

Novack, T. A., Banos, J. H., Brunner, R., Renfroe, S., & Meythaler, J. M. (2009, Nov). Impact of early administration of sertraline on depressive symptoms in the first year after traumatic brain injury. *J Neurotrauma, 26*(11), 1921-1928. https://doi.org/10.1089/neu.2009.0895

O'Donnell, M. L., Bryant, R. A., Creamer, M., & Carty, J. (2008). Mental health following traumatic injury: Toward a health system model of early psychological intervention. *Clin Psychol Rev, 28*(3), 387-406. http://www.scopus.com/inward/record.url?eid=2-s2.0-39749154821&partnerID=40&md5=cb491d7c6e20c6ed0fc9a6b2b55e59ef

http://ac.els-cdn.com/S0272735807001298/1-s2.0-S0272735807001298-main.pdf?_tid=4a6266b0-a2ff-11e3-9f67-00000aab0f26&acdnat=1393870490_9fa2ac6bfd20c2068c35c2bc7f686e76

O'Neill, M., & McMillan, T. M. (2012). Can deficits in empathy after head injury be improved by compassionate imagery? *Neuropsychol Rehabil, 22*(6), 836-851. https://doi.org/10.1080/09602011.2012.691886

O'Phelan, K., McArthur, D. L., Chang, C. W. J., Green, D., & Hovda, D. A. (2008). The impact of substance abuse on mortality in patients with severe traumatic brain injury. *Journal of Trauma - Injury, Infection and Critical Care, 65*(3), 674-677. http://www.scopus.com/inward/record.url?eid=2-s2.0-67650292875&partnerID=40&md5=031d6d8770ba10d2c290a0c4d37cd2d0

Oberholzer, M., & Müri, R. M. (2019, Mar 18). Neurorehabilitation of Traumatic Brain Injury (TBI): A Clinical Review. *Med Sci (Basel), 7*(3). https://doi.org/10.3390/medsci7030047

Osborn, A. J., Mathias, J. L., & Fairweather-Schmidt, A. K. (2014, November). Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics [Review]. *Neuroscience and Biobehavioral Reviews, 47*, 1-15. https://doi.org/http://dx.doi.org/10.1016/j.neubiorev.2014.07.007

Osborn, A. J., Mathias, J. L., & Fairweather-Schmidt, A. K. (2016). Prevalence of Anxiety Following Adult Traumatic Brain Injury: A Meta-Analysis Comparing Measures, Samples and Postinjury Intervals [In Press]. *Neuropsychology., 06*. https://doi.org/http://dx.doi.org/10.1037/neu0000221

Osborn, A. J., Mathias, J. L., Fairweather-Schmidt, A. K., & Anstey, K. J. (2018, 2018-03-19). Traumatic brain injury and depression in a community-based sample: A cohort study across the adult life span. *The Journal of Head Trauma Rehabilitation, 33*(1), 62-72.

Ostinelli, E. G., Hussein, M., Ahmed, U., Rehman, F. U., Miramontes, K., & Adams, C. E. (2018, Apr 10). Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation). *Cochrane Database Syst Rev, 4*(4), Cd009412. https://doi.org/10.1002/14651858.CD009412.pub2

Ouellet, M.-C., Beaulieu-Bonneau, S., Sirois, M.-J., Savard, J., Turgeon, A. F., Moore, L., Swaine, B., Roy, J., Giguère, M., & Laviolette, V. (2018, 2018 Jul 15

2018-07-12). Depression in the first year after traumatic brain injury. *J Neurotrauma, 35*(14), 1620-1629. https://doi.org/http://dx.doi.org/10.1089/neu.2017.5379

Ownsworth, T., Fleming, J., Tate, R., Beadle, E., Griffin, J., Kendall, M., Schmidt, J., Lane-Brown, A., Chevignard, M., & Shum, D. H. K. (2017, Dec). Do People With Severe Traumatic Brain Injury Benefit From Making Errors? A Randomized Controlled Trial of Error-Based and Errorless Learning. *Neurorehabil Neural Repair, 31*(12), 1072-1082. https://doi.org/10.1177/1545968317740635

Ownsworth, T. L., & Oei, T. P. (1998, Sep). Depression after traumatic brain injury: conceptualization and treatment considerations. *Brain Inj, 12*(9), 735-751.

Pąchalska, M., Góral-Półrola, J., Mirski, A., Grzywniak, C., Łuckoś, M., & Morga, R. (2019). The Amelioration of Behavioral Disturbances in TBI Patients with Chronic Frontal Syndrome after Treatment in Different Rehabilitation Programs. *Acta Neuropsychologica*.

Pachet, A., Friesen, S., Winkelaar, D., & Gray, S. (2003, Aug). Beneficial behavioural effects of lamotrigine in traumatic brain injury. *Brain Inj, 17*(8), 715-722. https://doi.org/10.1080/0269905031000110445

Padilla, R., & Domina, A. (2016, May-Jun). Effectiveness of Sensory Stimulation to Improve Arousal and Alertness of People in a Coma or Persistent Vegetative State After Traumatic Brain Injury: A Systematic Review. *Am J Occup Ther, 70*(3), 7003180030p7003180031-7003180038. https://doi.org/10.5014/ajot.2016.021022

Park, S., Williams, R. A., & Lee, D. (2016, Apr). Effect of Preferred Music on Agitation After Traumatic Brain Injury. *West J Nurs Res, 38*(4), 394-410. https://doi.org/10.1177/0193945915593180

Pavlovic, D., Pekic, S., Stojanovic, M., & Popovic, V. (2019, Jun). Traumatic brain injury: neuropathological, neurocognitive and neurobehavioral sequelae. *Pituitary, 22*(3), 270-282. https://doi.org/10.1007/s11102-019-00957-9

Perino, C., Rago, R., Cicolin, A., Torta, R., & Monaco, F. (2001). Mood and behavioural disorders following traumatic brain injury: Clinical evaluation and pharmacological management. *Brain Injury, 15*(2), 139-148. http://www.scopus.com/inward/record.url?eid=2-s2.0-0035138219&partnerID=40&md5=835fdf6e7aa15266a625bf92a53bfe76

http://www.ingentaconnect.com/content/apl/tbin/2001/00000015/00000002/art00006?token=004f1c41ec9e387434ab7e2a46762c6b795d7a763c7053745b6c5f673f7b2f27375f2a72752d70b

Perry, S. A., Coetzer, R., & Saville, C. W. N. (2018, 2018 May 16

2018-05-18). The effectiveness of physical exercise as an intervention to reduce depressive symptoms following traumatic brain injury: A meta-analysis and systematic review. *Neuropsychol Rehabil*. https://doi.org/http://dx.doi.org/10.1080/09602011.2018.1469417

Phelan, S. M., Griffin, J. M., Hellerstedt, W. L., Sayer, N. A., Jensen, A. C., Burgess, D. J., & van Ryn, M. (2011, Jul). Perceived stigma, strain, and mental health among caregivers of veterans with traumatic brain injury. *Disabil Health J, 4*(3), 177-184. https://doi.org/10.1016/j.dhjo.2011.03.003

