

Anxiety after TBI

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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)

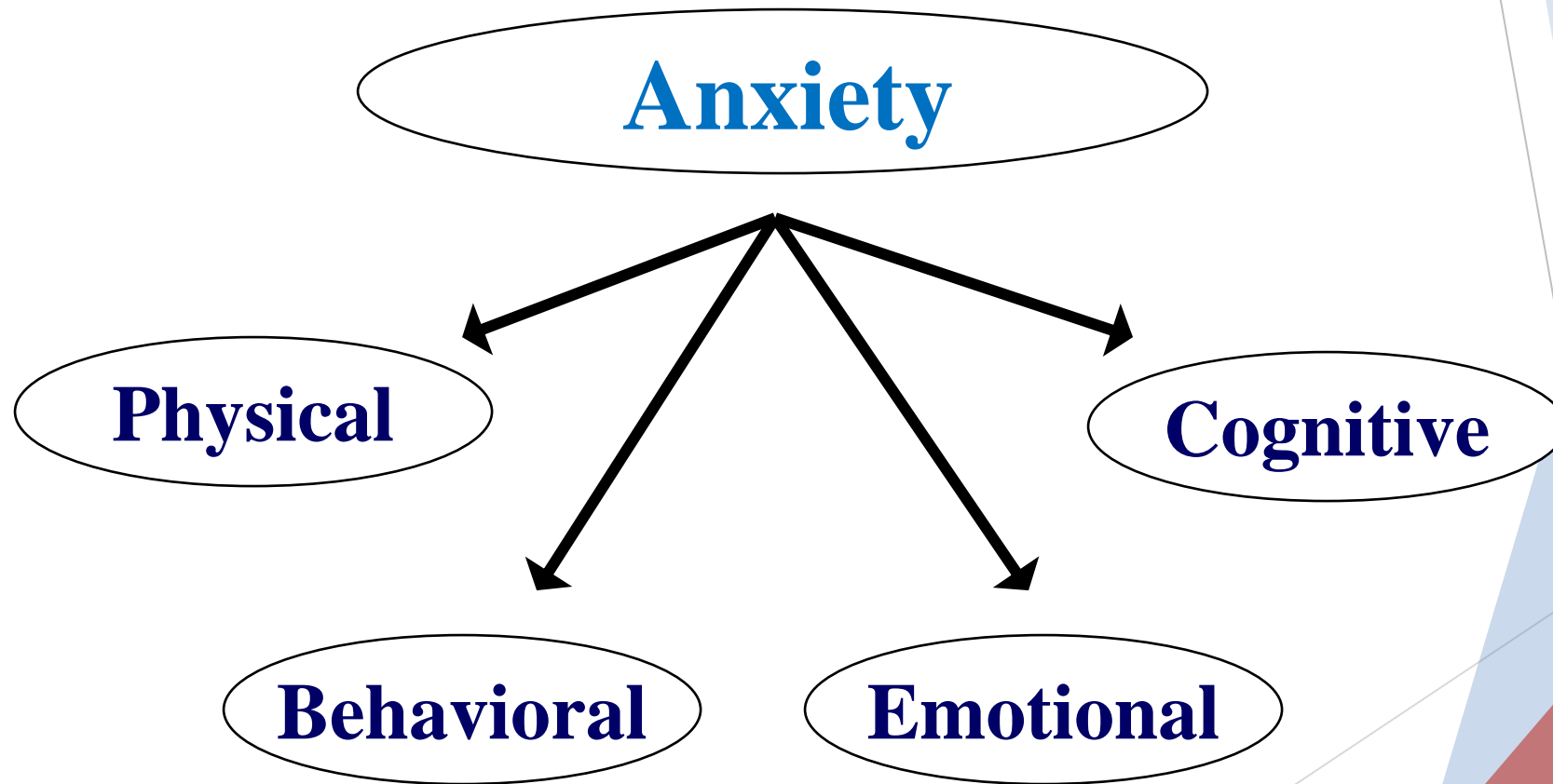


Signs of Anxiety

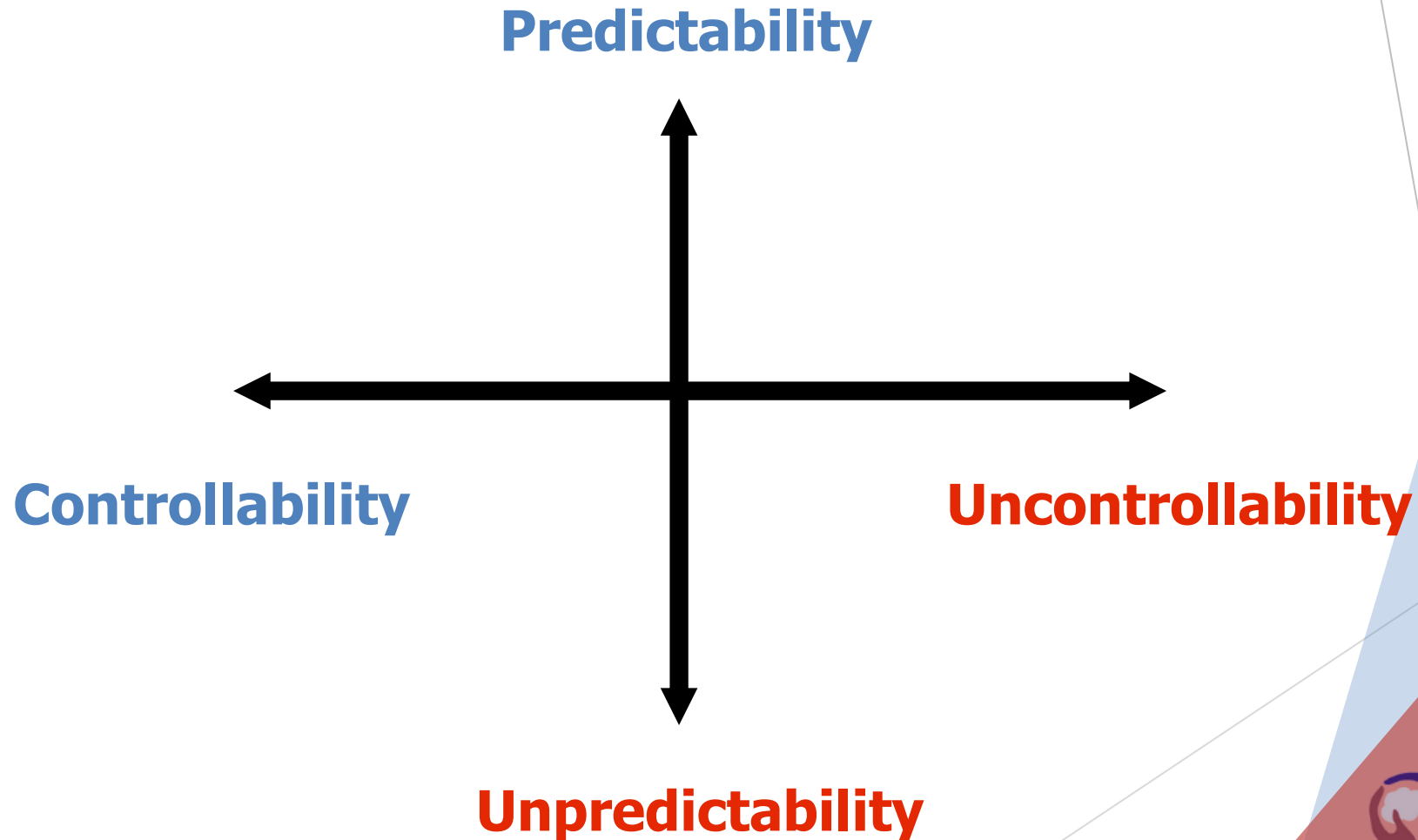
- ▶ Panic
- ▶ Irritable mood
- ▶ Excessive worry, fear, apprehension
- ▶ Restlessness
- ▶ Impulsive or aggressive behavior
- ▶ Quickened speech (differentiate from mania)
- ▶ Decreased sleep, appetite
- ▶ Shakiness, sweatiness, palpitations, chest pain, abdominal pain, dizziness, etc.
- ▶ **AVOIDANCE, 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

