Depression after TBI

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Objectives

- Describe the prevalence of depression following TBI
- Determine risk factors for depression following TBI
- Discuss assessment and treatment strategies for depression following TBI
  - Pharmacological
  - Psychoeducational & Behavioral
  - Neuromodulation

TBI is a ...

- **Neurobiological Injury**
  - **Consequences of direct injury to CNS**
- **Traumatic Event**
  - **e.g., Risk for Post-traumatic Stress Disorder, Depression, Anxiety**
- **Chronic Medical Condition**
  - **May lead to long-term symptoms & disability**

Major Depressive Disorder (MDD)

1. **Depressed mood***
2. **Loss of interest/pleasure***
3. Sleep disturbance
4. Poor energy
5. Motor change agitation or slowness
6. Weight/appetite change increase/decrease
7. Impaired concentration or indecision
8. Excessive worthlessness or guilt
9. Recurrent thoughts of death or suicide

- Patient endorses at least 5 symptoms; must include at least one essential symptom (*).

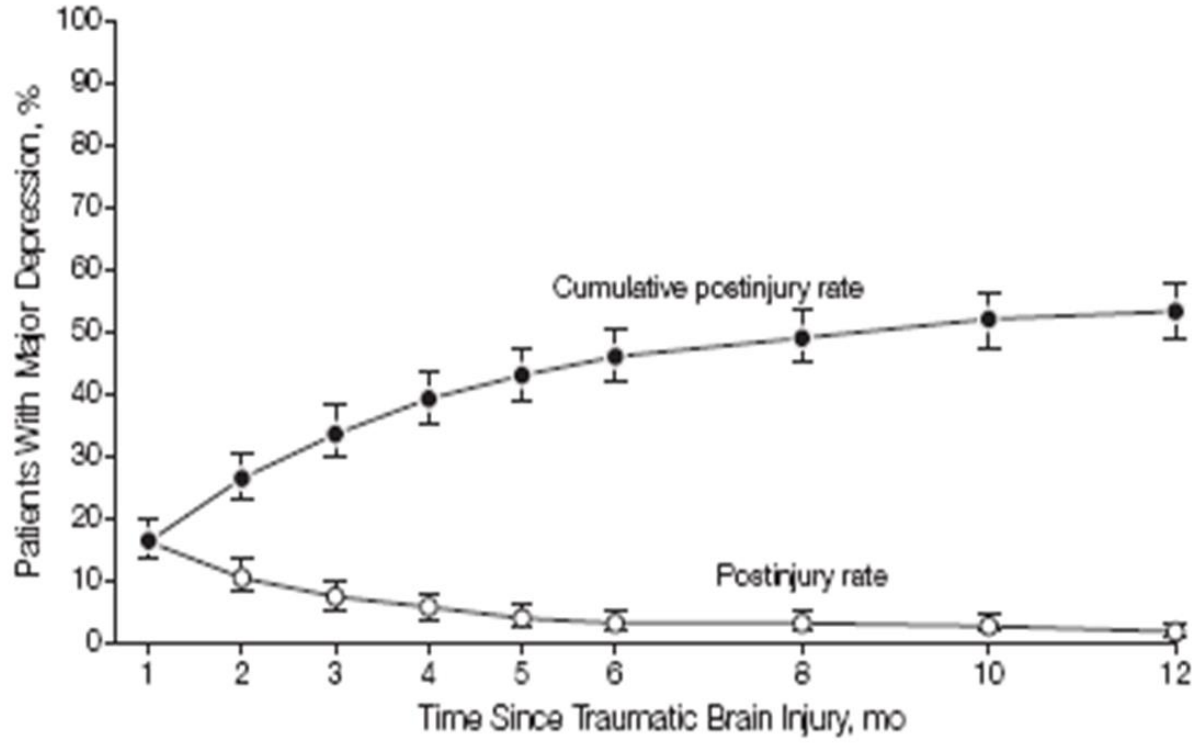
"**Depression**" is used to refer to results from non-diagnostic questionnaires

Rates of Depression in Other Populations

General population	**2-4%**
Primary care patients	**5-10%**
Diabetes	10-15%
Coronary artery disease	17-27%
Stroke	16-30%
Multiple sclerosis	16-36%
Spinal cord injury injury	11-38%

Katon & Ciechanowski, 2002; Rudisch & Nemeroff, 2003; Turner-Stokes & Hassan, 2002; Bombardier et al, 2004; Patten, 2003; Bombardier et al 2010; Craig, Middleton, Tran 2008

Trauma Population
County Hospital, N=559



Postinjury rate is the proportion of cases ascertained with major depressive disorder for the first time after traumatic brain injury at each assessment. The values underestimate the true rates because not all participants were assessed at each time. Error bars indicate 95% confidence intervals.

