Anxiety after TBI

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Project ECHO

TBI-BH ECHO

Overview

- Introduction
- Epidemiology & Screening
- Diagnosis
- Treatment
  - Psychopharmacology
  - Psychotherapy

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

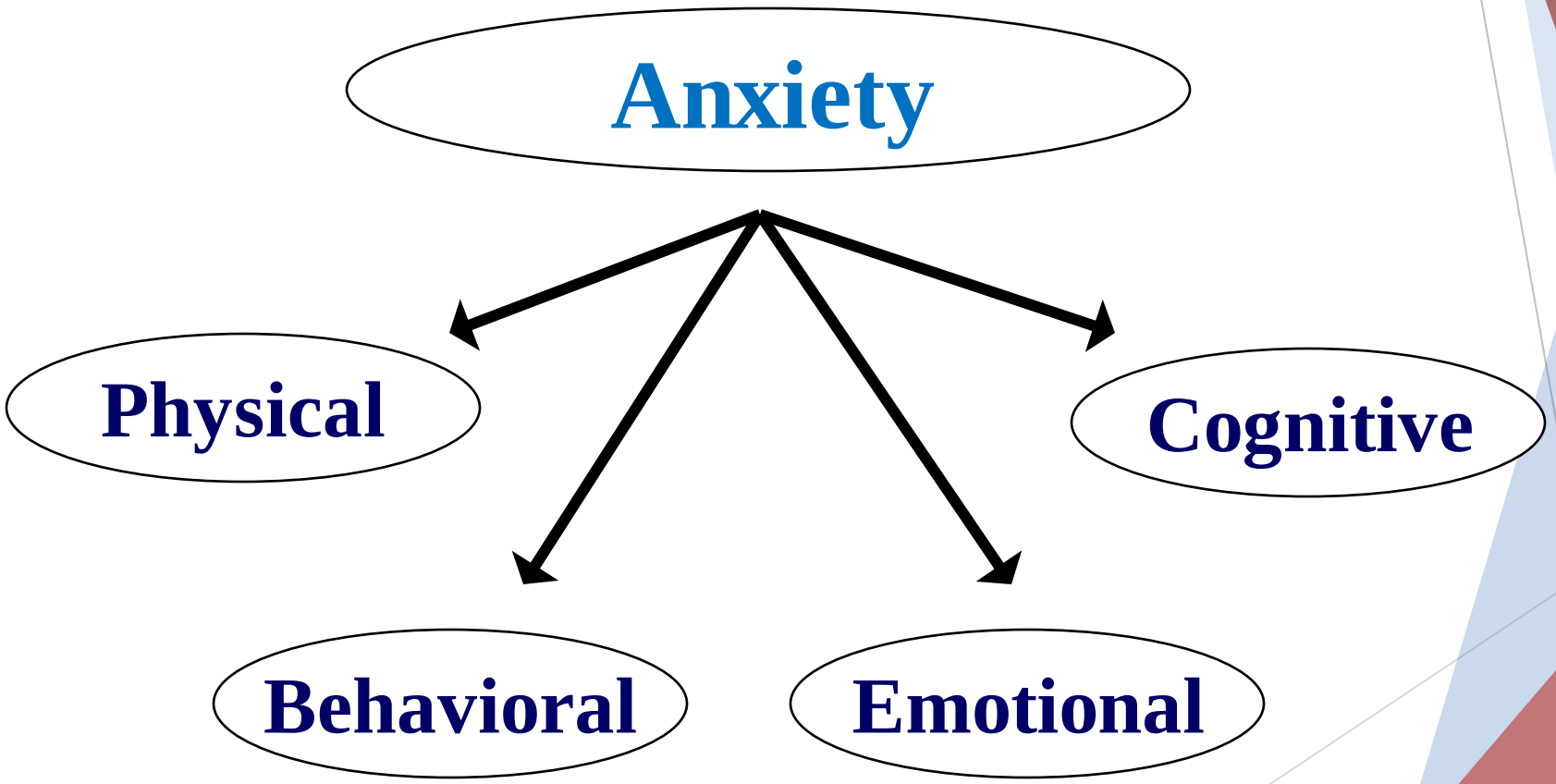
The Functional Value of Worry

- Allows for the anticipation of challenges/threats
- Plan and prepare for future
  - Attempt to establish improved prediction and control
- Motivational impact on behavior
- Can evoke proactive problem solving
- The system is usually adaptive, but at times, becomes "mis-wired", overwhelmed
- The goal of treatment is not to eliminate all anxiety (which is impossible)