Phyland, R. K., McKay, A., Olver, J., Walterfang, M., Hopwood, M., Ponsford, M., & Ponsford, J. L. (2023). Use of Olanzapine to Treat Agitation in Traumatic Brain Injury: A Series of N-of-One Trials. *J Neurotrauma, 40*(1-2), 33-51. https://doi.org/https://dx.doi.org/10.1089/neu.2022.0139

Plantier, D., & Luaute, J. (2016, Feb). Drugs for behavior disorders after traumatic brain injury: Systematic review and expert consensus leading to French recommendations for good practice. *Ann Phys Rehabil Med, 59*(1), 42-57. https://doi.org/10.1016/j.rehab.2015.10.003

Ponsford, J., Alway, Y., & Gould, K. R. (2018, 2018-12-16). Epidemiology and natural history of psychiatric disorders after TBI. *The Journal of Neuropsychiatry and Clinical Neurosciences, 30*(4), 262-270. https://doi.org/http://dx.doi.org/10.1176/appi.neuropsych.18040093

Ponsford, J., Janzen, S., McIntyre, A., Bayley, M., Velikonja, D., & Tate, R. (2014, Jul-Aug). INCOG recommendations for management of cognition following traumatic brain injury, part I: posttraumatic amnesia/delirium. *J Head Trauma Rehabil, 29*(4), 307-320. https://doi.org/10.1097/htr.0000000000000074

Ponsford, J., Lee, N. K., Wong, D., McKay, A., Haines, K., Alway, Y., Downing, M., Furtado, C., & O'Donnell, M. L. (2016, Apr). Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. *Psychol Med, 46*(5), 1079-1090. https://doi.org/10.1017/s0033291715002640

Ponsford, J., Trevena-Peters, J., Janzen, S., Harnett, A., Marshall, S., Patsakos, E., Kua, A., McIntyre, A., Teasell, R., Wiseman-Hakes, C., Velikonja, D., Bayley, M. T., & McKay, A. (2023, Jan-Feb 01). INCOG 2.0 Guidelines for Cognitive Rehabilitation Following Traumatic Brain Injury, Part I: Posttraumatic Amnesia. *J Head Trauma Rehabil, 38*(1), 24-37. https://doi.org/10.1097/htr.0000000000000840

Ponsford, J., Tweedly, L., Lee, N., & Taffe, J. (2012, Sep-Oct). Who responds better? Factors influencing a positive response to brief alcohol interventions for individuals with traumatic brain injury. *J Head Trauma Rehabil, 27*(5), 342-348. https://doi.org/10.1097/HTR.0b013e318265a576

Ponsford, J., Tweedly, L., & Taffe, J. (2013). The relationship between alcohol and cognitive functioning following traumatic brain injury. *J Clin Exp Neuropsychol, 35*(1), 103-112. https://doi.org/10.1080/13803395.2012.752437

Ponsford, J., Whelan-Goodinson, R., & Bahar-Fuchs, A. (2007). Alcohol and drug use following traumatic brain injury: A prospective study. *Brain Injury, 21*(13-14), 1385-1392. http://www.scopus.com/inward/record.url?eid=2-s2.0-37149000897&partnerID=40&md5=106f09eeb1cf7c2090be703881729220

http://informahealthcare.com/doi/pdfplus/10.1080/02699050701796960

Ponsford, J. L., Hicks, A. J., Gould, K. R., Downing, M. G., Hopwood, M., & Feeney, T. J. (2022). Positive behaviour support for adults with acquired brain injury and challenging behaviour: A randomised controlled trial. *Ann Phys Rehabil Med, 65*(2), 101604. https://doi.org/https://dx.doi.org/10.1016/j.rehab.2021.101604

Poon, W., Matula, C., Vos, P. E., Muresanu, D. F., von Steinbüchel, N., von Wild, K., Hömberg, V., Wang, E., Lee, T. M. C., Strilciuc, S., & Vester, J. C. (2020, Feb). Safety and efficacy of Cerebrolysin in acute brain injury

and neurorecovery: CAPTAIN I-a randomized, placebo-controlled, double-blind, Asian-Pacific trial. *Neurol Sci, 41*(2), 281-293. https://doi.org/10.1007/s10072-019-04053-5

Powell, J., Heslin, J., & Greenwood, R. (2002, Feb). Community based rehabilitation after severe traumatic brain injury: a randomised controlled trial. *J Neurol Neurosurg Psychiatry, 72*(2), 193-202. https://doi.org/10.1136/jnnp.72.2.193

Preskorn, S. H., & Lane, R. M. (1995, Sep). Sertraline 50 mg daily: the optimal dose in the treatment of depression. *Int Clin Psychopharmacol, 10*(3), 129-141. https://doi.org/10.1097/00004850-199510030-00001

Quera Salva, M.-A., Azabou, E., Hartley, S., Sauvagnac, R., Leotard, A., Vaugier, I., Pradat Diehl, P., Vallat-Azouvi, C., Barbot, F., & Azouvi, P. (2020). Blue-Enriched White Light Therapy Reduces Fatigue in Survivors of Severe Traumatic Brain Injury: A Randomized Controlled Trial. *Journal of Head Trauma Rehabilitation, 35*(2), E78-E85. https://doi.org/10.1097/HTR.0000000000000500

Rabelo, J. L., Cruz, B. F., Ferreira, J. D. R., Viana, B. M., & Barbosa, I. G. (2021, Dec 19). Psychoeducation in bipolar disorder: A systematic review. *World J Psychiatry, 11*(12), 1407-1424. https://doi.org/10.5498/wjp.v11.i12.1407

Radice-Neumann, D., Zupan, B., Tomita, M., & Willer, B. (2009, Sep-Oct). Training emotional processing in persons with brain injury. *J Head Trauma Rehabil, 24*(5), 313-323. https://doi.org/10.1097/HTR.0b013e3181b09160

Rahman, S., & Marwaha, R. (2023). Haloperidol. In *StatPearls*. StatPearls Publishing.

Rahmani, E., Lemelle, T. M., Samarbafzadeh, E., & Kablinger, A. S. (2021, Jul-Aug 01). Pharmacological Treatment of Agitation and/or Aggression in Patients With Traumatic Brain Injury: A Systematic Review of Reviews. *J Head Trauma Rehabil, 36*(4), E262-e283. https://doi.org/10.1097/htr.0000000000000656

Ramsey, J., Driver, S., Swank, C., Bennett, M., & Dubiel, R. (2018). Physical activity intensity of patient's with traumatic brain injury during inpatient rehabilitation. *Brain Inj, 32*(12), 1518-1524. https://doi.org/10.1080/02699052.2018.1500715

Ranke, M. B., & Wit, J. M. (2018, May). Growth hormone - past, present and future. *Nat Rev Endocrinol, 14*(5), 285-300. https://doi.org/10.1038/nrendo.2018.22