Bombardier, et al. JAMA 2010

Rates of MDD after TBI

Time Period	Point Prev	Period Prev	Author
1 yr	26% 26%	53%	Bombardier et al 2010 Hart et al 2011
2 yr	26%	37%	Hart et al 2012
6 yrs	11%	45%	Whelan-Goodinson et al 2009
8 yrs		61%	Hibbard et al 1998
30 yrs	10%	27%	Koponen et al 2002
50 yrs	11%	19%	Holsinger et al 2002

Among Army soldiers 3-4 mos. after deployment with:

Mild TBI with LOC: **22.9% MDD**

Mild TBI w/o LOC: **8.4% MDD**

Other injuries: **6.6% MDD** (Hoge et al, 2008)

Prevalence Meta-analysis

- 93 studies, 11,926 participants
- Overall point prevalence of MDD is 27%
- Mean prevalence of MDD appears to increase during first 5 years (21-43%) then declines to 22%
- MDD in mild TBI (16%) vs. mod-severe TBI (30%)
- Odds of developing MDD/dysthymia after TBI is 7.69 times greater than in non-injured community controls and 1.55 times greater than in medical controls

Osborn et al., Neuroscience and Biobehavioral Reviews 47 (2014) 1–15

Depression Risk Factors in TBI

- Age at injury (11-15, 30-44 vs. >60) *
- Female Gender *
- Black race *
- < HS education *
- Violent etiology
- Medicaid insurance
- Litigation involvement
- Lifetime alcohol dependence *
- Cocaine/Methamphetamine intoxication
- Prior psychiatric history *
- Unstable pre-injury work history
- Lower motor & cognitive functioning (FIM scores) *
- Poor social & family support *
- Poor problem solving
- Fear of job loss

* Multivariate analysis

Bombardier et al., JAMA 2010; Dikmen et al., Arch PM&R 2002; Hart et al, Arch PM&R 2012; Hamm et al 2000; Hayes & Dixon 1994; Gomez-Hernandez et al 1997; Orlovska et al, Am J Psych 2014; Stein et al, JAMA Psychiatry 2019