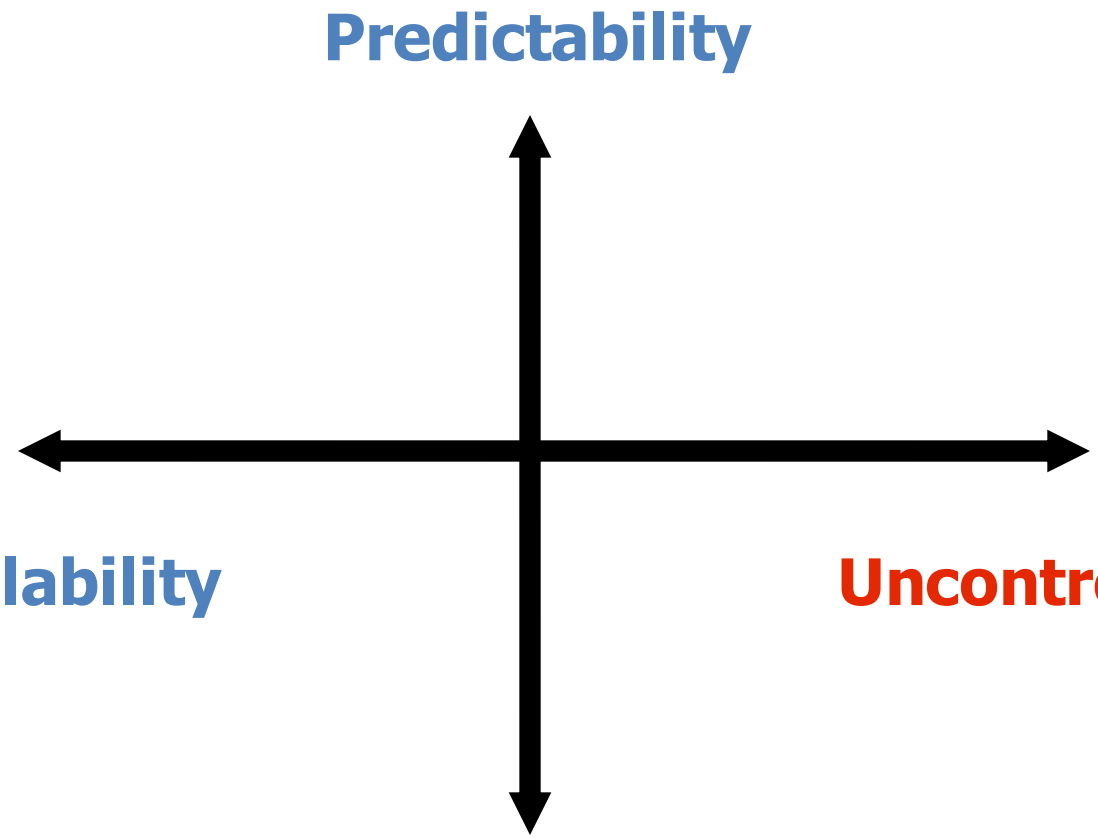
Signs of Anxiety

- Panic
- Irritable mood
- Excessive worry, fear, apprehension
- Restlessness
- Impulsive or aggressive behavior
- Quickened speech (differentiate from mania)
- Decreased sleep, appetite
- Shakiness, sweatiness, palpitations, chest pain, abdominal pain, dizziness, etc.
- AVOIDANCE, non-adherence
- Increased alcohol or substance use (e.g., cannabis)

Components of Anxiety



Factors Affecting the Volume Knob of the Anxiety Response



Anxiety Disorders

- Panic Disorder
- Generalized Anxiety Disorder
- Social Anxiety Disorder (Social Phobia)
- Specific Phobia – e.g., medical procedures
- Anxiety Disorder due to Another Medical Condition (e.g., hypoxia, infection, pain)
- Substance/Medication-induced Anxiety Disorder

Related Disorders

- Adjustment Disorder
- Obsessive-Compulsive Disorder
- Posttraumatic Stress Disorder

Epidemiology

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Mental Health Disorders after TBI

