



**TBI-BH ECHO**

Traumatic Brain Injury – Behavioral Health ECHO  
UW Medicine | Psychiatry and Behavioral Sciences

# 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
  - Neuromodulation
  - Psychoeducational & Behavioral

TBI is a ...

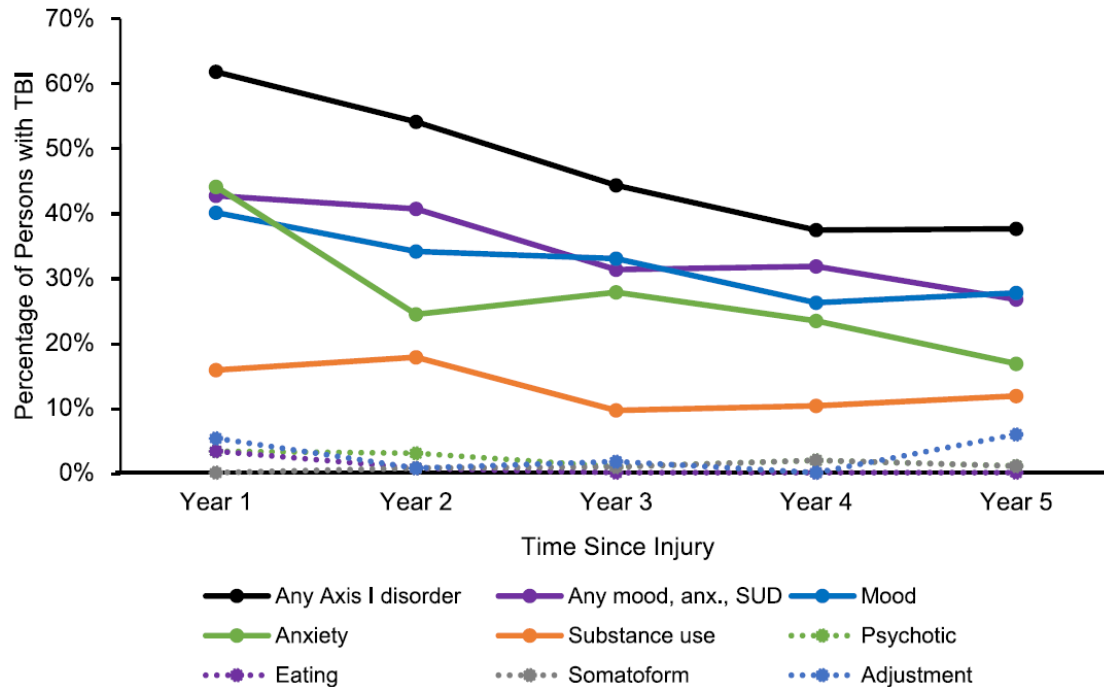
- **Neurobiological Injury**
  - Consequences of direct injury to CNS
- **Traumatic Event**
  - e.g., Risk for Post-traumatic Stress Disorder, Depression, Anxiety
- **Chronic Medical Condition**
  - May lead to long-term symptoms & disability

# 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

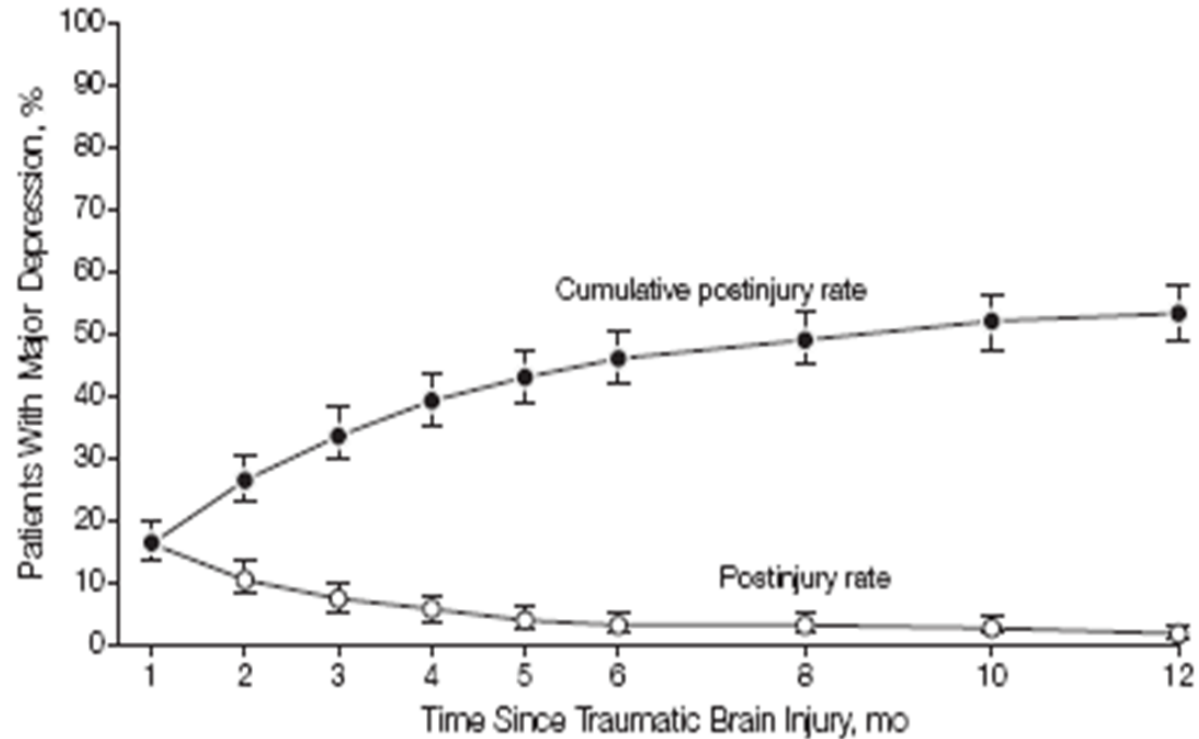
# Mental Health Disorders after TBI



**Figure 1.** Annual prevalence of different classes of psychiatric disorder in the prospective study of moderate to severe traumatic brain injury (TBI) from Alway *et al.* (54). DSM-IV Axis I diagnoses were determined via Structured Clinical Interview. Mood, anxiety (anx.), and substance use disorders (SUD) were the most prevalent DSM-IV Axis I disorders across 5 years of follow-up after injury, with a steady decline in prevalence over time.