Incarcerated Populations with TBI

Large study in Wisconsin & New Mexico

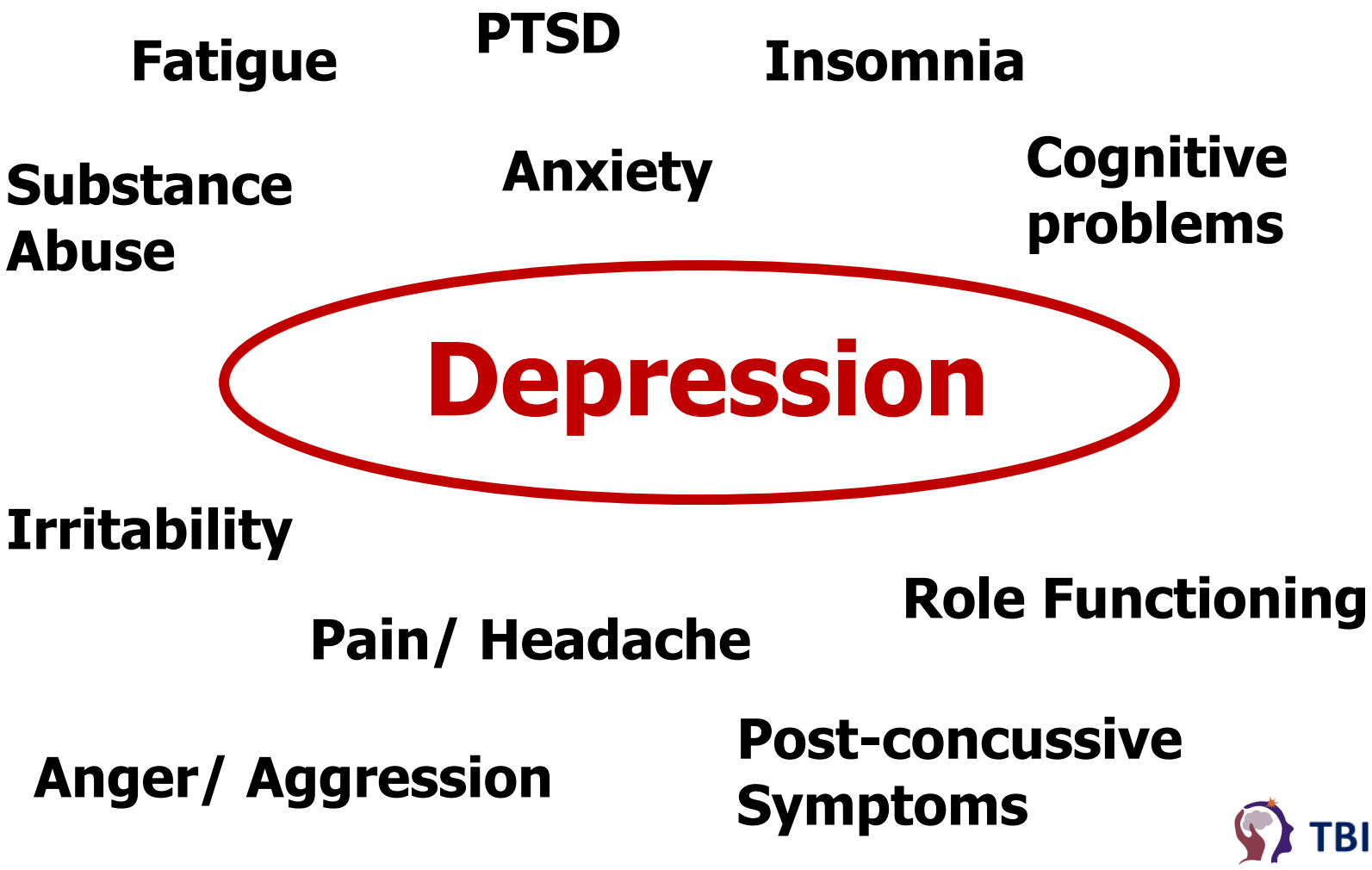
- Rates of TBI (80% mild) 5 times higher (men: 52-55%, women: 47-67%) than in general population
- 20-30% with >1 TBIs
- Higher rates of TBI caused by assault (>25% vs. 8%)
- High rates of Depression among men (12-36%) and women (46-55%) with TBI

Schneider et al. Brain Inj 2021

Hypopituitarism

- Unrelated to TBI severity in most studies
- Growth hormone deficiency, hypogonadism
- Can be assoc. with anxiety, depression, fatigue, irritability, insomnia, sexual dysfunction, cognitive impairment
- Assess GH-IGF-1 (Growth Hormone-Insulin-like Growth Factor-1) axis
- Hormone replacement may help

Common Depression Comorbidities



TBI-BH ECHO

Impact of Depression on Outcomes

Depression after TBI associated with:

- Poorer cognitive functioning (Rappoport et al., 2005)
- Lower health status and greater functional disability (Christensen et al., 1994; Levin et al 2001; Fann et al., 1995; Hibbard et al., 2004; Rapoport et al., 2003)
- More post-concussive symptoms (Fann et al., 1995; Rappoport et al., 2005)
- Increased aggressive behavior and anxiety (Tateno et al., 2003; Jorge et al., 2004; Fann et al., 1995)
- Poorer recovery and return to work (Mooney et al., 2005, Hoge et al, 2008)
- Higher rates (compared with non-TBI controls) of:
  - suicidal plans (Kishi et al., 2001)
  - suicide attempts (8x) (Silver et al., 2001),
  - completed suicides (3-4x) (Teasdale and Engberg, 2001)

Basic Treatment Principles

- Characterize & document diagnoses/ symptoms as precisely as possible
  - Neuropsychiatric symptoms may not fit DSM criteria
- Assess pre-TBI personality, coping, psychiatric history
  - Prior patterns may be accentuated
  - What's worked in the past?
- Define realistic treatment endpoints
  - Use validated instruments, when available

Fann JR, Kennedy R, Bombardier CH. Physical Medicine and Rehabilitation. In: Textbook of Psychosomatic Medicine, 2nd Ed. Levenson J (ed), American Psychiatric Publishing, Inc., Washington, D.C., 2018;

Fann JR, Quinn DK, Hart T. Treatment of Psychiatric Porlbems after Traumatic Brain Injury. Biol Psychiatry 2022