Rao, V., Rosenberg, P., Bertrand, M., Salehinia, S., Spiro, J., Vaishnavi, S., Rastogi, P., Noll, K., Schretlen, D. J., Brandt, J., Cornwell, E., Makley, M., & Miles, Q. S. (2009). Aggression after traumatic brain injury: Prevalence and correlates. *Journal of Neuropsychiatry and Clinical Neurosciences, 21*(4), 420-429. http://www.scopus.com/inward/record.url?eid=2-s2.0-73549120446&partnerID=40&md5=f025a1a3cc96e4bc1a52cb59c14120c1

http://psychiatryonline.org/data/Journals/NP/3977/09jnp420.PDF

Rath, J. F., Simon, D., Langenbahn, D. M., Sherr, R. L., & Diller, L. (2003, Sep 2003

2017-09-26). Group treatment of problem-solving deficits in outpatients with traumatic brain injury: A randomised outcome study. *Neuropsychol Rehabil, 13*(4), 461-488. https://doi.org/http://dx.doi.org/10.1080/09602010343000039

Recupero, P. R., Price, M., Garvey, K. A., Daly, B., & Xavier, S. L. (2011). Restraint and seclusion in psychiatric treatment settings: Regulation, case law, and risk management. *Journal of the American Academy of Psychiatry and the Law, 39*(4), 465-476. http://www.scopus.com/inward/record.url?eid=2-s2.0-84856897595&partnerID=40&md5=77c89dd056dbd0546ff2769148258978

http://www.jaapl.org/content/39/4/465.full.pdf

Reel, B., & Maani, C. V. (2023). Dexmedetomidine. In *StatPearls*. StatPearls Publishing.

Rigon, A., Duff, M. C., & Beadle, J. (2019, Mar). Lonely But Not Alone: Neuroticism Mediates the Relationship Between Social Network Size and Loneliness in Individuals With Traumatic Brain Injury. *J Int Neuropsychol Soc, 25*(3), 285-292. https://doi.org/10.1017/s1355617718001108

Ripley, D. L., Morey, C. E., Gerber, D., Harrison-Felix, C., Brenner, L. A., Pretz, C. R., Cusick, C., & Wesnes, K. (2014). Atomoxetine for attention deficits following traumatic brain injury: results from a randomized controlled trial. *Brain Inj, 28*(12), 1514-1522. https://doi.org/10.3109/02699052.2014.919530

Rodrigues, P. A., Zaninotto, A. L., Ventresca, H. M., Neville, I. S., Hayashi, C. Y., Brunoni, A. R., de Paula Guirado, V. M., Teixeira, M. J., & Paiva, W. S. (2020). The Effects of Repetitive Transcranial Magnetic Stimulation on Anxiety in Patients With Moderate to Severe Traumatic Brain Injury: A Post-hoc Analysis of a Randomized Clinical Trial. *Front Neurol, 11*, 564940. https://doi.org/10.3389/fneur.2020.564940

Rosati, D. L. (2002). Early polyneuropharmacologic intervention in brain injury agitation. *American Journal of Physical Medicine and Rehabilitation, 81*(2), 90-93. http://www.scopus.com/inward/record.url?eid=2-s2.0-0036152203&partnerID=40&md5=a570bf391a7c1e5bfc1b5c3eeea9d323

http://graphics.tx.ovid.com/ovftpdfs/FPDDNCFBEEDGLD00/fs001/ovft/live/gv002/00002060/00002060-200202000-00003.pdf

Rosen, V., & Ayers, G. (2020). An Update on the Complexity and Importance of Accurately Diagnosing Post-Traumatic Stress Disorder and Comorbid Traumatic Brain Injury. *Neurosci Insights, 15*, 2633105520907895. https://doi.org/10.1177/2633105520907895

Rosenthal, M., Christensen, B. K., & Ross, T. P. (1998, Jan). Depression following traumatic brain injury. *Arch Phys Med Rehabil, 79*(1), 90-103.

Ruff, R., Mahaffey, R., Engel, J., Farrow, C., Cox, D., & Karzmark, P. (1994, Jan). Efficacy study of THINKable in the attention and memory retraining of traumatically head-injured patients. *Brain Inj, 8*(1), 3-14.

Ruff, R. M., & Niemann, H. (1990). Cognitive rehabilitation versus day treatment in head-injured adults: Is there an impact on emotional and psychosocial adjustment? *Brain Injury, 4*(4), 339-347. http://www.scopus.com/inward/record.url?eid=2-s2.0-0025038556&partnerID=40&md5=8af790f1bd19a8015e1aecc1bee52b24

Rushby, J. A., De Blasio, F. M., Logan, J. A., Wearne, T., Kornfeld, E., Wilson, E. J., Loo, C., Martin, D., & McDonald, S. (2021, 01 Jun). tDCS effects on task-related activation and working memory performance in traumatic brain injury: A within group randomized controlled trial. *Neuropsychol Rehabil, 31*(5), 814-836.

Sabaz, M., Simpson, G. K., Walker, A. J., Rogers, J. M., Gillis, I., & Strettles, B. (2014). Prevalence, comorbidities, and correlates of challenging behavior among community-dwelling adults with severe traumatic brain injury: A multicenter study. *Journal of Head Trauma Rehabilitation, 29*(2), E19-E30. https://doi.org/10.1097/HTR.0b013e31828dc590

Sacco, K., Galetto, V., Dimitri, D., Geda, E., Perotti, F., Zettin, M., & Geminiani, G. C. (2016, 2016). Concomitant Use of Transcranial Direct Current Stimulation and Computer-Assisted Training for the Rehabilitation of Attention in Traumatic Brain Injured Patients: Behavioral and Neuroimaging Results. *Frontiers in behavioral neuroscience, 10*, 57. https://doi.org/10.3389/fnbeh.2016.00057

Sackett DL, S. S., Richardson WS, Rosenberg W, Hayes RB. (2000). *Evidence-based medicine: how to practice and teach EBM* (2nd ed. ed.).

Salazar, A. M., Warden, D. L., Schwab, K., Spector, J., Braverman, S., Walter, J., Cole, R., Rosner, M. M., Martin, E. M., Ecklund, J., & Ellenbogen, R. G. (2000, Jun 21). Cognitive rehabilitation for traumatic brain injury: A randomized trial. Defense and Veterans Head Injury Program (DVHIP) Study Group. *Jama, 283*(23), 3075-3081. https://jamanetwork.com/journals/jama/articlepdf/192806/joc91265.pdf

Salim, A., Ley, E. J., Cryer, H. G., Margulies, D. R., Ramicone, E., & Tillou, A. (2009, Sep). Positive serum ethanol level and mortality in moderate to severe traumatic brain injury. *Arch Surg, 144*(9), 865-871. https://doi.org/10.1001/archsurg.2009.158

Salim, A., Teixeira, P., Ley, E. J., Dubose, J., Inaba, K., & Margulies, D. R. (2009). Serum ethanol levels: Predictor of survival after severe traumatic brain injury. *Journal of Trauma - Injury, Infection and Critical Care, 67*(4), 697-703. http://www.scopus.com/inward/record.url?eid=2-s2.0-72449150689&partnerID=40&md5=4f72b0d0660e9b75bdef5f9d34b411a5

Sander, A. M., Bogner, J., Nick, T. G., Clark, A. N., Corrigan, J. D., & Rozzell, M. (2012). A randomized controlled trial of brief intervention for problem alcohol use in persons with traumatic brain injury. *Journal of Head Trauma Rehabilitation, 27*(5), 319-330. http://www.scopus.com/inward/record.url?eid=2-s2.0-84866254486&partnerID=40&md5=4c8e2c115caaeefd5d47c8de98055f44

http://graphics.tx.ovid.com/ovftpdfs/FPDDNCFBEEDGLD00/fs047/ovft/live/gv024/00001199/00001199-201209000-00002.pdf

Sander, A. M., Clark, A. N., Arciniegas, D. B., Tran, K., Leon-Novelo, L., Ngan, E., Bogaards, J., Sherer, M., & Walser, R. (2021). A randomized controlled trial of acceptance and commitment therapy for psychological distress among persons with traumatic brain injury. *Neuropsychol Rehabil, 31*(7), 1105-1129.