Howlett, Nelson, Stein. *Biol Psychiatry* 2022

# 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

# 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) \*
- Repetitive TBI \*
- Female Gender \*
- Black race \*
- < HS education \*
- Violent etiology
- Medicaid insurance
- Litigation involvement
- Lifetime alcohol dependence \*
- Cocaine/Methamphetamine intoxication
- Prior psychiatric history, sleep disturbance \*
- 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; Etemad et al, JAMA Netw Open 2023



# Incarcerated Populations with TBI

Large study in Wisconsin & New Mexico

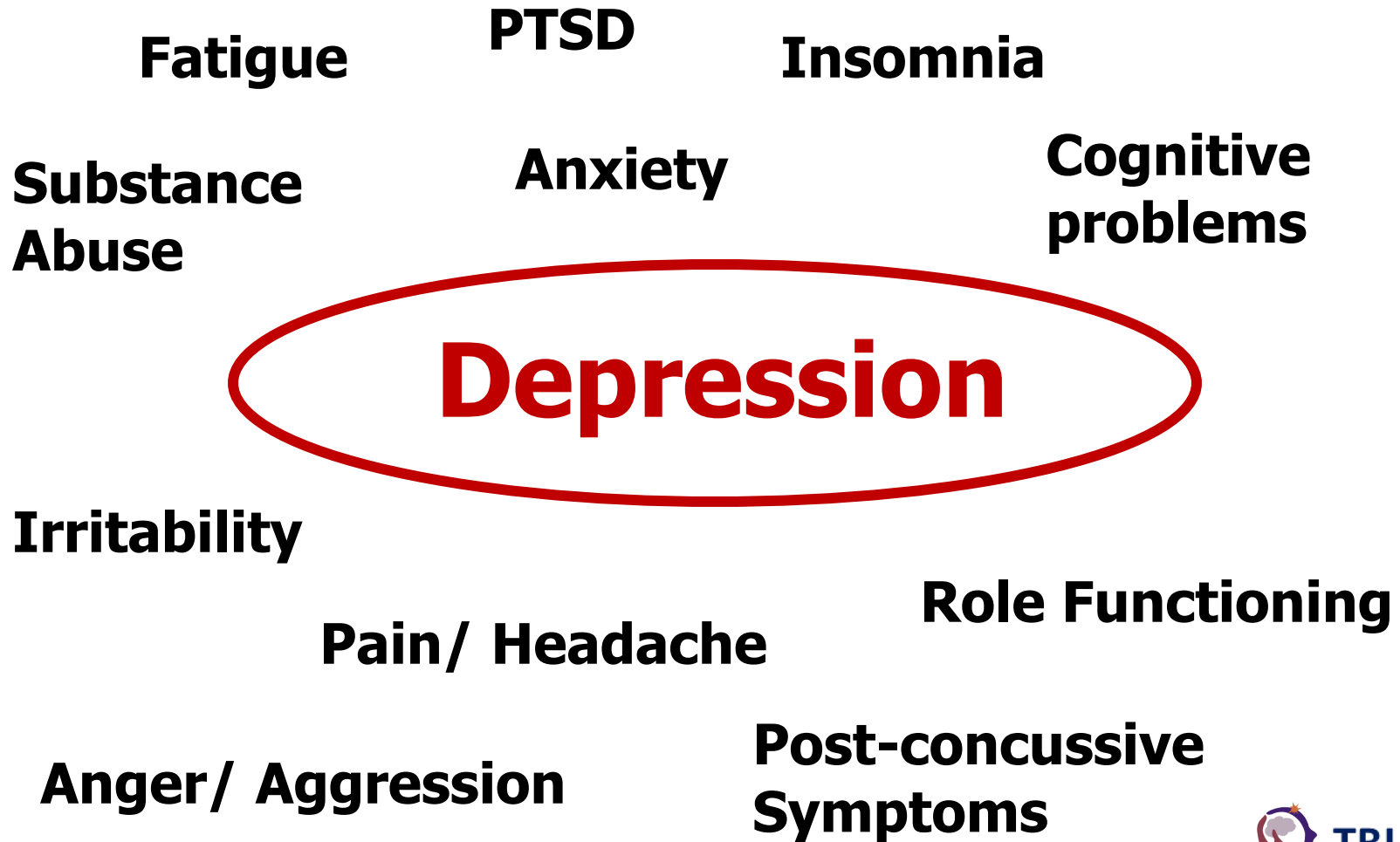
- **Rates of TBI** (80% mild) 5 times higher (men: 52-55%, women: 47-67%) than in general population
- 20-30% with **>1 TBIs**
- Higher rates of TBI caused by **assault** (>25% vs. 8%)
- High rates of **Depression** among men (12-36%) and women (46-55%) with TBI