Patient Health Questionnaire - 9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving .around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Spitzer et al. JAMA 1999; Fann et al, JHTR 2005

Transdiagnostic Symptoms

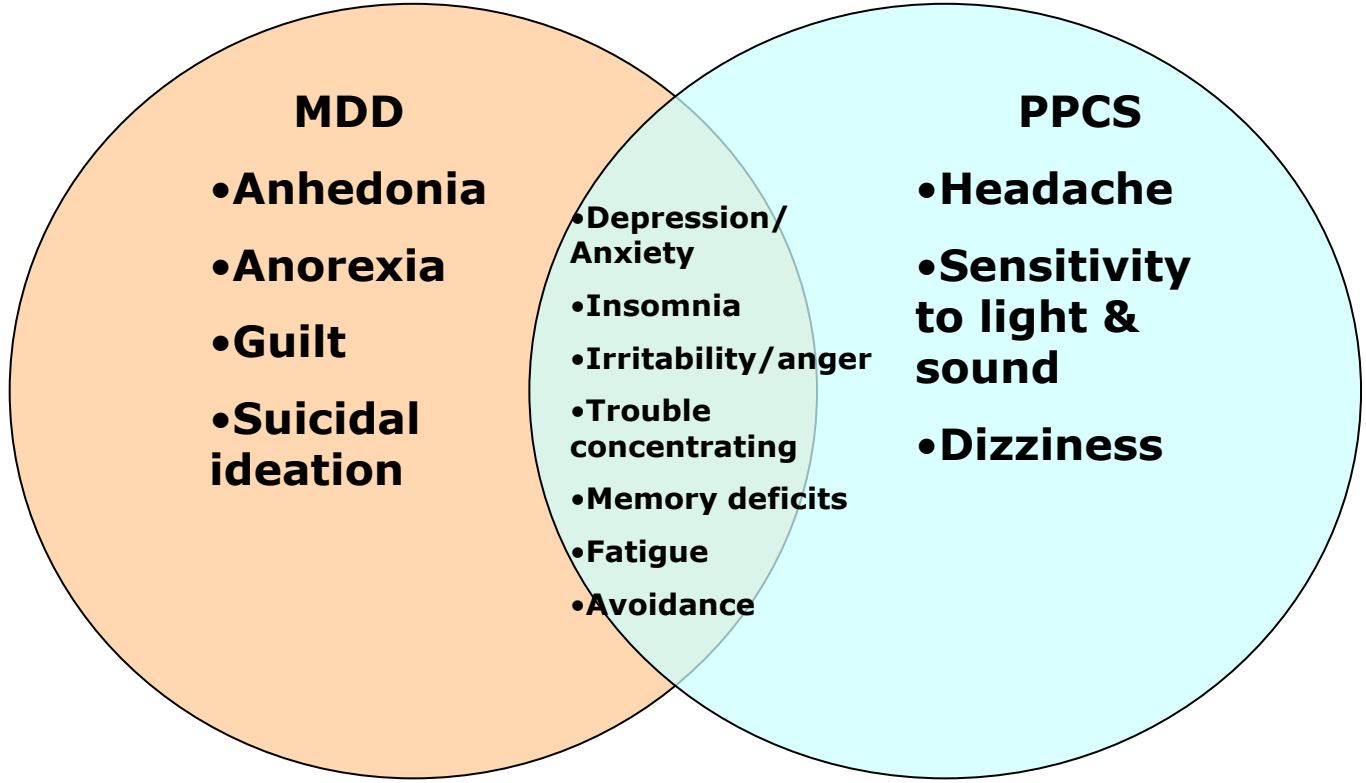
		TBI
1.	Depressed mood	
2.	Anhedonia	
3.	Weight loss/gain	
4.	Insomnia/hypersomnia	X
5.	Psychomotor changes	X
6.	Fatigue	X
7.	Worthlessness/guilt	
8.	Poor concentration	X
9.	Thoughts of death/suicide	

Depression / Apathy

- Assess pre-injury depression and alcohol use
- Use ‘inclusive’ diagnostic technique
- May occur acutely or post-acutely
- Not always related to TBI severity
- Older adults (≥65) less likely to have MDD
- Addressing PCS may decrease risk of depression

- Apathy alone - prevalence 10%
  - disinterest, disengagement, inertia, lack of motivation, lack of emotional responsivity