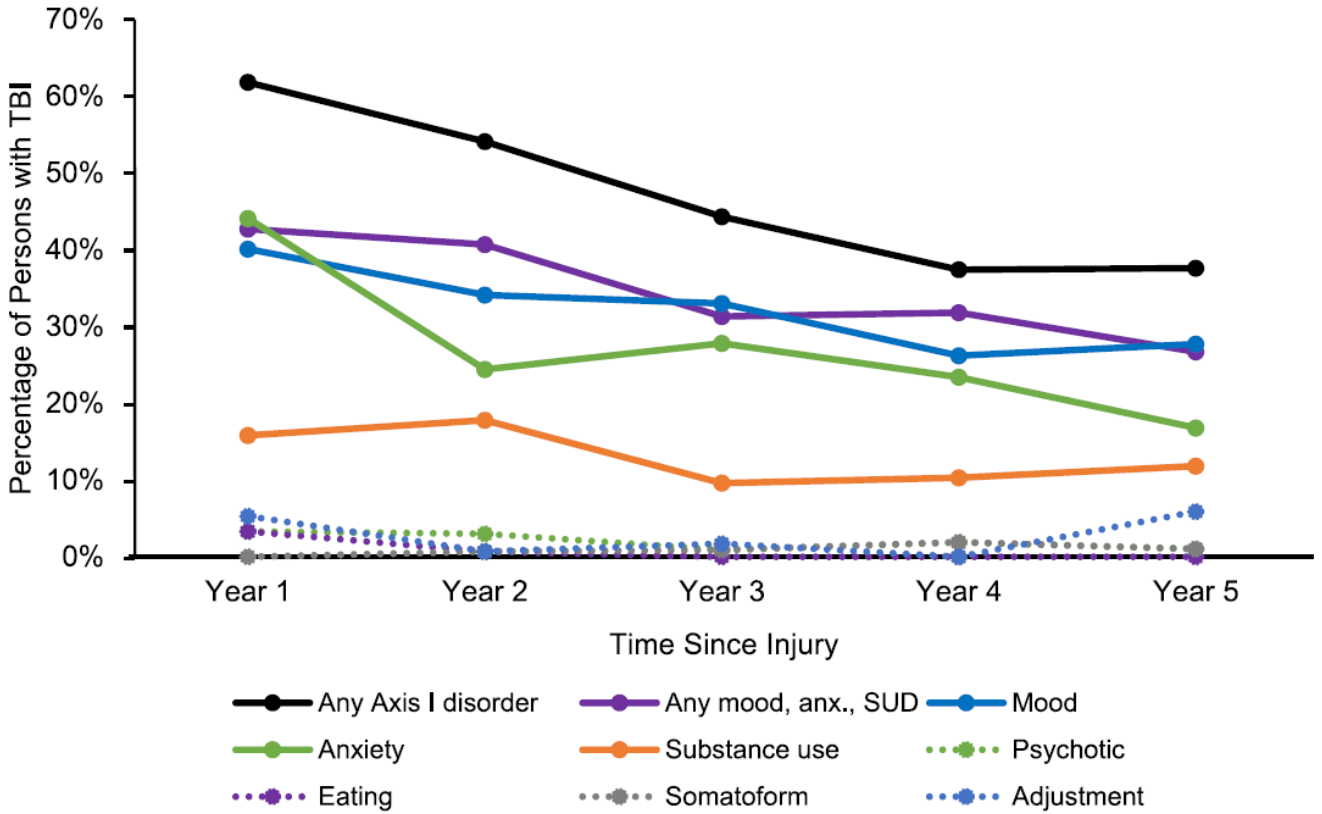

Figure 1. Annual prevalence of different classes of psychiatric disorder in the prospective study of moderate to severe traumatic brain injury (TBI) from Alway *et al.* (54). DSM-IV Axis I diagnoses were determined via Structured Clinical Interview. Mood, anxiety (anx.), and substance use disorders (SUD) 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. Biolog Psychiatry 2022

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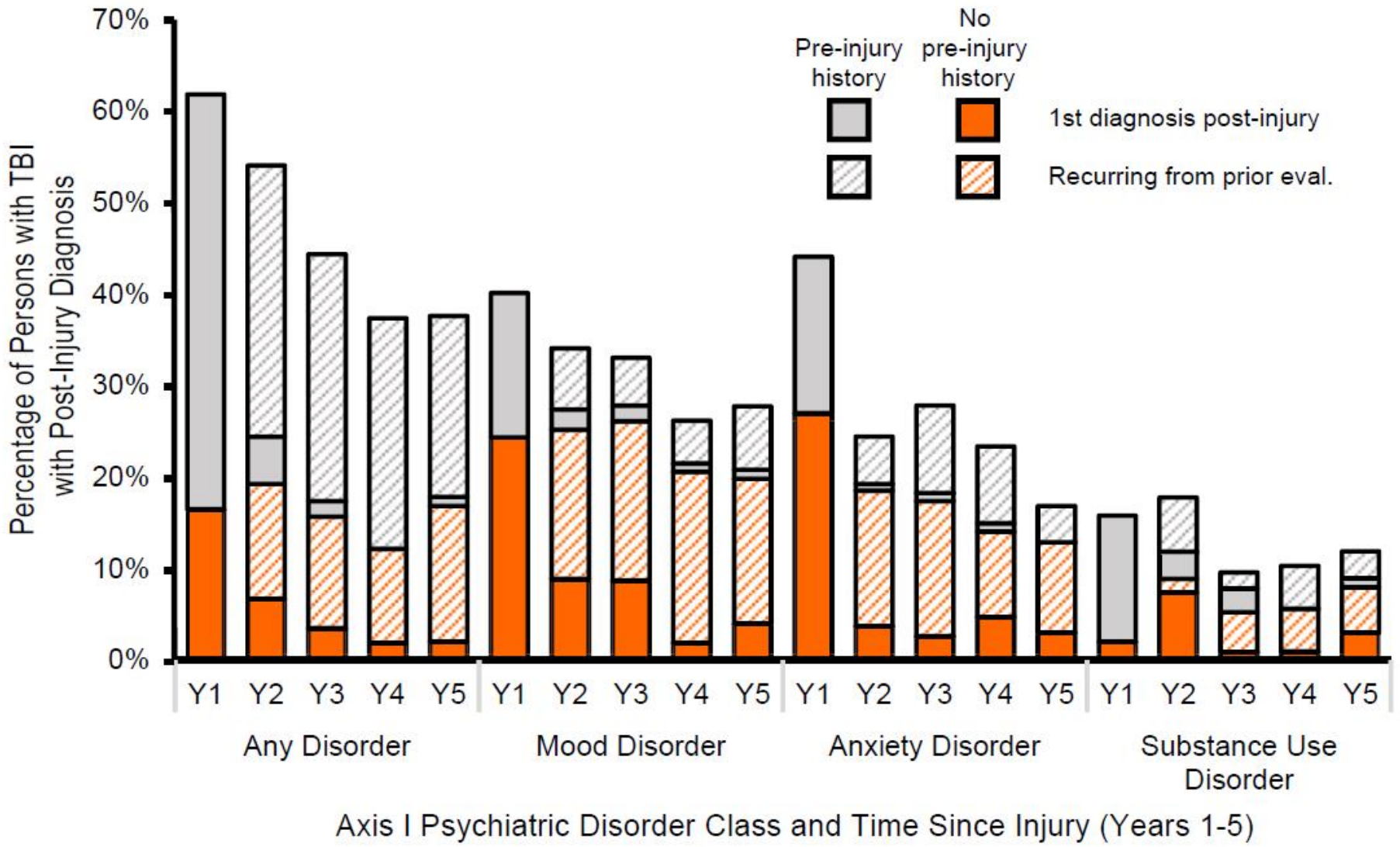
Mental Health Disorders after TBI