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



# 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

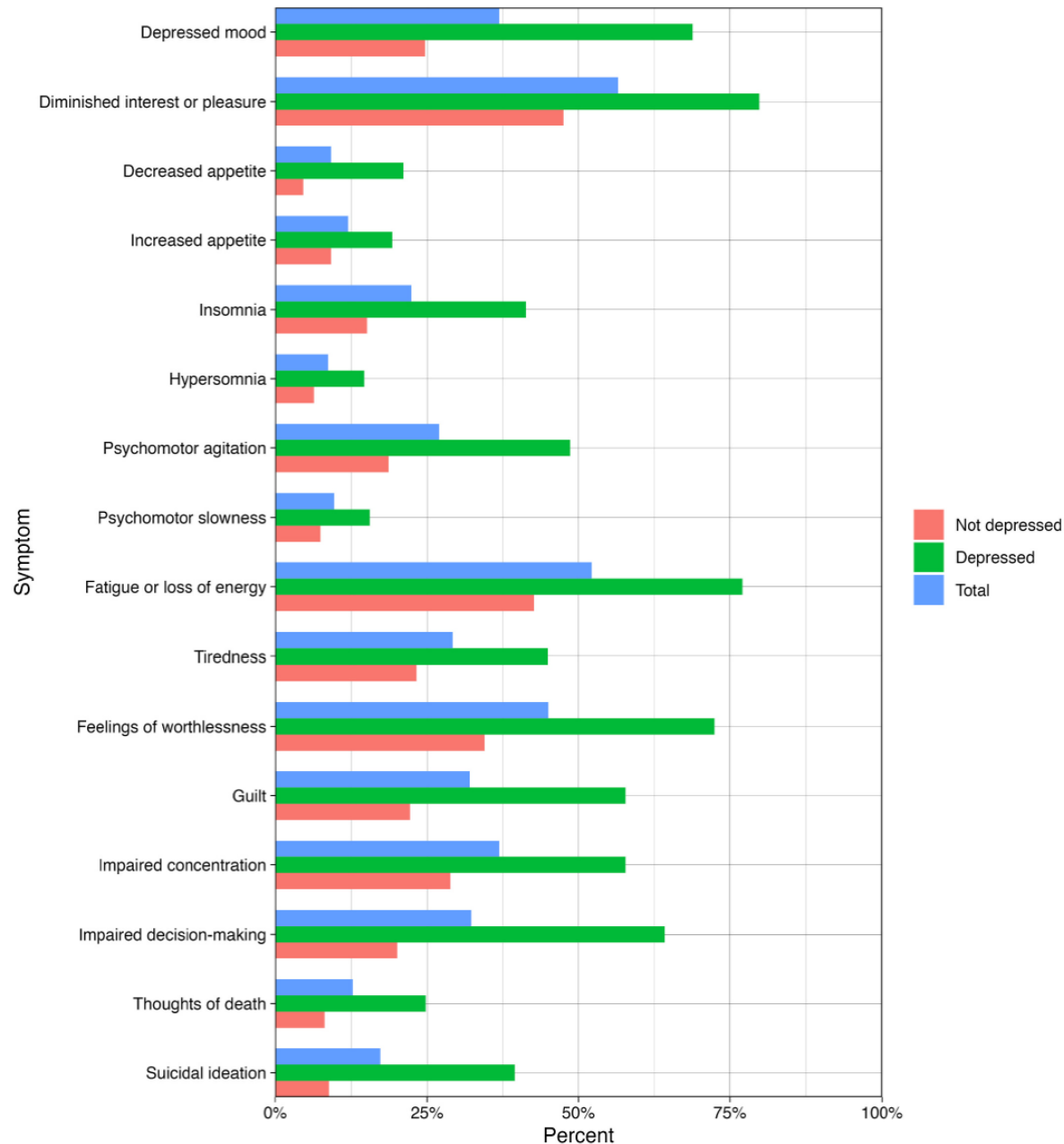
Fann JR, Kennedy R, Bombardier CH. Physical Medicine and Rehabilitation. In: Textbook of Psychosomatic Medicine, 2nd Ed. Levenson J (ed), American Psychiatric Publishing, Inc., Washington, D.C., 2018;

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

# 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



**Carmichael et al, J  
Affect Dis 2024**

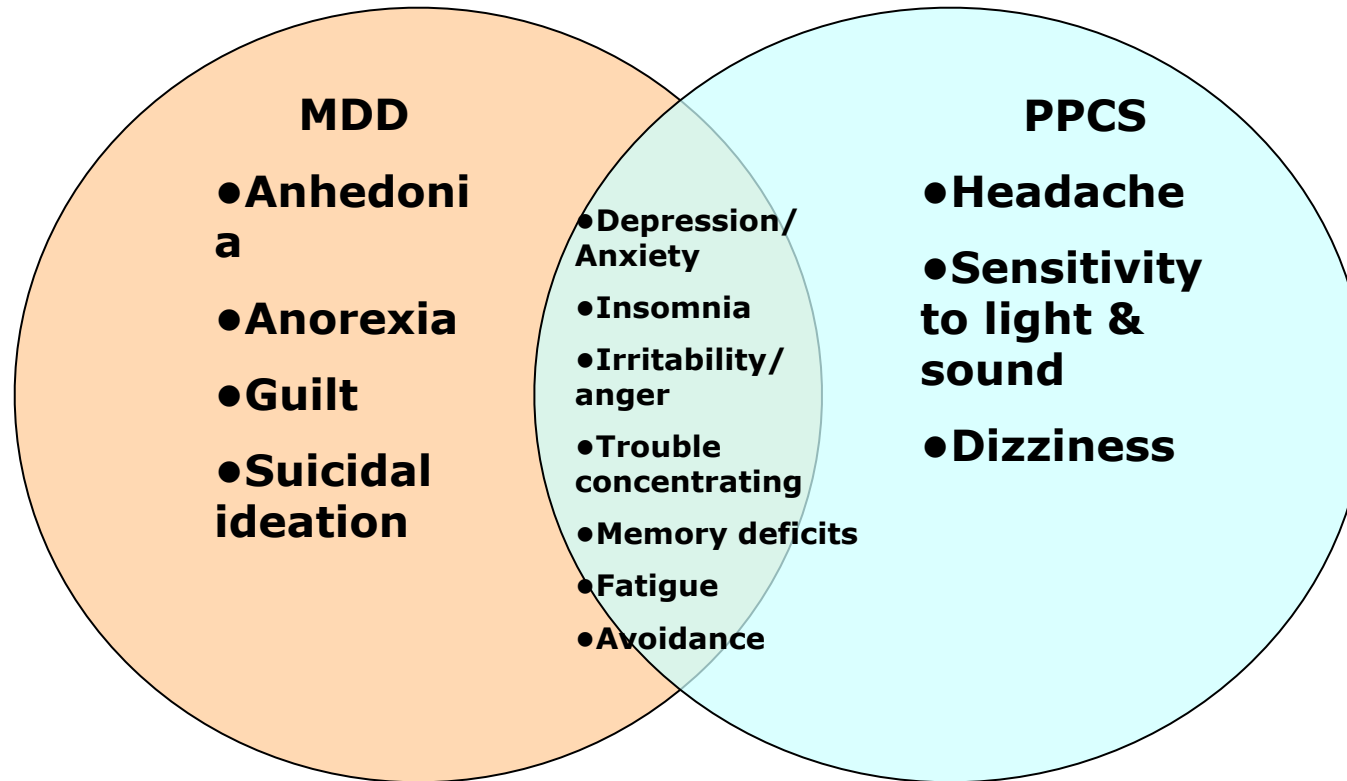
Fig. 1. Frequency of specific depressive symptoms in the total sample ( $n = 393$ ; blue) as well as among participants who did self-report ( $n = 109$ ; green) and did not self-report a current diagnosis of depression ( $n = 284$ ; pink). Note. The items used to assess each symptom are listed in Table 1. A symptom was considered present in an individual based on a score of  $\geq 3$  on the relevant IDAS item/s (or  $\geq 2$  for suicidal ideation). Controlling for age, sex, and TBI severity, participants who self-reported a depression diagnosis had significantly greater odds of endorsing each symptom. The statistical outputs can be found in Supplemental Table S1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