Interface of MDD & Persistent PCS



Basic Treatment Principles

- Focus on maximizing functioning
- Treat maximum Sxs with fewest possible medications
  - TBI patients more sensitive to side effects

    START LOW, GO SLOW, …BUT GO
- Start at 25-50% usual dose, but may still need maximum doses
- Therapeutic onset may be delayed
- Medications may lower seizure threshold
- Medications may slow cognitive recovery
- When adjusting meds, make one change at a time

TBI Depression Treatment Modality Preferences

Table 2. Subjects Likely To Participate In Treatment

Treatment Modality	Depressed n=37		Non-Depressed N=108		Total Sample N=145	
Physical Exercise	**33**	**(89.2%)[a]**	**88**	**(82.2%)[c]**	**121**	**(84.0%)[c]**
Counseling/Psychotherapy	**29**	**(78.4%)[a]**	**69**	**(63.9%)[a,b]**	**98**	**(67.6%)[b]**
Antidepressants	**27**	**(73.0%)**	**42**	**(38.9%)**	**69**	**(47.6%)**
Alternative or Herbal	**25**	**(67.6%)**	**66**	**(61.1%)[b]**	**91**	**(62.8%)[a]**
Self-Help Materials	**23**	**(62.2%)**	**68**	**(63.0%)[a,b]**	**91**	**(62.8%)[a]**
Group Therapy	**16**	**(43.2%)**	**47**	**(43.5%)**	**63**	**(43.4%)**

Note: Differences reported are among treatment modalities within each column.
a: Favored over Group Therapy
b: Favored over Antidepressants
c: Favored over all modalities

Fann et al, JHTR 2009

TBI-BH ECHO

Inadequate TBI Depression Treatment

Among our 53% with TBI and MDD:

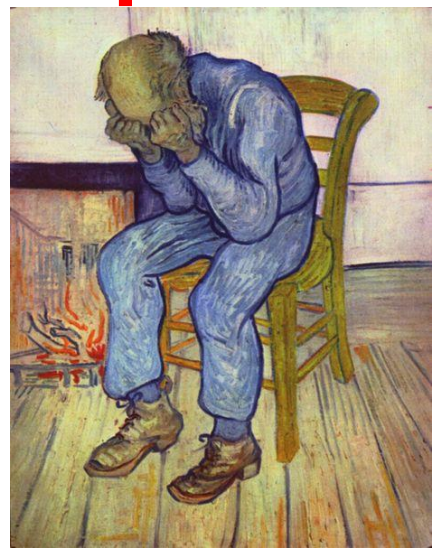
- 44% received any depression treatment
  - 41% received any antidepressant
  - 20% received any psychotherapy

In primary care, 1/3 of depressed Pts receive any mental health treatment. Of these, ~50% receive 'minimally adequate treatment'

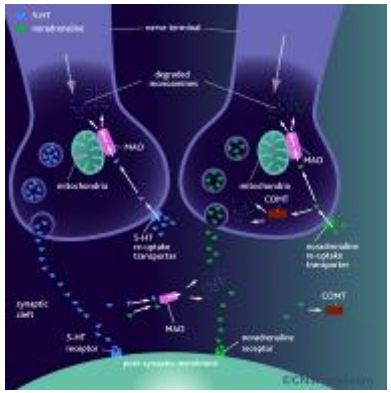
Wang et al, Arch Gen Psychiatry 2010; Bombardier, et al. JAMA 2010; Rockhill et al, J Neurotrauma 2012