Sandhu, S. K., Mion, L. C., Khan, R. H., Ludwick, R., Claridge, J., Pile, J. C., Harrington, M., Winchell, J., & Dietrich, M. S. (2010). Likelihood of ordering physical restraints: Influence of physician characteristics. *Journal of the American Geriatrics Society, 58*(7), 1272-1278. http://www.scopus.com/inward/record.url?eid=2-s2.0-77954342197&partnerID=40&md5=aa470bdef8364db5bd4745c4e4f7bfb9

http://onlinelibrary.wiley.com/store/10.1111/j.1532-5415.2010.02950.x/asset/j.1532-5415.2010.02950.x.pdf?v=1&t=hsc2z9gl&s=21fd3c826efd2a3aa72499aee61478c1618281cf

Sarkamo, T., Huttula, L., Hokkanen, L., Koskinen, S., Leppelmeier, J., Saynevirta, K., Molander, K., Forsbom, M.-B., Kullberg-Turtiainen, M., Turtiainen, P., Sarajuuri, J., & Rantanen, P. (2021). DARE to move: feasibility study of a novel dance-based rehabilitation method in severe traumatic brain injury. *Brain Injury, 35*(3), 335-344. https://doi.org/http://dx.doi.org/10.1080/02699052.2021.1873420

Schmidt, J., Fleming, J., Ownsworth, T., & Lannin, N. A. (2013, May). Video feedback on functional task performance improves self-awareness after traumatic brain injury: a randomized controlled trial. *Neurorehabil Neural Repair, 27*(4), 316-324. https://doi.org/10.1177/1545968312469838

Schneider, W. N., Drew-Cates, J., Wong, T. M., & Dombovy, M. L. (1999, Nov). Cognitive and behavioural efficacy of amantadine in acute traumatic brain injury: an initial double-blind placebo-controlled study. *Brain Inj, 13*(11), 863-872.

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., Van Beeck, E. F., & Polinder, S. (2016a). Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: a systematic review. *J Neurotrauma, 33*(22), 1969-1994.

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., van Beeck, E. F., & Polinder, S. (2016b, Nov 15). Prevalence of and Risk Factors for Anxiety and Depressive Disorders after Traumatic Brain Injury: A Systematic Review. *J Neurotrauma, 33*(22), 1969-1994. https://doi.org/10.1089/neu.2015.4252

Schonberger, M., Ponsford, J., McKay, A., Wong, D., Spitz, G., Harrington, H., & Mealings, M. (2014). Development and predictors of psychological adjustment during the course of community-based rehabilitation of traumatic brain injury: A preliminary study. *Neuropsychol Rehabil, 24*(2), 202-219. https://doi.org/10.1080/09602011.2013.878252

Schuch, F. B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2016, Jun). Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *J Psychiatr Res, 77*, 42-51. https://doi.org/10.1016/j.jpsychires.2016.02.023

Schutte, C., & Hanks, R. (2010). Impact of the presence of alcohol at the time of injury on acute and one-year cognitive and functional recovery after traumatic brain injury. *International Journal of Neuroscience, 120*(8), 551-556. http://www.scopus.com/inward/record.url?eid=2-s2.0-77954522668&partnerID=40&md5=40305d3c44c58d2c6ab41f0cd6a16736

http://informahealthcare.com/doi/abs/10.3109/00207454.2010.494789

Sedghi, T., Ghaljeh, M., Faghihi, H., & Sarani, H. (2020). The Effect of Auditory and Tactile Stimulation by a Family Member on the Level of Agitation in Patients with Traumatic Brain Injury and Decreased Consciousness: A Quasi-Experimental Study. *Medical-Surgical Nursing Journal, 9*(2), 1-8. https://doi.org/10.5812/msnj.108844

Seel, R. T., MacCiocchi, S., & Kreutzer, J. S. (2010). Clinical considerations for the diagnosis of major depression after moderate to severe tBI. *Journal of Head Trauma Rehabilitation, 25*(2), 99-112. http://www.scopus.com/inward/record.url?eid=2-s2.0-77949595669&partnerID=40&md5=995b663a08ee67fbf3528604fae2de4a

http://graphics.tx.ovid.com/ovftpdfs/FPDDNCFBEEDGLD00/fs046/ovft/live/gv025/00001199/00001199-201003000-00005.pdf

Shahin, H., Gopinath, S. P., & Robertson, C. S. (2010). Influence of alcohol on early glasgow coma scale in head-injured patients. *Journal of Trauma - Injury, Infection and Critical Care, 69*(5), 1176-1181. http://www.scopus.com/inward/record.url?eid=2-s2.0-78549244413&partnerID=40&md5=28248fef588cd4658e3faec866c6ac86

Sherer, M., Clark, A. N., Sander, A. M., Struchen, M. A., Bogaards, J., Leon-Novelo, L., & Ngan, E. (2022, Sep). Relationships of self-awareness and facial affect recognition to social communication ability in persons with traumatic brain injury. *Neuropsychol Rehabil, 32*(8), 2013-2028. https://doi.org/10.1080/09602011.2022.2084118

Shura, R. D., Nazem, S., Miskey, H. M., Hostetter, T. A., Rowland, J. A., Brenner, L. A., Workgroup, V. A. M.-A. M., & Taber, K. H. (2018). Relationship between traumatic brain injury history and recent suicidal ideation in

Iraq/Afghanistan-era veterans. *Psychological Services*. https://doi.org/http://dx.doi.org/10.1037/ser0000208

Sigurdardottir, S., Andelic, N., Røe, C., & Schanke, A. K. (2013). Depressive symptoms and psychological distress during the first five years after traumatic brain injury: Relationship with psychosocial stressors, fatigue and pain. *Journal of Rehabilitation Medicine, 45*(8), 808-814. https://doi.org/10.2340/16501977-1156

Silver, J. M., Koumaras, B., Chen, M., Mirski, D., Potkin, S. G., Reyes, P., Warden, D., Harvey, P. D., Arciniegas, D., Katz, D. I., & Gunay, I. (2006, Sep 12). Effects of rivastigmine on cognitive function in patients with traumatic brain injury. *Neurology, 67*(5), 748-755. https://doi.org/10.1212/01.wnl.0000234062.98062.e9

Silver, J. M., Koumaras, B., Meng, X., Potkin, S. G., Reyes, P. F., Harvey, P. D., Katz, D. I., Gunay, I., & Arciniegas, D. B. (2009, Feb). Long-term effects of rivastigmine capsules in patients with traumatic brain injury. *Brain Inj, 23*(2), 123-132. https://doi.org/10.1080/02699050802649696