# Depression & Apathy

- Assess pre-injury depression and alcohol use
- Use 'inclusive' diagnostic technique
- Older adults ( $\geq 65$ ) less likely to have MDD
- Addressing PCS (e.g., sleep) may decrease risk of depression
- **Apathy** alone - prevalence 10%
  - disinterest, disengagement, inertia, lack of motivation, lack of emotional responsivity



# Interface of MDD & Persistent PCS



# TBI Depression Treatment Modality Preferences

## Subjects Likely To Participate In Treatment

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

# Inadequate TBI Depression Treatment

Among our 53% with TBI and MDD:

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

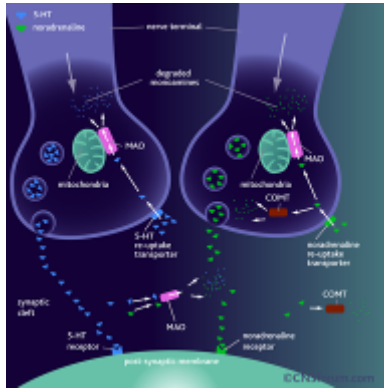
In **primary care**, 1/3 of depressed Pts receive any mental health treatment. Of these, ~50% receive 'minimally adequate treatment'

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

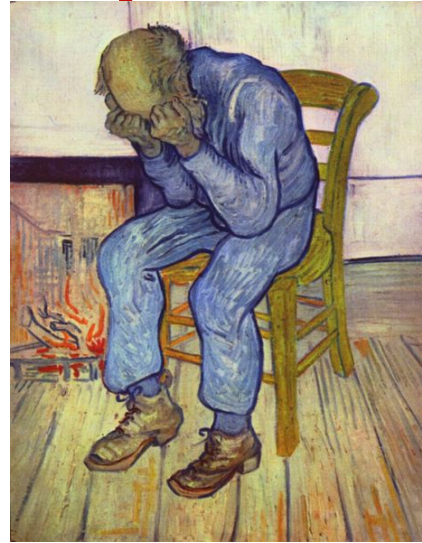
# Modifiable Risk Factors

## Depression

### Neurobiological Factors



### Cognitive Impairment, Bias, Distortions



### No Pleasant Activities



### Psychosocial Adversity



### Sedentary Lifestyle



# Possible Interventions

## Depression

**Pharmacotherapy, Light, Neuromodulation**



**Cognitive Behavioral Tx, Mindfulness, Environmental**



**Behavioral Activation**



**Case Mgt, Social Support, Problem Solving Tx**



**Exercise, Motivational Interviewing**



# Pharmacological Interventions

# Basic Medication 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



# Depression, Apathy, Pseudobulbar Affect (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



# Depression, Apathy, PBA

- **TCAs, moclobemide (reversible MAOI, 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 – possibly decrease inflammation & organ damage?
- 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, improves cognition
- Newer ADs not yet studied in TBI
  
- **Apathy**: Dopaminergic agents - methylphenidate, pemoline, bupropion, amantadine, bromocriptine, selegiline, modafinil, armodafinil (no RCTs in TBI)

# Common Polypharmacy Pitfalls

- **Depression**
  - Antidepressants
- **Anxiety / Worry / Panic**
  - Benzodiazepines, antihistamines
- **Insomnia**
  - Sedative-hypnotics
- **Headache / Pain**
  - Opioids, gabapentin
- **Irritability / Anger**
  - Beta-blockers, antipsychotics, anticonvulsants
- **Fatigue / Cognitive Impairment**
  - Psychostimulant, amantadine, AChE inhibitors