Modifiable Risk Factors

Depression



Neurobiological Factors



Cognitive Impairment, Bias, Distortions

No Pleasant Activities

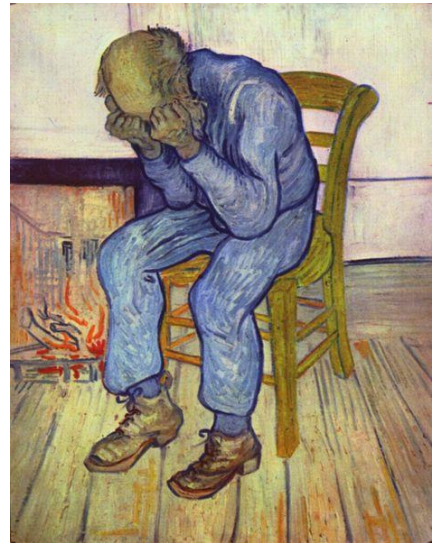
Psychosocial Adversity

Sedentary Lifestyle

Possible Interventions

Pharmacotherapy, Light, Neuromodulation

Depression



Cognitive Behavioral Tx, Mindfulness, Environmental

Behavioral Activation

Case Mgt, Social Support, Problem Solving Tx Problem Solving

Exercise, Motivational Interviewing

Pharmacological Interventions

Depression, Apathy, PBA

- Meta-analyses: ADs reduce depression, not significantly different from placebo, SSRIs/SNRIs best tolerated
- Two Class I RCTs of sertraline:
  - N=62: complicated mild-sev TBI, *post-acute phase* (mean 5 months post-TBI), high psych comorbidity
  - N=52: 36% mTBI, *chronic phase* (mean 18 years post-TBI)
    - showed trends toward superiority of sertraline over placebo in chronic, but not post-acute phase
    - May improve information processing speed post-acutely

Fann et al, JHTR 2017; Ashman et al, Arch PM&R 2009

Depression, Apathy, PBA

- TCAs, moclobemide (not in US): efficacy in small studies
- Methylphenidate: AD effect in small studies; decreases mental fatigue, apathy; improve arousal, cognitive processing speed, anger, participation
- Selegiline (MAO-B inhibitor): may decrease apathy
- Dextromethorphan/quinidine: decreased PBA in uncontrolled studies (SSRIs & TCAs may also help)
- (Blue) Light therapy: preliminary evidence for positive effects on depression, fatigue/daytime sleepiness, sleep disturbance (Srisurapanont et al, PLoS One 2021)

Not formally tested in TBI:

- Bupropion: may help with fatigue, apathy
- Mirtazapine: may decrease anxiety, increase sleep, appetite
- Newer ADs, e.g., vilazodone, vortioxetine, levomilnacipran, esketamine: not yet systematically studied

Pharmacologic Options

- Selective serotonin re-uptake inhibitors (SSRIs)
  - sertraline - paroxetine - fluoxetine
  - citalopram - escitalopram
  - Can help with anxiety, pain, anger
- SNRIs - venlafaxine/desvenlafaxine, duloxetine, levomilnacipran (help with pain, esp. neuropathic; can cause HTN rarely)
- bupropion (may decrease seizure threshold), activating
- mirtazapine (may be too sedating), increase appetite/weight
- Tricyclics: nortriptyline, desipramine (blood levels available)
- methylphenidate, dextroamphetamine – decreases fatigue
- Newer ADs not yet studied in TBI

- Apathy: Dopaminergic agents - methylphenidate, pemoline, bupropion, amantadine, bromocriptine, selegiline, modafinil, armmodafinil (no RCTs in TBI)

Common Polypharmacy Pitfalls

- Depression
  - Antidepressants
- Anxiety / Panic
  - Benzodiazepines
- Insomnia
  - Sedative-hypnotics
- Headache / Pain
  - Opioids, gabapentin

- Irritability / Anger
  - Beta-blockers, antipsychotics, anticonvulsants
- Fatigue / Cognitive Impairment
  - Psychostimulant, amantadine, AChE inhibitors

Potential Consequences of Polypharmacy

- Drug-drug interactions
- Accidental or volitional overdose
- Non-adherence
- Cumulative adverse effects
  - E.g., sedation, lightheadedness, cognitive impairment, fatigue
- Delirium
- Accidents (falls, MVAs)
- Unnecessary health care utilization & costs