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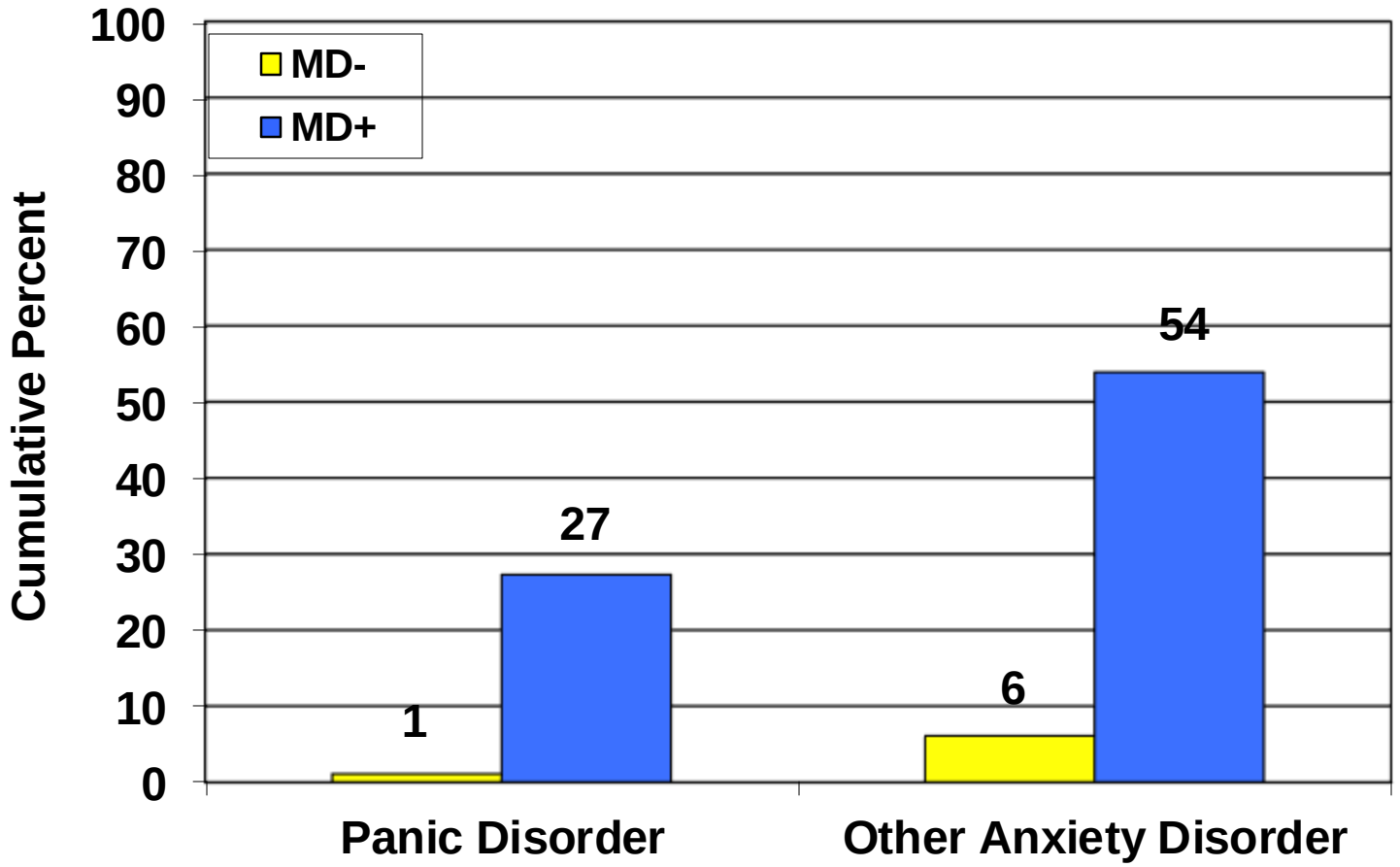
Rates after TBI

(Lifetime Prevalence in General Population)

Time	GAD (5.7)	PTSD (6.8)	OCD 1.6)	Panic (4.7)	Phobias (Agor 1.4; SP 12.1)	Author
1 year	13.4%	13%	4%	7.5%	13% Agoraphobia 9% Social Phobia	Bryant et al 2010
1 year	3%	12%	2%	2%	6% Specif Phobia 5% Social Phobia	Gould et al 2014
1 year	3%	3%	2%	9%	1%	Deb et al 1999
33 months	24%			4%	2% Agoraphobia	Fann et al 1995
6 year period	17%	14%	1%	6%	7% Specif Phobia 6% Social Phobia 1% Agorophobia	Whelan-Goodinson et al 2009
8 year period	8%	17%	14%	11%	7%	Hibbard et al 1998
30 year period	2%			8%	17% Specif Phobia 7% Social Phobia	Koponen et al 2002

Fann & Jakupcak 2013; Kessler et al, 2005

Comorbidity of Anxiety and MDD



Any comorbid anxiety disorder in MDD+ vs. MDD- (60% vs. 7%; RR, 8.77; CI, 5.56-13.83)