# Potential Consequences of Polypharmacy

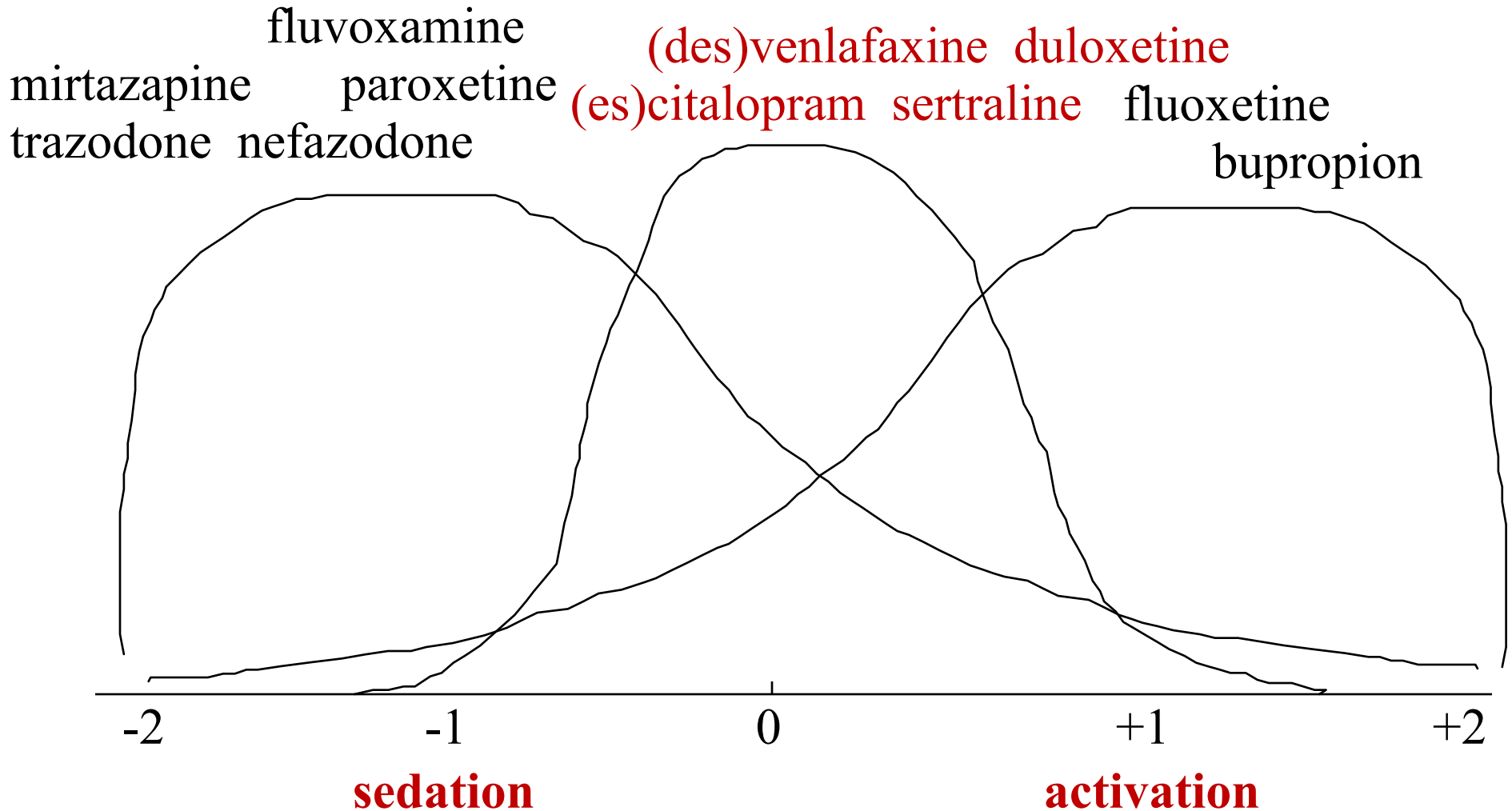
- Drug-drug interactions
- Accidental or volitional overdose
- Non-adherence
- **Cumulative adverse effects**
  - E.g., sedation, lightheadedness, cognitive impairment, fatigue
- Delirium
- Accidents (falls, MVAs)
- Unnecessary health care utilization & costs

**Table 2. Potential Pharmacological Strategies Across Neuropsychiatric Syndromes**

Drug Mechanism (Examples)	Depression	Apathy	Anxiety	PTSD	Agitation, Anger, Irritability	Mania	Psychosis	Insomnia
5-HT <sub>2</sub> Reuptake Inhibition (Sertraline, Citalopram)	x		x	x	x			
5-HT <sub>2</sub> /NE Reuptake Inhibition (Venlafaxine, Duloxetine, TCAs)	x		x	x	x			
5-HT <sub>2</sub> /α <sub>2</sub> Antagonism (Mirtazapine)	x		x	x				x