Simpson, G., & Tate, R. (2002). Suicidality after traumatic brain injury: Demographic, injury and clinical correlates. *Psychological Medicine, 32*(4), 687-697. https://doi.org/http://dx.doi.org/10.1017/S0033291702005561

Simpson, G., & Tate, R. (2005, October). Clinical features of suicide attempts after traumatic brain injury. *Journal of Nervous and Mental Disease, 193*(10), 680-685. https://doi.org/http://dx.doi.org/10.1097/01.nmd.0000180743.65943.c8

Simpson, G. K., Sabaz, M., & Daher, M. (2013, May-June). Prevalence, clinical features, and correlates of inappropriate sexual behavior after traumatic brain injury: A multicenter study. *Journal of Head Trauma Rehabilitation, 28*(3), 202-210. https://doi.org/http://dx.doi.org/10.1097/HTR.0b013e31828dc5ae

Simpson, G. K., & Tate, R. L. (2007, December). Suicidality in people surviving a traumatic brain injury: Prevalence, risk factors and implications for clinical management [Review]. *Brain Injury, 21*(13-14), 1335-1351. https://doi.org/http://dx.doi.org/10.1080/02699050701785542

Simpson, G. K., Tate, R. L., Whiting, D. L., & Cotter, R. E. (2011, July-August). Suicide prevention after traumatic brain injury: A randomized controlled trial of a program for the psychological treatment of hopelessness. *Journal of Head Trauma Rehabilitation, 26*(4), 290-300. https://doi.org/http://dx.doi.org/10.1097/HTR.0b013e3182225250

Singh, H. K., & Saadabadi, A. (2019). *Sertraline*. NIH StatPearls Retrieved Nov 2023 from

Singh, R., Mason, S., Lecky, F., & Dawson, J. (2018). Prevalence of depression after TBI in a prospective cohort: The SHEFBIT study. *Brain Inj, 32*(1), 84-90. https://doi.org/10.1080/02699052.2017.1376756

Singh, R., Venkateshwara, G., Nair, K. P. S., Khan, M., & Saad, R. (2014). Agitation after traumatic brain injury and predictors of outcome. *Brain Injury, 28*(3), 336-340. https://doi.org/10.3109/02699052.2013.873142

Sinnakaruppan, I., Downey, B., & Morrison, S. (2005). Head injury and family carers: A pilot study to investigate an innovative community-based educational programme for family carers and patients. *Brain Injury, 19*(4), 283-308. https://doi.org/10.1080/02699050400003924

Siponkoski, S.-T., Martinez-Molina, N., Sarkamo, T., Koskinen, S., Lipsanen, J., Laitinen, S., Holma, M., Ahlfors, M., Jordan-Kilkki, P., Ala-Kauhaluoma, K., Melkas, S., Laine, M., Ylinen, A., Zasler, N., & Rantanen, P. (2022). Effects of neurological music therapy on behavioural and emotional recovery after traumatic brain injury: A randomized controlled cross-over trial. *Neuropsychol Rehabil*, 1-33. https://doi.org/http://dx.doi.org/10.1080/09602011.2021.1890138

Smyth, J., & Helm, R. (2003, Feb). Focused expressive writing as self-help for stress and trauma. *J Clin Psychol, 59*(2), 227-235. https://doi.org/10.1002/jclp.10144

Soltani, F., Tabatabaei, S., Jannatmakan, F., Nasajian, N., Amiri, F., Darkhor, R., & Moravej, M. (2021). Comparison of the effects of haloperidol and dexmedetomidine on delirium and agitation in patients with a traumatic brain injury admitted to the intensive care unit. *Anesthesiology and Pain Medicine, 11*(3), e113802. https://doi.org/https://dx.doi.org/10.5812/aapm.113802

Souery, D., Serretti, A., Calati, R., Oswald, P., Massat, I., Konstantinidis, A., Linotte, S., Kasper, S., Montgomery, S., Zohar, J., & Mendlewicz, J. (2011, Aug). Citalopram versus desipramine in treatment resistant

depression: effect of continuation or switching strategies: a randomized open study. *World J Biol Psychiatry, 12*(5), 364-375. https://doi.org/10.3109/15622975.2011.590225

Speech, T. J., Rao, S. M., Osmon, D. C., & Sperry, L. T. (1993, Jul-Aug). A double-blind controlled study of methylphenidate treatment in closed head injury. *Brain Inj, 7*(4), 333-338.

Sperry, J. L., Gentilello, L. M., Minei, J. P., Diaz-Arrastia, R. R., Friese, R. S., & Shafi, S. (2006). Waiting for the patient to "sober up": Effect of alcohol intoxication on glasgow coma scale score of brain injured patients. *Journal of Trauma - Injury, Infection and Critical Care, 61*(6), 1305-1311. http://www.scopus.com/inward/record.url?eid=2-s2.0-33845752905&partnerID=40&md5=8a6a1a7e0c314e8a716df3180880aada

Spitz, G., SchÃ¶nberger, M., & Ponsford, J. (2013). The Relations Among Cognitive Impairment, Coping Style, and Emotional Adjustment Following Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation, 28*(2), 116-125. https://doi.org/10.1097/HTR.0b013e3182452f4f

St. Joseph's Health Care. (2012). *Minimal Use of Restraints of Voluntary Patients and Residents* http://intra.sjhc.london.on.ca/policy/search_res.php

Stanislav, S. W., & Childs, A. (2000). Evaluating the usage of droperidol in acutely agitated persons with brain injury. *Brain Injury, 14*(3), 261-265. http://www.scopus.com/inward/record.url?eid=2-s2.0-0034032815&partnerID=40&md5=b2e27aa1eb234a7445cb0b7092582ef5

http://www.ingentaconnect.com/content/apl/tbin/2000/00000014/00000003/art00006?token=004a15c303168405847447b496e2f7b40516f5b6b675d2333757e6f4f2858592f3f3b572ea

Stein, A. T., Carl, E., Cuijpers, P., Karyotaki, E., & Smits, J. A. J. (2021, Jul). Looking beyond depression: a meta-analysis of the effect of behavioral activation on depression, anxiety, and activation. *Psychol Med, 51*(9), 1491-1504. https://doi.org/10.1017/s0033291720000239

Stevens, F., & Taber, K. (2021, Aug 20). The neuroscience of empathy and compassion in pro-social behavior. *Neuropsychologia, 159*, 107925. https://doi.org/10.1016/j.neuropsychologia.2021.107925

Struchen, M. A., Davis, L. C., Bogaards, J. A., Hudler-Hull, T., Clark, A. N., Mazzei, D. M., Sander, A. M., & Caroselli, J. S. (2011). Making connections after brain injury: development and evaluation of a social peer-mentoring program for persons with traumatic brain injury. *J Head Trauma Rehabil, 26*(1), 4-19. https://doi.org/10.1097/HTR.0b013e3182048e98

Stuke, L., Diaz-Arrastia, R., Gentilello, L. M., & Shafi, S. (2007). Effect of alcohol on Glasgow Coma Scale in head-injured patients. *Annals of Surgery, 245*(4), 651-655. http://www.scopus.com/inward/record.url?eid=2-s2.0-34147182687&partnerID=40&md5=3769ff03de6fb3c4d23f14338beb744e

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1877033/pdf/20070400s00023p651.pdf

Sultan, S., Linskens, E., Allison Gustavson, D., Sayer, N., Murdoch, M., MacDonald, R., McKenzie, L., Ullman, K., Venables, N., & Wilt, T. J. (2021). Systematic Review, Population and Community-based Interventions to Prevent Suicide.