Bombardier, Fann, Temkin, et al, JAMA 2010

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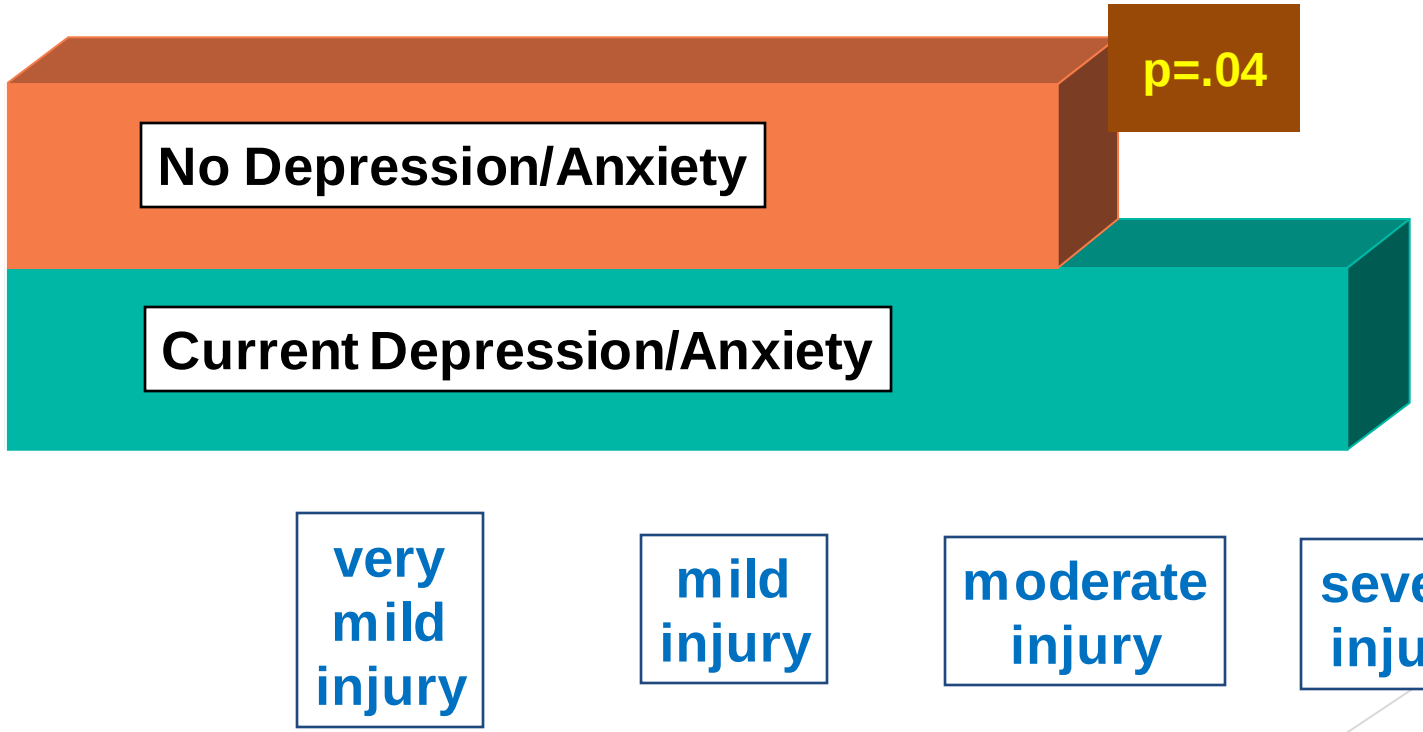
Self-Perception of Injury Severity



Fann et al, Am J Psychiatry 1995

Recommendations for Anxiety Screening in TBI

- **Frequency**
  - All new patients identified w/ TBI
  - Every visit x 2 yrs, then annually vs. every visit if high risk
- **Screening Instruments**
  - GAD-2≥3 (PHQ-4) → GAD-7
  - In TBI, consider threshold of 'several days' as significant
- **Risk Stratification**
  - particular focus on patients w/ depression, pre-TBI psych hx, substance abuse, multiple TBI, ongoing functional / cognitive impairment, previously elevated scores

Galveston TBI Conference, 2014

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Spitzer et al, Arch Intern Med 2006

Diagnosis

Clinical Presentation

- Patients often present with nonspecific somatic symptoms (e.g., pain, SOB, dizziness, ‘PCS’)
- Patients usually present to non-mental health providers
- Avoidance behaviors are common

Adjustment Disorders

A. Clinically significant emotional symptoms or behaviors in response to and occuring within 3 months of identifiable stressor(s)
B. Causing marked distress that is out of proportion to the severity or intensity of the stressor or significant impairment in social, occupational, or other functioning

- **Treatment:**
  - Short-term benzodiazepine (antihistamine, beta-blocker?)
  - Stress reduction (e.g., diaphragmatic breathing, progressive muscle relaxation, exercise)
  - Symptom reduction (e.g., insomnia, pain, headache)
  - Brief psychotherapy (e.g., psychoeducation, CBT, problem-solving, mindfulness-based stress reduction strategies)
  - Close monitoring for developing anxiety disorder

Panic Attack

- Abrupt surge of intense fear or discomfort
- At least 4 symptoms peak within minutes
  - palpitations, pounding heart, or accelerated heart rate
  - sweating
  - trembling or shaking
  - shortness of breath or smothering
  - feeling of choking
  - chest pain or discomfort
  - nausea or abdominal distress
  - feeling dizzy, unsteady, light-headed, or faint
  - chills or heat sensations
  - paresthesias (numbness or tingling sensations)
  - derealization or depersonalization
  - fear of losing control or ‘going crazy’
  - fear of dying