5-HT <sub>2</sub> Antagonism/Reuptake Inhibition (Trazodone)	x		x	x	x			x
5-HT <sub>1</sub> 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 <sub>2</sub> 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.

# Sedation and activation profiles



# Neuromodulation Interventions

- Transcranial Magnetic Stimulation (TMS) \*
  - Promise for individualized precision targeting using MRI
- Transcranial Electrical Stimulation (TES)
- Photobiomodulation \*
- Electroconvulsive Therapy (ECT) \*
- Vagal Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS) \*

\* Some evidence for depression in TBI

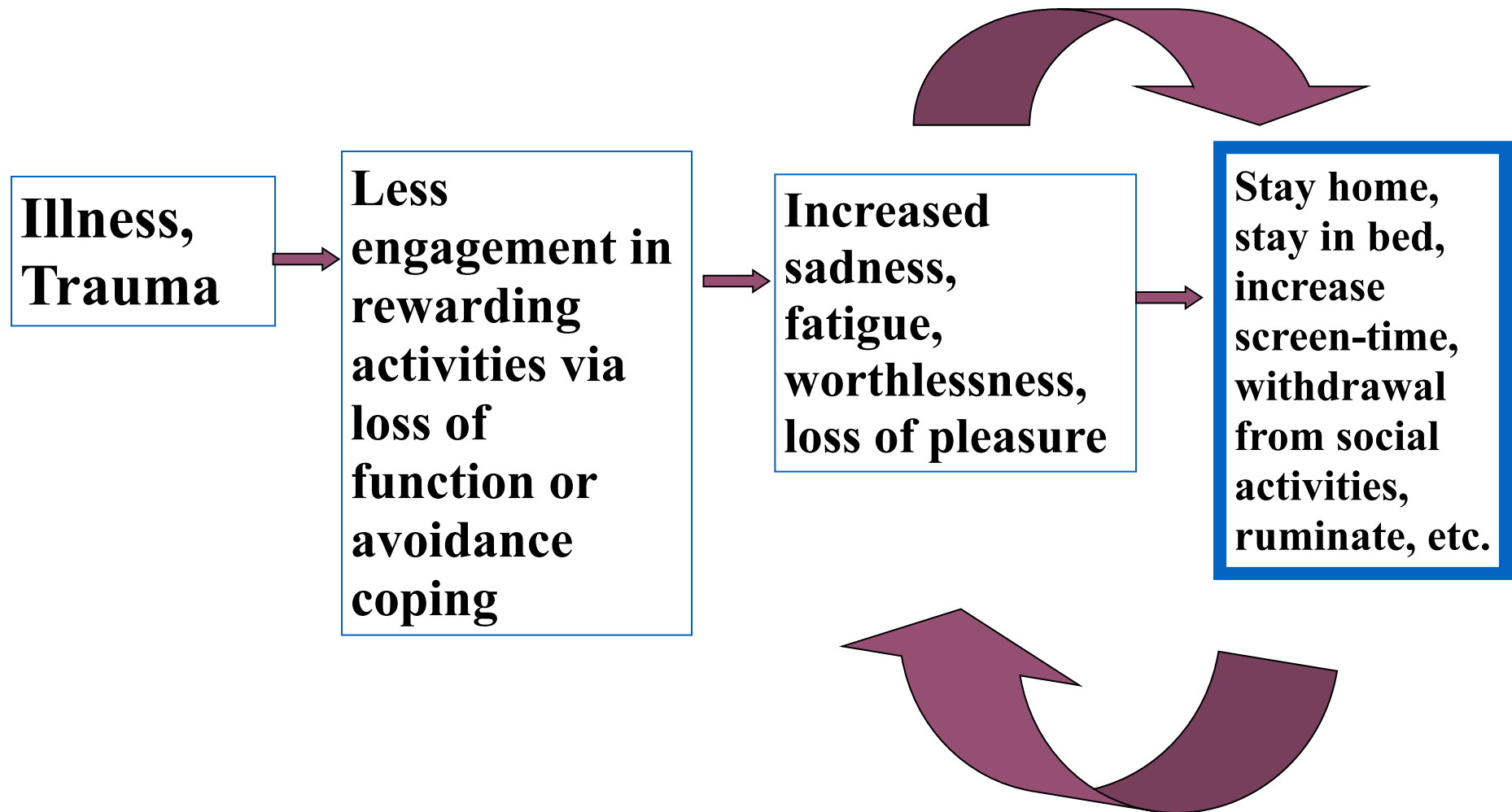
Other target outcomes in TBI: arousal, cognition, anxiety, impulsivity, functioning, QOL