Tani, J., Wen, Y. T., Hu, C. J., & Sung, J. Y. (2022, Jul 6). Current and Potential Pharmacologic Therapies for Traumatic Brain Injury. *Pharmaceuticals (Basel), 15*(7). https://doi.org/10.3390/ph15070838

Tao, L., Jiang, R., Zhang, K., Qian, Z., Chen, P., Lv, Y., & Yao, Y. (2020, Sep). Light therapy in non-seasonal depression: An update meta-analysis. *Psychiatry Res, 291*, 113247. https://doi.org/10.1016/j.psychres.2020.113247

Tate, P. S., Freed, D. M., Bombardier, C. H., Harter, S. L., & Brinkman, S. (1999). Traumatic brain injury: Influence of blood alcohol level on post-acute cognitive function. *Brain Injury, 13*(10), 767-784. http://www.scopus.com/inward/record.url?eid=2-s2.0-0032832113&partnerID=40&md5=deaf01d26b0efc6016f3e5b01de18283

http://www.ingentaconnect.com/content/apl/tbin/1999/00000013/00000010/art00003?token=00481442fe277e2a46762c6b795d7a763c705c494a455f673f7b2f27375f2a72752d70c1

Tateno, A., Jorge, R. E., & Robinson, R. G. (2003). Clinical correlates of aggressive behavior after traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences, 15*(2), 155-160. http://www.scopus.com/inward/record.url?eid=2-s2.0-0037368131&partnerID=40&md5=19f02a283829a0e6b5cabf41dfd2aef3

http://psychiatryonline.org/data/Journals/NP/3924/155.pdf

Tcheremissine, O. V., & Rachal, J. C. (2017, Mar-Apr). Modafinil Augmentation Therapy in Patient with Traumatic Brain Injury. *Innov Clin Neurosci, 14*(3-4), 11.

Tenovuo, O., Alin, J., & Helenius, H. (2009, Jun 2009

2017-09-25). A randomized controlled trial of rivastigmine for chronic sequels of traumatic brain injury—What it showed and taught? *Brain Injury, 23*(6), 548-558. https://doi.org/http://dx.doi.org/10.1080/02699050902926275

Thaut, M. H., Gardiner, J. C., Holmberg, D., Horwitz, J., Kent, L., Andrews, G., Donelan, B., & McIntosh, G. R. (2009). *Neurologic music therapy improves executive function and emotional adjustment in traumatic brain injury rehabilitation*. http://www.scopus.com/inward/record.url?eid=2-s2.0-68649096161&partnerID=40&md5=face1cf4285ad7ff05a0f5150e544949

Thibaut, F. (2017, Jun). Anxiety disorders: a review of current literature. *Dialogues Clin Neurosci, 19*(2), 87-88. https://doi.org/10.31887/DCNS.2017.19.2/fthibaut

Thomas, K., & Saadabadi, A. (2023). Olanzapine. In *StatPearls*. StatPearls Publishing.

Thompson, H. J., McCormick, W. C., & Kagan, S. H. (2006). Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. *Journal of the American Geriatrics Society, 54*(10), 1590-1595.

Thour, A., & Marwaha, R. (2019). *Amitriptyline*. S. Publishing.

Tien, H. C. N., Tremblay, L. N., Rizoli, S. B., Gelberg, J., Chughtai, T., Tikuisis, P., Shek, P., & Brenneman, F. D. (2006). Association between alcohol and mortality in patients with severe traumatic head injury. *Archives of Surgery, 141*(12), 1185-1191. http://www.scopus.com/inward/record.url?eid=2-s2.0-33845612828&partnerID=40&md5=5b63c268133006acb377cfc92cb49692

http://archsurg.jamanetwork.com/data/Journals/SURG/9638/soa50162_1185_1191.pdf

Tramontana, M. G., Cowan, R. L., Zald, D., Prokop, J. W., & Guillamondegui, O. (2014). Traumatic brain injury-related attention deficits: treatment outcomes with lisdexamfetamine dimesylate (Vyvanse). *Brain Inj, 28*(11), 1461-1472. https://doi.org/10.3109/02699052.2014.930179

Trevena-Peters, J., McKay, A., Spitz, G., Suda, R., Renison, B., & Ponsford, J. (2018, Feb). Efficacy of Activities of Daily Living Retraining During Posttraumatic Amnesia: A Randomized Controlled Trial. *Arch Phys Med Rehabil, 99*(2), 329-337.e322. https://doi.org/10.1016/j.apmr.2017.08.486

Tsaousides, T., Cantor, J. B., & Gordon, W. A. (2011). Suicidal ideation following traumatic brain injury: prevalence rates and correlates in adults living in the community. *Journal of Head Trauma Rehabilitation, 26*(4), 265-275. https://doi.org/http://dx.doi.org/10.1097/HTR.0b013e3182225271

Turner, A. P., Bombardier, C. H., & Rimmele, C. T. (2003). A Typology of Alcohol Use Patterns Among Persons With Recent Traumatic Brain Injury or Spinal Cord Injury: Implications for Treatment Matching. *Arch Phys Med Rehabil, 84*, 358-364.

Turner, D., Schöttle, D., Krueger, R., & Briken, P. (2015, Mar). Sexual behavior and its correlates after traumatic brain injury. *Curr Opin Psychiatry, 28*(2), 180-187. https://doi.org/10.1097/yco.0000000000000144

Tweedly, L., Ponsford, J., & Lee, N. (2012, Sep-Oct). Investigation of the effectiveness of brief interventions to reduce alcohol consumption following traumatic brain injury. *J Head Trauma Rehabil, 27*(5), 331-341. https://doi.org/10.1097/HTR.0b013e318262200a

Underhill, A. T., Lobello, S. G., Stroud, T. P., Terry, K. S., Devivo, M. J., & Fine, P. R. (2003). Depression and life satisfaction in patients with traumatic brain injury: A longitudinal study. *Brain Injury, 17*(11), 973-982. http://www.scopus.com/inward/record.url?eid=2-s2.0-0142216241&partnerID=40&md5=7c013c2ffd7886526b3ae8a0ce52fc4b

http://www.ingentaconnect.com/content/apl/tbin/2003/00000017/00000011/art00004?token=00531d64386c12e58cdbb7e442f20672123763c252c493e46247a63687627502b333e3568263c2bfc00

Uphoff, E., Ekers, D., Robertson, L., Dawson, S., Sanger, E., South, E., Samaan, Z., Richards, D., Meader, N., & Churchill, R. (2020, Jul 6). Behavioural activation therapy for depression in adults. *Cochrane Database Syst Rev, 7*(7), Cd013305. https://doi.org/10.1002/14651858.CD013305.pub2