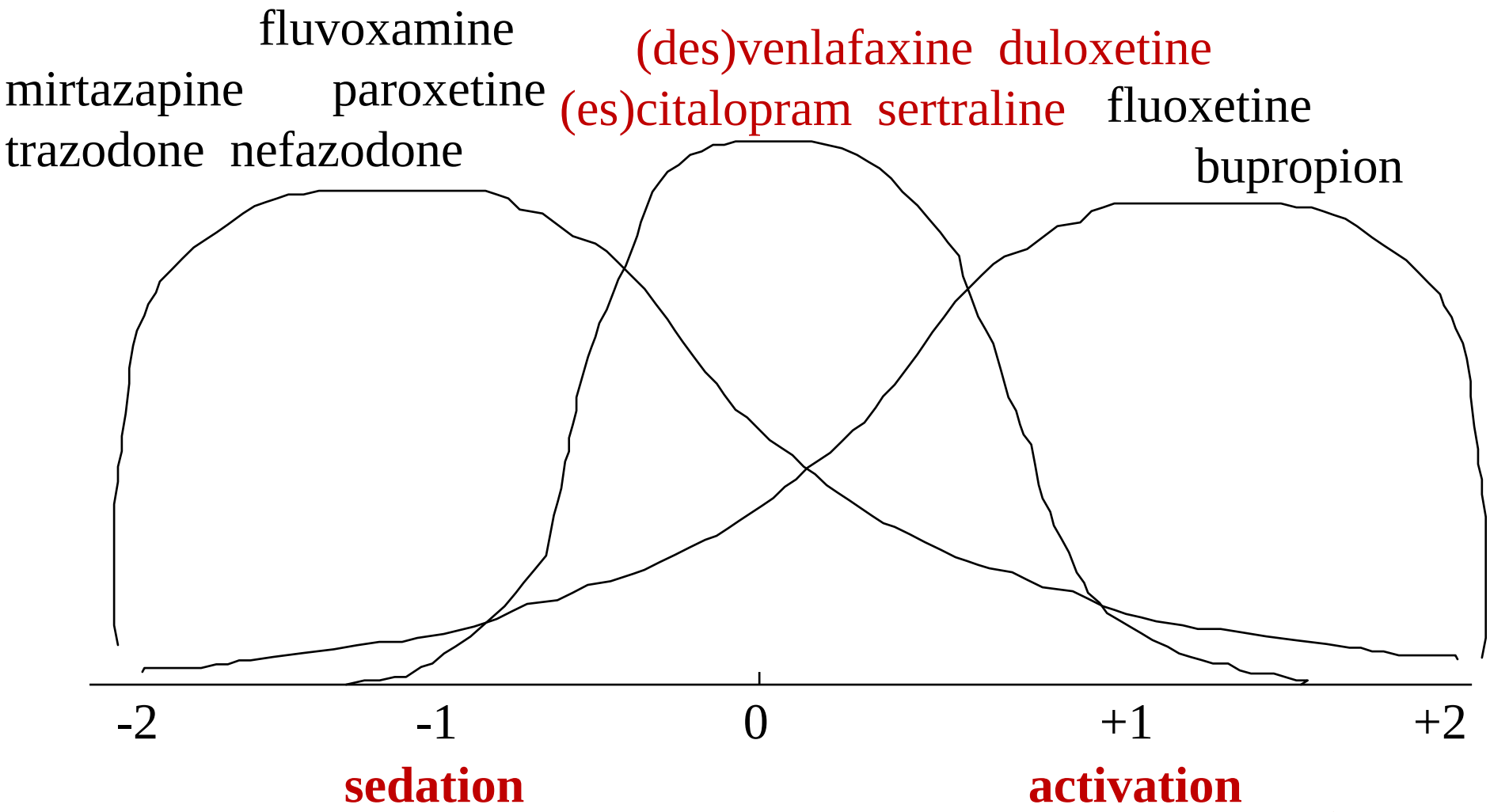
Table 2. Potential Pharmacological Strategies Across Neuropsychiatric Syndromes

Drug Mechanism (Examples)	Depression	Apathy	Anxiety	PTSD	Agitation, Anger, Irritability	Mania	Psychosis	Insomnia
5-HT_2 Reuptake Inhibition (Sertraline, Citalopram)	x		x	x	x			
5-HT_2/NE Reuptake Inhibition (Venlafaxine, Duloxetine, TCAs)	x		x	x	x			
5-HT_2/α_2 Antagonism (Mirtazapine)	x		x	x				x
5-HT_2 Antagonism/Reuptake Inhibition (Trazodone)	x		x	x	x			x
5-HT_1 Agonism (Buspirone)			x		X			
DA/NE Reuptake Inhibition/Release (Bupropion, Methylphenidate, Dextroamphetamine)	x	x			x			
GABA Agonism (Lorazepam, Clonazepam)			x		x	x		x
Sodium Channel Inhibition (Valproate, Carbamazepine, Lamotrigine)			x	x	x	x		
Calcium Channel Inhibition (Gabapentin, Pregabalin)			x		x	x		x
Glutamate Modulation (Lithium)		x			x	x		
DA Agonism (Amantadine, Bromocriptine, Pramipexole)		x			x			
DA/5-HT_2 Antagonism (Quetiapine, Olanzapine)	x		x	x	x	x	x	x
Alpha-Adrenergic Modulation (Prazosin, Clonidine)				x	x			
Beta-Adrenergic Modulation (Propranolol, Nadolol)			x	x	x			
Histamine Antagonism (Hydroxyzine)			x	x				x

5-HT, serotonin; DA, dopamine; GABA, gamma-aminobutyric acid; NE, norepinephrine; PTSD, posttraumatic stress disorder; TCA, tricyclic antidepressant.