Panic Disorder

A. Recurrent unexpected panic attacks (w/ 4+ symptoms, e.g., palpitations, sweating, etc.)

B. 1 month or more of either

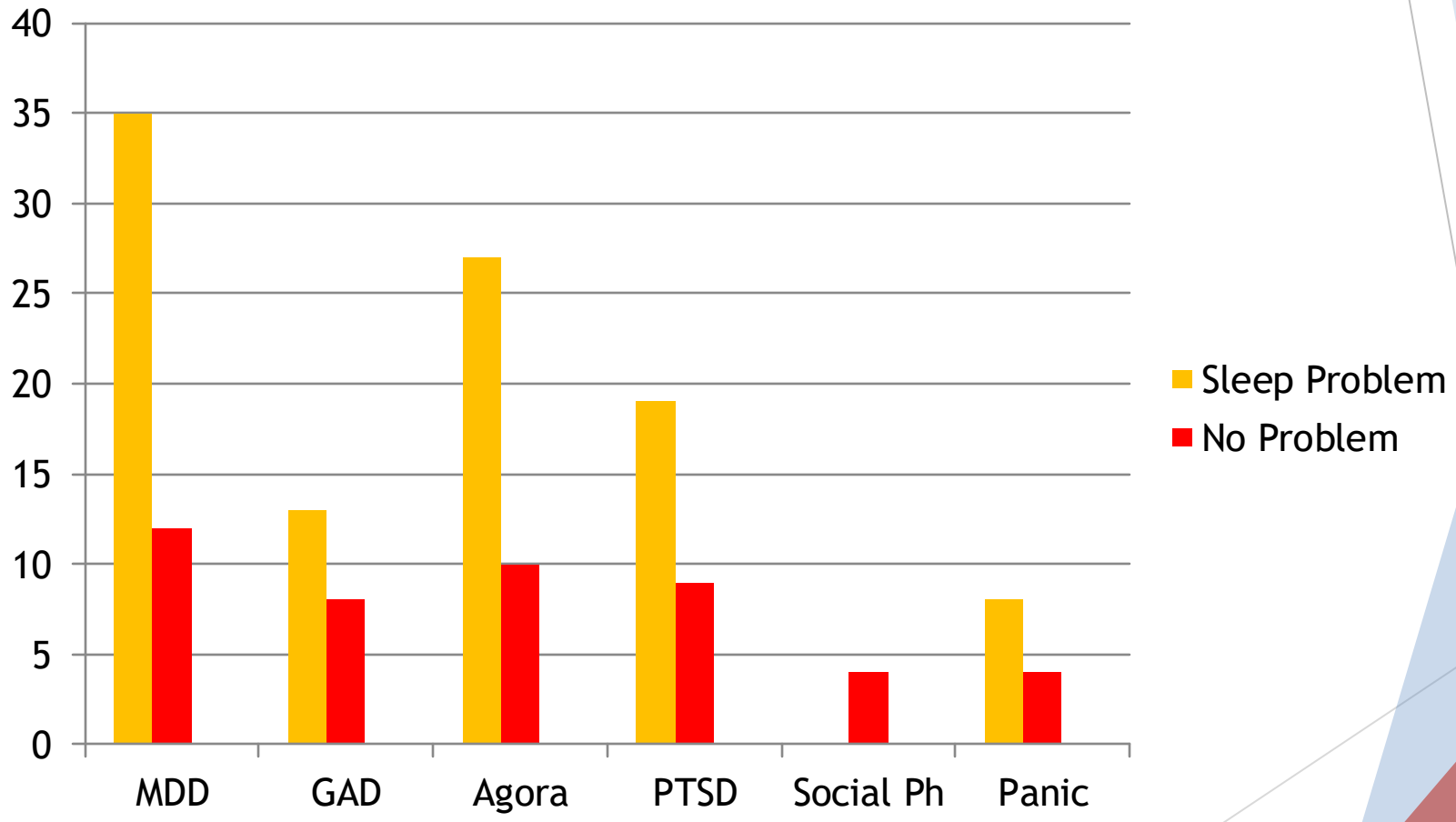
   1. persistent concern or worry about having additional attacks or their consequences (eg, losing control, having a heart attack, ‘going crazy’) or

   2. a significant change in behavior related to the attacks (e.g., avoidance)

Generalized Anxiety Disorder

A. Excessive anxiety and worry, occurring more days than not, for at least 6 months, about a number of events of activities
B. Difficult to control the worry
C. Associated with 3 or more symptoms (some present more days than not for at least 6 months)
    1. Restless, keyed up, or on edge
    2. Easily fatigued
    3. Difficult concentrating or mind going blank
    4. Irritable
    5. Muscle tension
    6. Difficulty falling or staying asleep, or restless sleep
D. Clinically significant distress or impairment

Psychiatric Disorder & Prior Sleep Problems



Bryant et al., Sleep 2010

Treatment

Basic Treatment Principles

- **Characterize diagnosis/ 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
  - Shared decision-making is critical for adherence
- **Combination of approaches often needed**

Common Polypharmacy Pitfalls

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

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

Medical Conditions Associated with Anxiety

Cardiovascular

- Angina pectoris
- Arrhythmia
- Congestive heart failure
- Hypovolemia
- Myocardial infarction
- Valvular disease

Endocrine

- Carcinoid
- Hyperadrenalism
- Hypercalcemia
- Hyperthyroidism
- Hypocalcemia
- Hypothyroidism
- Pheochromocytoma

Metabolic

- Hyperkalemia
- Hyperthermia
- Hypoglycemia
- Hyponatremia
- Hypoxia
- Porphyria

Neurologic

- Akathisia
- Encephalopathy
- Mass lesion
- Postconcussion syndrome
- Seizure disorder
- Vertigo