Van Praag, D. L., Cnossen, M. C., Polinder, S., Wilson, L., & Maas, A. I. (2019). Post-traumatic stress disorder after civilian traumatic brain injury: A systematic review and meta-analysis of prevalence rates. *J Neurotrauma, 36*(23), 3220-3232.

van Reekum, R., Bolago, I., Finlayson, M. A., Garner, S., & Links, P. S. (1996, May). Psychiatric disorders after traumatic brain injury. *Brain Inj, 10*(5), 319-327. http://www.ingentaconnect.com/content/apl/tbin/1996/00000010/00000005/art00001?token=004513e0e185a666f3a7b6c2a405142386b654c7d782a49264f65263a3d4f58762f46

Vanderploeg, R. D., Schwab, K., Walker, W. C., Fraser, J. A., Sigford, B. J., Date, E. S., Scott, S. G., Curtiss, G., Salazar, A. M., & Warden, D. L. (2008, Dec). Rehabilitation of traumatic brain injury in active duty military personnel and veterans: Defense and Veterans Brain Injury Center randomized controlled trial of two rehabilitation approaches. *Arch Phys Med Rehabil, 89*(12), 2227-2238. https://doi.org/10.1016/j.apmr.2008.06.015

VanderVeen, J. D. (2021, Jun). TBI as a Risk Factor for Substance Use Behaviors: A Meta-analysis. *Arch Phys Med Rehabil, 102*(6), 1198-1209. https://doi.org/10.1016/j.apmr.2020.10.112

Verberne, D. P. J., Spauwen, P. J. J., & van Heugten, C. M. (2019, Dec). Psychological interventions for treating neuropsychiatric consequences of acquired brain injury: A systematic review. *Neuropsychol Rehabil, 29*(10), 1509-1542. https://doi.org/10.1080/09602011.2018.1433049

Vickery, C. D., Sherer, M., Nick, T. G., Nakase-Richardson, R., Corrigan, J. D., Hammond, F., Macciocchi, S., Ripley, D. L., & Sander, A. (2008). Relationships Among Premorbid Alcohol Use, Acute Intoxication, and Early Functional Status After Traumatic Brain Injury. *Archives of Physical Medicine and Rehabilitation, 89*(1), 48-55. http://www.scopus.com/inward/record.url?eid=2-s2.0-37349085307&partnerID=40&md5=26f0fab3276918dd482eccd9c05d3420

http://ac.els-cdn.com/S0003999307015924/1-s2.0-S0003999307015924-main.pdf?_tid=1eada42a-a305-11e3-83e6-00000aab0f6c&acdnat=1393872993_2c879f93e235493864fa241a2c180f74

Wade, D. T., King, N. S., Wenden, F. J., Crawford, S., & Caldwell, F. E. (1998, Aug). Routine follow up after head injury: a second randomised controlled trial. *J Neurol Neurosurg Psychiatry, 65*(2), 177-183. https://doi.org/10.1136/jnnp.65.2.177

Wadhawan, A., Stiller, J. W., Potocki, E., Okusaga, O., Dagdag, A., Lowry, C. A., Benros, M. E., & Postolache, T. T. (2019). Traumatic brain injury and suicidal behavior: a review. *Journal of Alzheimer's disease, 68*(4), 1339-1370.

Waldron, B., Casserly, L. M., & O'Sullivan, C. (2013). Cognitive behavioural therapy for depression and anxiety in adults with acquired brain injury: what works for whom? [Review]. *Neuropsychol Rehabil, 23*(1), 64-101. https://doi.org/http://dx.doi.org/10.1080/09602011.2012.724196

Walker, A. J., Nott, M. T., Doyle, M., Onus, M., McCarthy, K., & Baguley, I. J. (2010). Effectiveness of a group anger management programme after severe traumatic brain injury. *Brain Inj, 24*(3), 517-524. https://doi.org/10.3109/02699051003601721

Warden, D. L., Gordon, B., McAllister, T. W., Silver, J. M., Barth, J. T., Bruns, J., Drake, A., Gentry, T., Jagoda, A., Katz, D. I., Kraus, J., Labbate, L. A., Ryan, L. M., Sparling, M. B., Walters, B., Whyte, J., Zapata, A., & Zitnay, G. (2006, Oct). Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma, 23*(10), 1468-1501. https://doi.org/10.1089/neu.2006.23.1468

Warden, D. L., Labbate, L. A., Salazar, A. M., Nelson, R., Sheley, E., Staudenmeier, J., & Martin, E. (1997). Posttraumatic stress disorder in patients with traumatic brain injury and amnesia for the event? *Journal of Neuropsychiatry and Clinical Neurosciences, 9*(1), 18-22.

Warriner, E. M., & Velikonja, D. (2006). Psychiatric disturbances after traumatic brain injury: Neurobehavioral and personality changes. *Current Psychiatry Reports, 8*(1), 73-80. http://www.scopus.com/inward/record.url?eid=2-s2.0-33645077627&partnerID=40&md5=a1d10175b146d57e6465846e5d739ffa

Wearne, T. A., Logan, J. A., Trimmer, E. M., Wilson, E., Filipcikova, M., Kornfeld, E., Rushby, J. A., & McDonald, S. (2021, Sep 19). Regulating emotion following severe traumatic brain injury: a randomized controlled trial of heart-rate variability biofeedback training. *Brain Inj, 35*(11), 1390-1401. https://doi.org/10.1080/02699052.2021.1972337

Wehman, P., Targett, P., Yasuda, S., & Brown, T. (2000). Return to work for individuals with TBI and a history of substance abuse. *NeuroRehabilitation, 15*(1), 71-77. http://www.scopus.com/inward/record.url?eid=2-s2.0-0033786056&partnerID=40&md5=59b910f8b570ca340b627d7196151422

http://iospress.metapress.com/content/1w6qy308t8p3fn9c/?genre=article&issn=1053-8135&volume=15&issue=1&spage=71

Weil, Z. M., Corrigan, J. D., & Karelina, K. (2018). Alcohol Use Disorder and Traumatic Brain Injury. *Alcohol Res, 39*(2), 171-180.