Long-term efficacy needs to be established (Chang et al, J Clin Med 2023)

# Psychological & Behavioral Interventions



# Behavioral Conceptualization of Depression

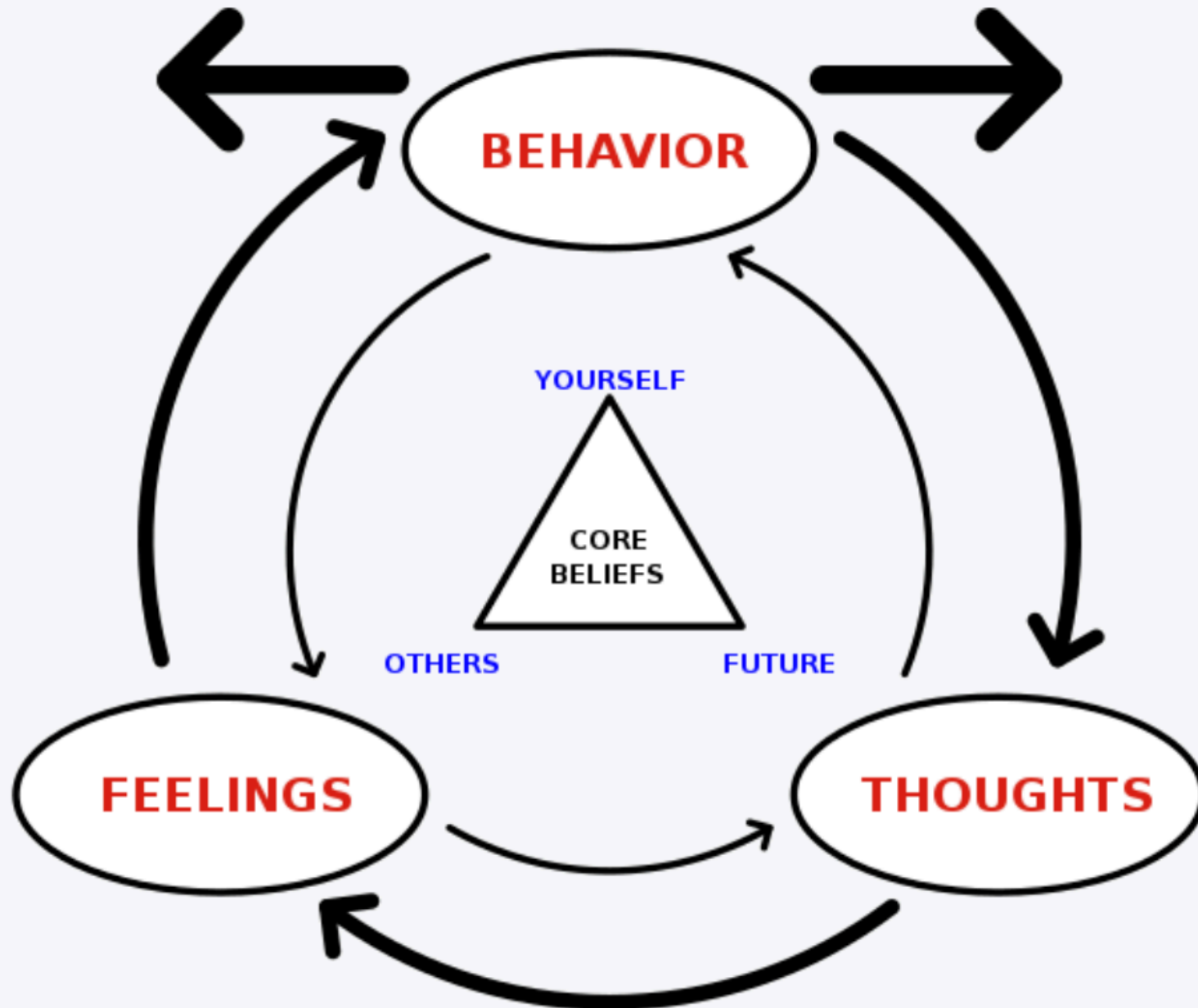


Adapted from Chris Martell, PhD

# 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

# Cognitive behavioral therapy



# 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

# Symptom Cluster Trajectories with CBT

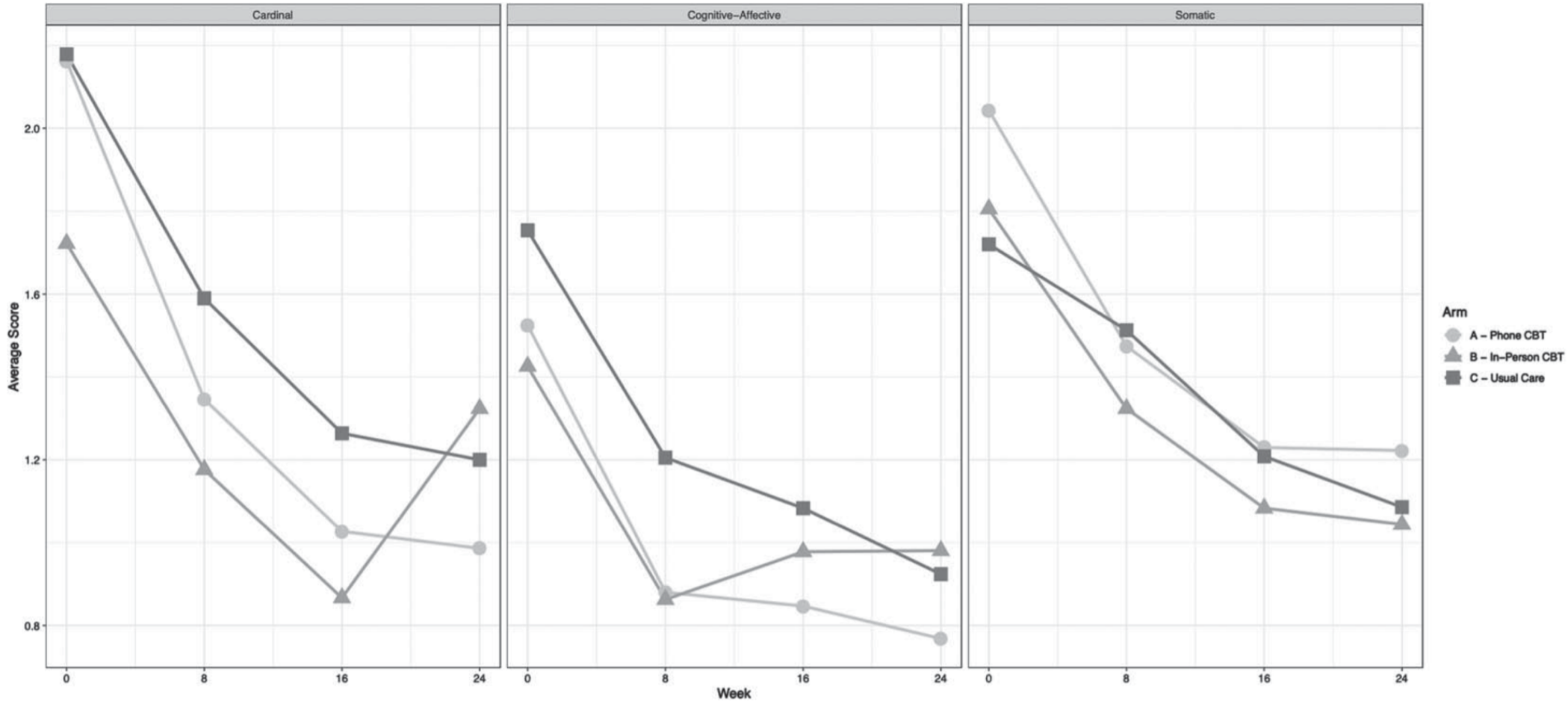


Fig. 1b. Graphic display of symptom cluster trajectories.

Erickson et al, NeuroRehabilitation 2024; Fann et al, J Neurotrauma 2015

# The 'ABC's' of Problem Solving Therapy

- **A**ssess the problem; achievable aims
- **B**rainstorm possible solutions
- **C**onsider & **C**hoose the best solution
- **D**evelop a plan and **D**o it
- **E**valuate your progress
- **F**lex and **F**ight on!

# 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

# 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



# 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,

# Exercise for Depression in TBI

- RCT (n=16) demonstrated improved mood after 8-week aquatic aerobics class vs. vocational rehabilitation class
- RCT (n=157) demonstrated no differences in depression between 12 weeks of cycle aerobics vs. relaxation classes
- RCT (n=84) demonstrated no differences in depression after 10 week supervised+home exercise program, but those who exercised > 90 min/week had lower depression scores
- Randomized crossover study of walking program vs. nutrition class (n=123 enrolled; 69 completers) showed walkers had improved depression compared to nutrition class