COVID-19

Gastrointestinal

- Peptic ulcer disease
- Irritable Bowel Syndrome

Respiratory

- Asthma
- COPD
- Pneumothorax
- Pulmonary edema
- Pulmonary embolism

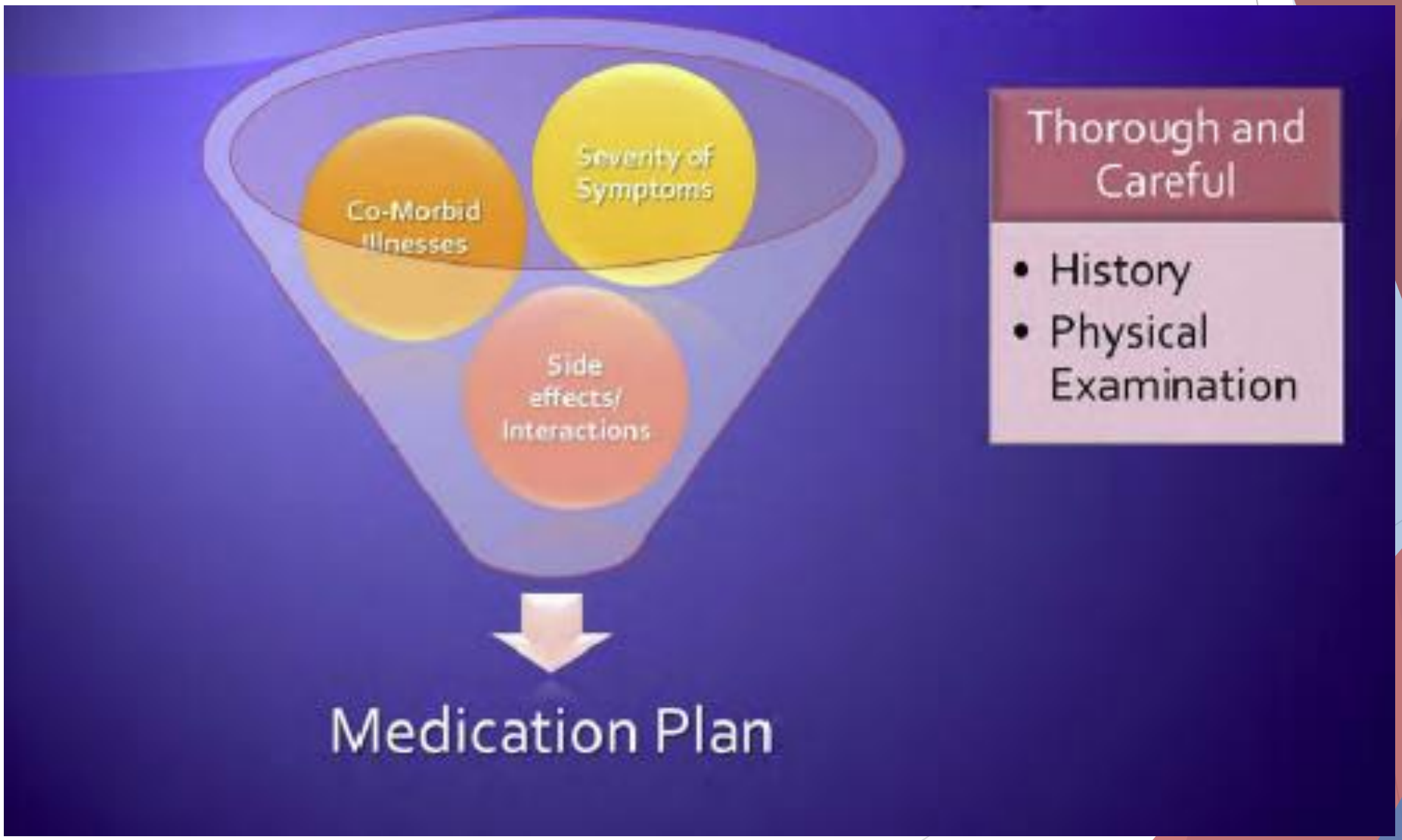
Immunologic

- Anaphylaxis
- Systemic lupus erythematosus

Medications / Substances That Can Cause Anxiety

Alcohol (withdrawal)
Amphetamine
Aminophylline
Anticholinergics
Antihypertensives:
reserpine, hydralazine
Antituberculous agents:
isoniazid, cycloserine
Barbiturates (withdrawal)
Benzodiazepines (withdrawal)
Caffeine
Cannabis
Cocaine
Digitalis
Dopamine
Ephedrine
Epinephrine
Levodopa
Lidocaine
Methylphenidate & other stimulants
MDMA (Ecstasy)
Monosodium glutamate
Neuroleptics (akathisia)
Nicotinic Acid
Phenylephrine
Phenylpropanolaminde
Procarbazine
Pseudoephedrine
Steroids
Theophylline
Thyroid preparations

Anxiety Pharmacotherapy



Treatment of Panic Disorder

- **Acute**: Benzodiazepine (short-term)
  - Avoid with opioids, recent h/o substance misuse
  - Watch for sedation, unsteadiness, amnesia, cognitive impairment, delirium
- **Maintenance & prevention** (1+ year, taper gradually), combine w/ psychotherapy (e.g., CBT)

Selective serotonin reuptake inhibitors (SSRI) &

Serotonin-norepinephrine reuptake inhibitors (SNRI)

- Start low - may cause initial increase in anxiety

Tricyclic antidepressant (TCA)

Monoamine oxidase inhibitors (MAOI) – phenelzine

- Dangerous food interactions, rarely used in TBI

Others – mirtazapine, trazodone, anticonvulsant (valproate, gabapentin, pregabalin, vigabatrin, tiagabine) moclobemide, olanzapine, quetiapine, verapamil, clonidine, rTMS

Treatment of Generalized Anxiety Disorder

Combine meds w/ psychotherapy

Onset of effect may take 4-6 wks

Continue treatment for 12-18 months

SSRIs – sertraline, paroxetine, citalopram, escitalopram

SNRIs – venlafaxine, duloxetine

TCAs - imipramine

Buspirone – monotherapy or augment SSRI/SNRI

Benzodiazepines – use scheduled, longer-acting, taper when possible

Pregabalin - 50-300 mg, watch for sedation, dizziness, tolerance

Others - mirtazapine, hydroxyzine, quetiapine, olanzapine, beta-blockers (for anticipatory/ performance anxiety, physically-focused pts)

Cognitive Behavioral Therapy (CBT)

- High structure & self-monitoring advantageous after TBI
- RCT for depression &/or anxiety after moderate-severe TBI
  - Anxiety improved quickly
  - Depression improved only after boosters
  - MI offered no additional benefit to CBT

Ponsford et al, Psychol Med 2016

Behavioral Activation (BA)

- Increase environmental reward via exposure to predictable pleasant, values-concordant activities
  - People with TBI often isolated & avoidant with decreased participation
- RCT of 8 weeks of text-messaging of BA vs. motivational messages
  - Pts had PHQ-9 and/or GAD-7 ≥ 5
  - Both groups had improved mood (BSI)
  - BA group reported more environmental reward, decreased avoidance

Hart et al, Neuropsychol Rehabil 2020

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Problem Solving Therapy (PST)