Weinstein, A. A., Chin, L. M. K., Collins, J., Goel, D., Keyser, R. E., & Chan, L. (2017). Effect of Aerobic Exercise Training on Mood in People With Traumatic Brain Injury: A Pilot Study [In Press]. *Journal of Head Trauma Rehabilitation., 06*. https://doi.org/http://dx.doi.org/10.1097/HTR.0000000000000253

West, S. L., Graham, C. W., & Cifu, D. X. (2009, 2009/07/01). Rates of Alcohol/Other Drug Treatment Denials to Persons With Physical Disabilities: Accessibility Concerns. *Alcoholism Treatment Quarterly, 27*(3), 305-316. https://doi.org/10.1080/07347320903008190

Westerhof-Evers, H. J., Visser-Keizer, A. C., Fasotti, L., Schonherr, M. C., Vink, M., van der Naalt, J., & Spikman, J. M. (2017, Sep/Oct). Effectiveness of a Treatment for Impairments in Social Cognition and Emotion Regulation (T-ScEmo) After Traumatic Brain Injury: A Randomized Controlled Trial. *J Head Trauma Rehabil, 32*(5), 296-307. https://doi.org/10.1097/htr.0000000000000332

Whelan-Goodinson, R., Ponsford, J., Johnston, L., & Grant, F. (2009, Sep-Oct). Psychiatric disorders following traumatic brain injury: their nature and frequency. *J Head Trauma Rehabil, 24*(5), 324-332. https://doi.org/10.1097/HTR.0b013e3181a712aa

Whiting, D., Deane, F., McLeod, H., Ciarrochi, J., & Simpson, G. (2020, Aug). Can acceptance and commitment therapy facilitate psychological adjustment after a severe traumatic brain injury? A pilot randomized controlled trial. *Neuropsychol Rehabil, 30*(7), 1348-1371. https://doi.org/10.1080/09602011.2019.1583582

Wiart, L., Richer, E., Destaillats, J. M., Joseph, P. A., Dehail, P., & Mazaux, J. M. (2012, Sep). Psychotherapeutic follow up of out patients with traumatic brain injury: preliminary results of an individual neurosystemic approach. *Ann Phys Rehabil Med, 55*(6), 375-387. https://doi.org/10.1016/j.rehab.2012.04.002

Wilde, E. A., Bigler, E. D., Gandhi, P. V., Lowry, C. M., Blatter, D. D., Brooks, J., & Ryser, D. K. (2004). Alcohol Abuse and Traumatic Brain Injury: Quantitative Magnetic Resonance Imaging and Neuropsychological Outcome. *J Neurotrauma, 21*(2), 137-147. http://www.scopus.com/inward/record.url?eid=2-s2.0-1242321066&partnerID=40&md5=9af852e821a29bdad92e03dc7f02e28c

http://online.liebertpub.com/doi/abs/10.1089/089771504322778604?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Williamson, D., Frenette, A. J., Burry, L. D., Perreault, M., Charbonney, E., Lamontagne, F., Potvin, M. J., Giguere, J. F., Mehta, S., & Bernard, F. (2019). Pharmacological interventions for agitated behaviours in patients with traumatic brain injury: A systematic review. *BMJ Open, 9*(7), e029604. https://doi.org/http://dx.doi.org/10.1136/bmjopen-2019-029604

Williamson, D., Frenette, A. J., Perreault, M., Burry, L., Charbonney, E., Lamontagne, F., Potvin, M. J., Giguere, J. F., Mehta, S., & Bernard, F. (2018). Pharmacological interventions for agitation in traumatic brain injury: A systematic review. *Critical Care. Conference: 38th International Symposium on Intensive Care and Emergency Medicine, ISICEM, 22*(Supplement 1).

Wisco, B. E., Marx, B. P., Holowka, D. W., Vasterling, J. J., Han, S. C., Chen, M. S., Gradus, J. L., Nock, M. K., Rosen, R. C., & Keane, T. M. (2014, 01 Apr). Traumatic brain injury, PTSD, and current suicidal ideation among Iraq and Afghanistan U.S. veterans. *Journal of traumatic stress, 27*(2), 244-248. https://doi.org/http://dx.doi.org/10.1002/jts.21900

Wolffbrandt, M. M., Poulsen, I., Engberg, A. W., & Hornnes, N. (2013, May-Jun). Occurrence and severity of agitated behavior after severe traumatic brain injury. *Rehabil Nurs, 38*(3), 133-141. https://doi.org/10.1002/rnj.82

Wroblewski, B. A., Joseph, A. B., & Cornblatt, R. R. (1996). Antidepressant pharmacotherapy and the treatment of depression in patients with severe traumatic brain injury: A controlled, prospective study. *Journal of Clinical Psychiatry, 57*(12), 582-587. http://www.scopus.com/inward/record.url?eid=2-s2.0-0030462833&partnerID=40&md5=d847a8b384ab4aca339fd3fc91cf0211

Wroblewski, B. A., Joseph, A. B., Kupfer, J., & Kalliel, K. (1997). Effectiveness of valproic acid on destructive and aggressive behaviours in patients with acquired brain injury. *Brain Injury, 11*(1), 37-47. http://www.scopus.com/inward/record.url?eid=2-s2.0-0031035680&partnerID=40&md5=baa22810a6ec027c2b7d8a63f6e78181

http://www.ingentaconnect.com/content/apl/tbin/1997/00000011/00000001/art00004?token=004c103a275c277b42572b6747483f343e2c3a2b59592f653b2a2d3a7c4e724770929a6ecab5

Wroblewski, B. A., McColgan, K., Smith, K., Whyte, J., & Singer, W. D. (1990, Apr). The incidence of seizures during tricyclic antidepressant drug treatment in a brain-injured population. *J Clin Psychopharmacol, 10*(2), 124-128. https://doi.org/10.1097/00004714-199004000-00009

Xie, Z., Chen, F., Li, W. A., Geng, X., Li, C., Meng, X., Feng, Y., Liu, W., & Yu, F. (2017). A review of sleep disorders and melatonin. *Neurological research, 39*(6), 559-565.

Yeh, T. C., Chien, W. C., Chung, C. H., Liang, C. S., Chang, H. A., Kao, Y. C., Yeh, H. W., Yang, Y. J., & Tzeng, N. S. (2020, May). Psychiatric Disorders After Traumatic Brain Injury: A Nationwide Population-Based Cohort Study and the Effects of Rehabilitation Therapies. *Arch Phys Med Rehabil, 101*(5), 822-831. https://doi.org/10.1016/j.apmr.2019.12.005

Zafonte, R. D., Fregni, F., Bergin, M. J. G., Goldstein, R., Boudreau, N., Monge, I., Luz, M., Frazier, J., & Giacino, J. T. (2020). Huperzine A for the treatment of cognitive, mood, and functional deficits after moderate and severe TBI (HUP-TBI): results of a Phase II randomized controlled pilot study: implications for understanding the placebo effect. *Brain Inj, 34*(1), 34-41. https://doi.org/10.1080/02699052.2019.1677941

Zare, M., Ebrahimi, A. A., & Birashk, B. (2010, Dec). The effects of music therapy on reducing agitation in patients with Alzheimer's disease, a pre-post study. *Int J Geriatr Psychiatry, 25*(12), 1309-1310. https://doi.org/10.1002/gps.2450

Zatzick, D. F., Rivara, F. P., Jurkovich, G. J., Hoge, C. W., Wang, J., Fan, M.-Y., Russo, J., Trusz, S. G., Nathens, A., & MacKenzie, E. J. (2010). Multisite Investigation of Traumatic Brain Injuries, Posttraumatic Stress Disorder, and Self-reported Health and Cognitive Impairments. *Arch Gen Psychiatry, 67*(12), 1291-1300.

Zheng, W., Xiang, Y. Q., Ungvari, G. S., Chiu, F. K., C, H. N., Wang, Y., & Xiang, Y. T. (2016, Apr 25). Huperzine A for treatment of cognitive impairment in major depressive disorder: a systematic review of randomized controlled trials. *Shanghai Arch Psychiatry, 28*(2), 64-71. https://doi.org/10.11919/j.issn.1002-0829.216003