Fann, Quinn, Hart. Biol Psychiatry 2022

Sedation and activation profiles



TBI-BH ECHO

Psychoeducational & Behavioral Interventions

Cognitive Behavioral Therapy (CBT)

- High structure & self-monitoring advantageous after TBI
- Three RCTs after mod-sev TBI
  - 2 for depression: no signif improvement compared to UC/ supportive Tx
    - Worked equally in severe vs. moderate TBI
    - Phone CBT as effective as in-person
    - Behavioral activation may be more effective than cognitive restructuring
  - 1 for depression &/or anxiety
    - Anxiety improved quickly, depression improved after boosters. MI offered no additional benefit to CBT.

Ashman et al, JHTR 2014; Fann et al, J Neurotrauma 2015:
Ponsford et al, Psychol Med 2016

Behavioral Activation (BA)

- Increase environmental reward via pleasant, values-concordant activities
  - TBI patients often isolated with decreased participation
- RCT of 8 weeks of text-messaging of BA vs. motivational messages
  - Both groups had improved mood
  - BA group reported more environmental reward, decreased avoidance

Hart et al, Neuropsychol Rehabil 2020

Problem Solving Therapy (PST)

- Stepwise algorithm to identify & solve problems
- Similar strategies used for:
  - Remediation of executive dysfunction after TBI
  - Depression in elderly
- RCT of 12-session phone-delivered PST vs. Education in active duty Service Members with mTBI
  - Significant improvement in emotional status, depression, PTSD, sleep, physical function
  - Gains at 6-mos. not sustained at 12-mos.

- MBSR + CBT vs. Waitlist improved depression
- ACT appears to be mediated by psychological flexibility

Bell et al, J Neurotrauma 2017; Gann et al, Biol Psychiatry 2022

Environmental Modification

- Important for pts unable to engage in talk therapy
- Consists of contingencies to alter frequency of targeted behaviors
- Positive Behavior Support
  - Emphasizes evaluation & prevention of antecedents (triggers) vs. consequences
  - Teaches prosocial skills
  - Provides patients choice of behaviors
  - Caregiver training enables long-term changes

Fann, Quinn, Hart. Biol Psychiatry 2022

Exercise

- Meta-analyses show ~8-12 weeks of moderate to vigorous exercise has a large effect on depression severity
- Mind-body exercise, aerobic exercise, and to a lesser extent resistive exercise have moderate to large effects on depression
- The efficacy of exercise for depression after TBI is uncertain
  - RCT (n=84) demonstrated no differences in depression after 10 week supervised + home exercise program, but those who exercised > 90 mins/week had lower depression
  - Randomized crossover study of walking program vs. nutrition class (n=123) showed walkers had improved depression compared to nutrition class

Schuch et al., J Psychiatric Res, 2016; Miller et al., 2021, F1000 Research; Miller et al 2020 Ageing Research Reviews; Driver S, Ede A. Brain Injury 2009;23:203–212; 82:174–182; Hoffman J, PM&R 2010;2:911–919; Bellon, K. Brain Injury 2015;29:3, 313-319,

Opportunities

- With some adaptations, many interventions are promising for those with significant cognitive impairment after TBI
- Treatment based on skills training (e.g., CBT, PST) likely need booster sessions
- Need to better define interventions, identify & measure active ingredients
- Need to test theoretically based interventions that align with causative factors (e.g., BA or ACT to counteract loss of meaningful activity, associated with post-TBI depression)
- Remote technologies have great potential to enhance & facilitate delivery of interventions

Fann, Quinn, Hart. Biol Psychiatry 2022

Neuromodulation Interventions

- Transcranial Magnetic Stimulation (TMS) *
- Transcranial Electrical Stimulation (TES)
- Photobiomodulation *
- Electroconvulsive Therapy (ECT) *
- Vagal Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS) *

* Some evidence for depression in TBI

Other target outcomes in TBI: arousal, cognition, anxiety, impulsivity, functioning, QOL

Questions?

TBI-BH ECHO