**Driver S, Ede A. Brain Injury March 2009;23:203–212**

**Bateman A, Arch Phys Med Rehab 2001; 82:174–182**

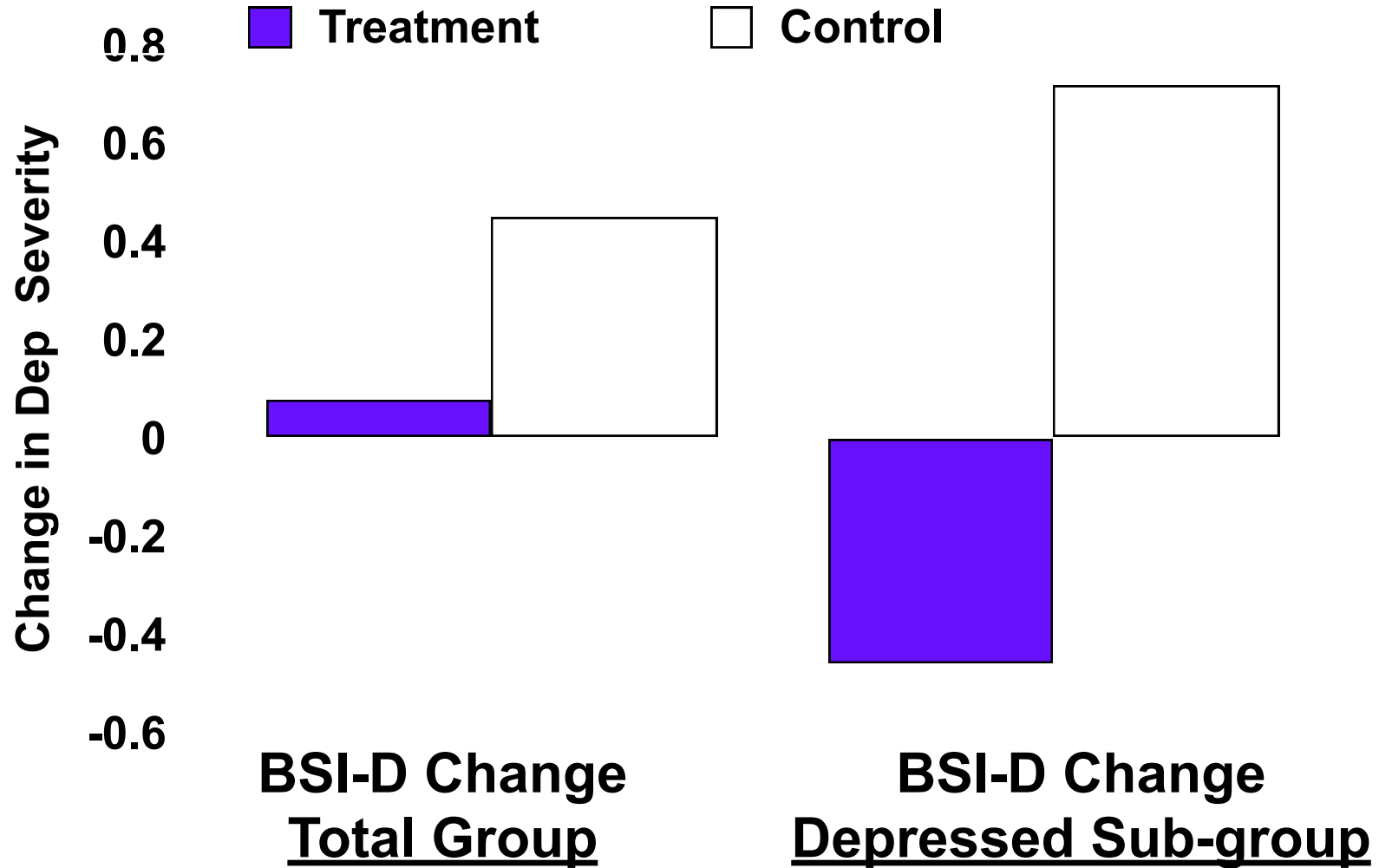
**Hoffman J, PM&R 2010;2:911–919**

**Bellon, K. Brain Injury 2015;29:3, 313-319,**

# Telephone Counseling to Improve TBI Recovery: Effect on Depression

- Reanalysis of Bell et al., Arch PM&R, 2005
- At discharge from inpatient rehabilitation 171 persons randomly assigned 1:1 to telephone counseling or usual care
- Intervention consisted of 30-45 min calls at about 2, 4, 8, 12, 20, 35 and 45 weeks after discharge
- Counselor used motivational interviewing techniques to elicit concerns, provide information and facilitate problem-solving to help with overall recovery/functioning after TBI
- Outcomes collected at one year by examiner unaware of group assignment

# Change in Depression Severity: 0-12 Months



BSI-D, Brief Symptom Inventory-Depression; p=.02, p=.004, respectively

# Key Components & TBI-Related Adaptations

**Table 3. Key Components and TBI-Related Adaptations in Psychoeducational/Behavioral Treatment Approaches**

Therapeutic Approach	Key Components	Adaptations to Improve Treatment Receipt/Treatment Enactment in TBI
Cognitive Behavioral Therapy	<p>Cognitive restructuring: challenge automatic negative thoughts and replace them with more realistic ones, often using evidence from in vivo behavioral experiments</p> <p>Schedule pleasant events and plan behaviors that reduce fear-based avoidance and improve self-esteem</p> <p>May also include skills training, e.g., muscle relaxation, coping, problem-solving, assertiveness</p>	<p>Changes to treatment sessions: shorter sessions/slower pace, repetition and review within and across sessions, avoidance of multitasking (e.g., no note-taking while listening)</p> <p>Strategies to support memory: written handouts summarizing session content; written or electronic schedules completed with help from therapist or support person at home; assistance in planning when/how to complete homework, with prompts at designated time</p> <p>Practice of new skills/behavioral experiments within session, with therapist feedback</p> <p>Frequent checks for understanding of material</p>
Behavioral Activation	<p>Explicit self-monitoring of activities and associated moods; recognition of behavioral avoidance</p> <p>Identification of personal values and activities consonant with values; gradually increasing scheduling of pleasant (reinforcing) and value-based activities</p> <p>May also include skills training (e.g., social skills) as needed to initiate activities</p>	<p>Provision of simple written or electronic aids for monitoring behaviors and concurrent moods and for creating activity schedules</p> <p>Visual aids for understanding theoretical rationale for behavioral activation and relationship of values to reinforcing activities and behaviors</p> <p>Assistance in selecting and scheduling activities; prompts to complete planned activities at designated time</p>
Problem-Solving Therapy	<p>Application of a step-by-step algorithm to:</p> <ul style="list-style-type: none"> <li>• Identify, characterize, and prioritize problems; choose one to work on</li> <li>• Brainstorm possible solutions</li> <li>• Evaluate solutions as to feasibility and potential effects, and choose one to try</li> <li>• Make and carry out a specific plan to apply the chosen solution</li> <li>• Evaluate the success of the solution</li> <li>• Modify the plan as needed or, if successful, continue with solution</li> </ul>	<p>Begin with relatively simple problem to illustrate method and ensure success</p> <p>Therapist prompts and assistance in defining problems and brainstorming solutions</p> <p>Visual aids to illustrate cyclic nature of problem-solving process and remind patient of steps</p> <p>Worksheets to help accomplish each step and record progress toward solutions</p> <p>Caregiver involvement to assist with formulating and/or carrying out plans</p>
Mindfulness-Based Stress Reduction	<p>Focus on staying in here-and-now</p> <p>Developing awareness of thoughts/feelings</p> <p>Meditation/breathing exercises</p>	<p>Brief sessions with repetition and review</p> <p>Simplified language</p> <p>Visual aids and handouts</p>

# Opportunities

- With some adaptations, many interventions are promising for those with significant cognitive impairment after TBI
- A team-based collaborative care approach was shown to decrease pain, depression, & anxiety (Hoffman et al, JAMA Netw Open 2024)
- 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



# Questions?