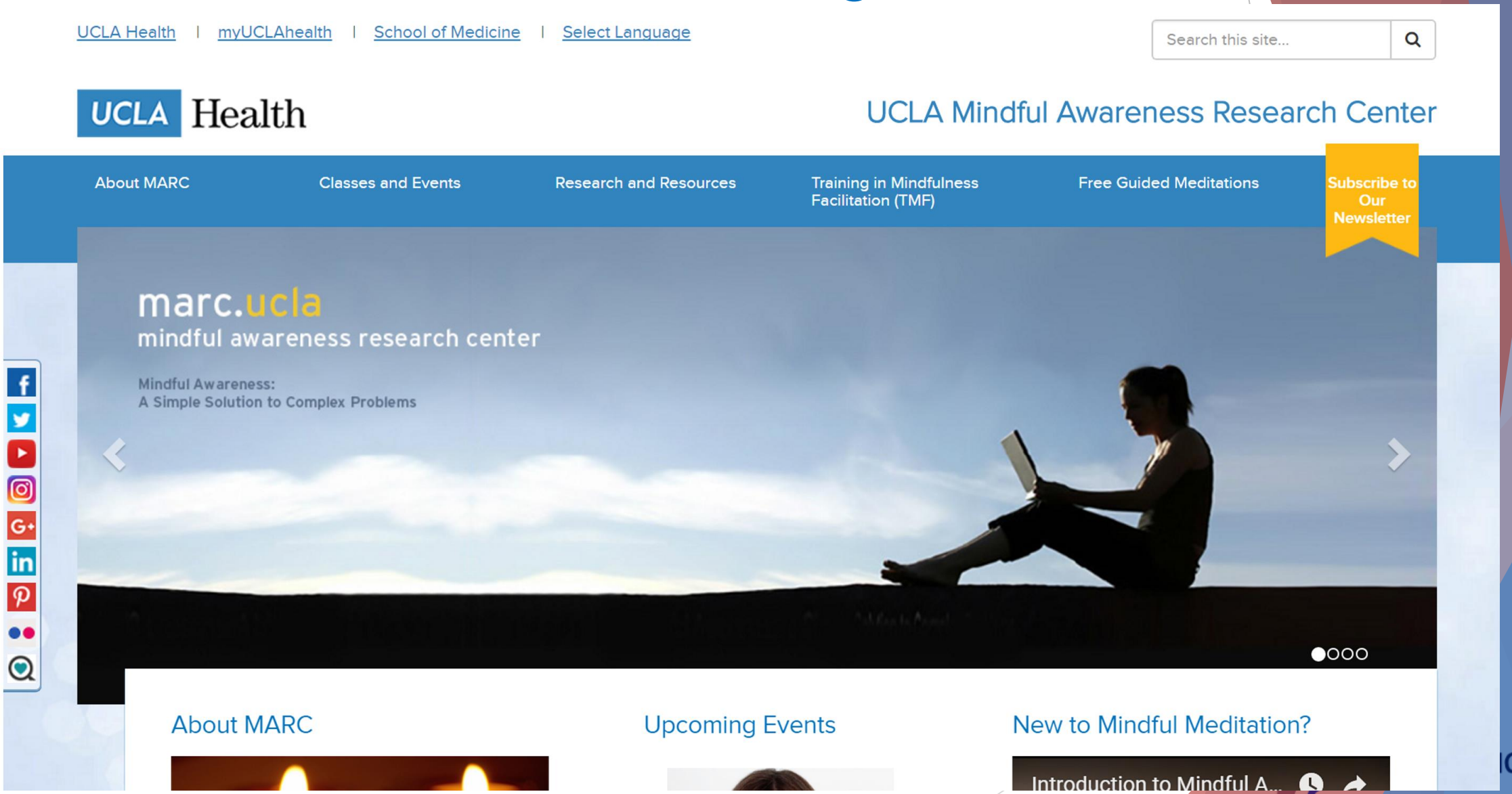
- Stepwise algorithm to identify & solve problems (decreased feelings of being overwhelmed)
- Similar strategies used for:
  - Remediation of executive dysfunction & depression, which can increase anxiety after TBI
- RCT of 12-session phone-delivered PST vs. Education in active duty Service Members with mTBI
  - Significant improvement in emotional distress, depression, anxiety, PTSD, sleep, physical function
  - Gains at 6-mos. not sustained at 12-mos.

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

Other Behavioral Strategies

- Based on specific symptoms, stresses, developmental history, and patient preferences
- Can be used in combination
  - Psycho-education (e.g., regarding course of TBI recovery)
  - Supportive therapy
  - Dynamic therapy (may be limited by cognitive Impairment)
  - Marital/Family/Group (optimize support system)
  - Support groups
  - Mindfulness strategies (accept, observe)
  - Acceptance-based therapies (psychological flexibility, can be combined w/ e.g., exposure)
  - Relaxation Techniques (diaphragmatic breathing, progressive muscle relaxation)
  - Biofeedback, acupuncture, music therapy
  - Aerobic exercise

Mindful Awareness Research Center
uclahealth.org/marc



Environmental Modification

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

Fann, Quinn, Hart. Biol Psychiatry 2022

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 test theoretically based interventions that align with causative factors (e.g., BA or ACT to increase exposure to meaningful activity)
- Multimodal, stepped approaches likely most effective
- Remote technologies (phone, web, mobile) have great potential to enhance & facilitate delivery of interventions, e.g., for patients who are reluctant to engage.

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Websites

General sites on anxiety:

- National Institute of Mental Health: http://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml
- National Alliance on Mental Illness: https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Anxiety-Disorders
- Anxieties.com: http://www.anxieties.com/
- Anxiety & Depression Association of America: http://www.adaa.org/

Sites on anxiety after brain injury:

- Brainline.org: http://www.brainline.org/content/2008/11/depression-and-anxiety.html
- Model System Knowledge Translation Center: http://www.msktc.org/

Apps & Digital Health Mental Health Resources

- One Mind PsyberGuide: https://onemindpsyberguide.org/


Questions?