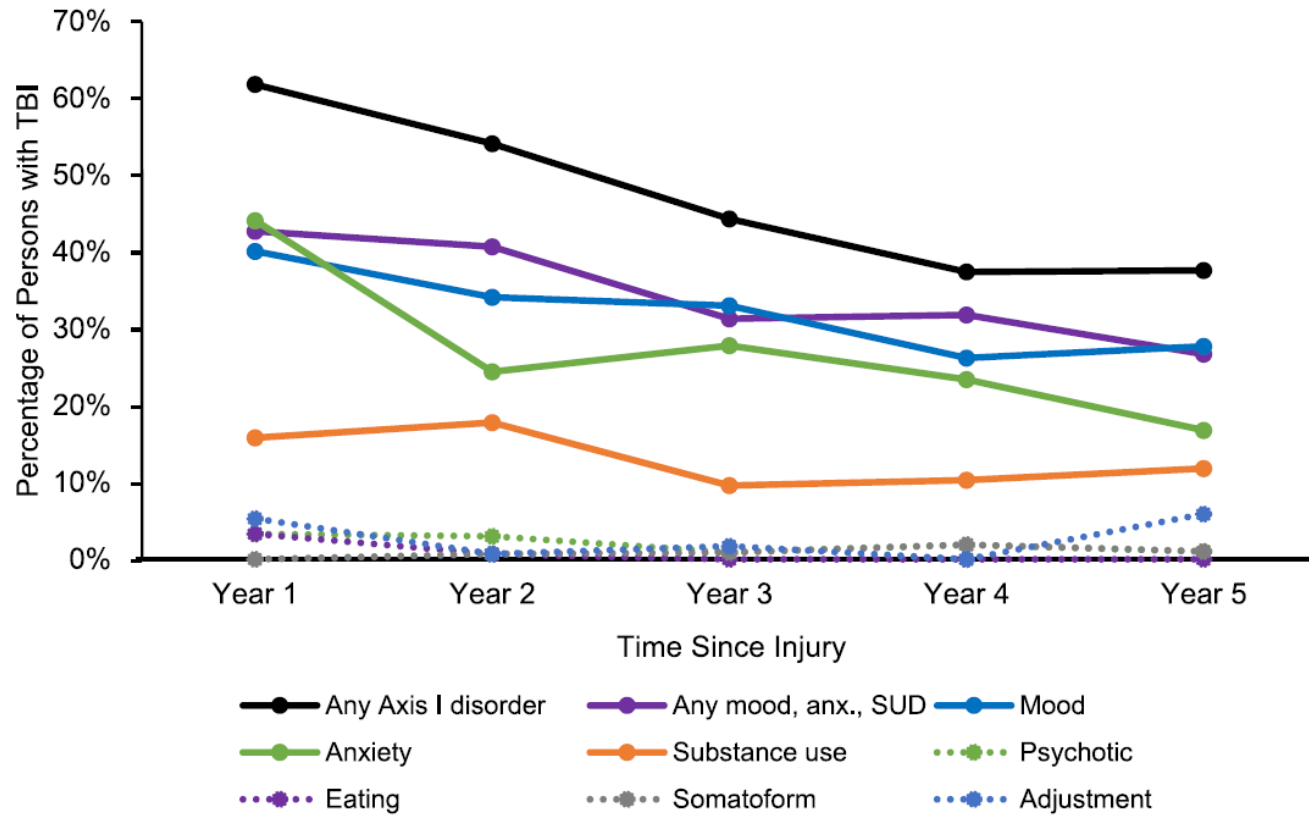
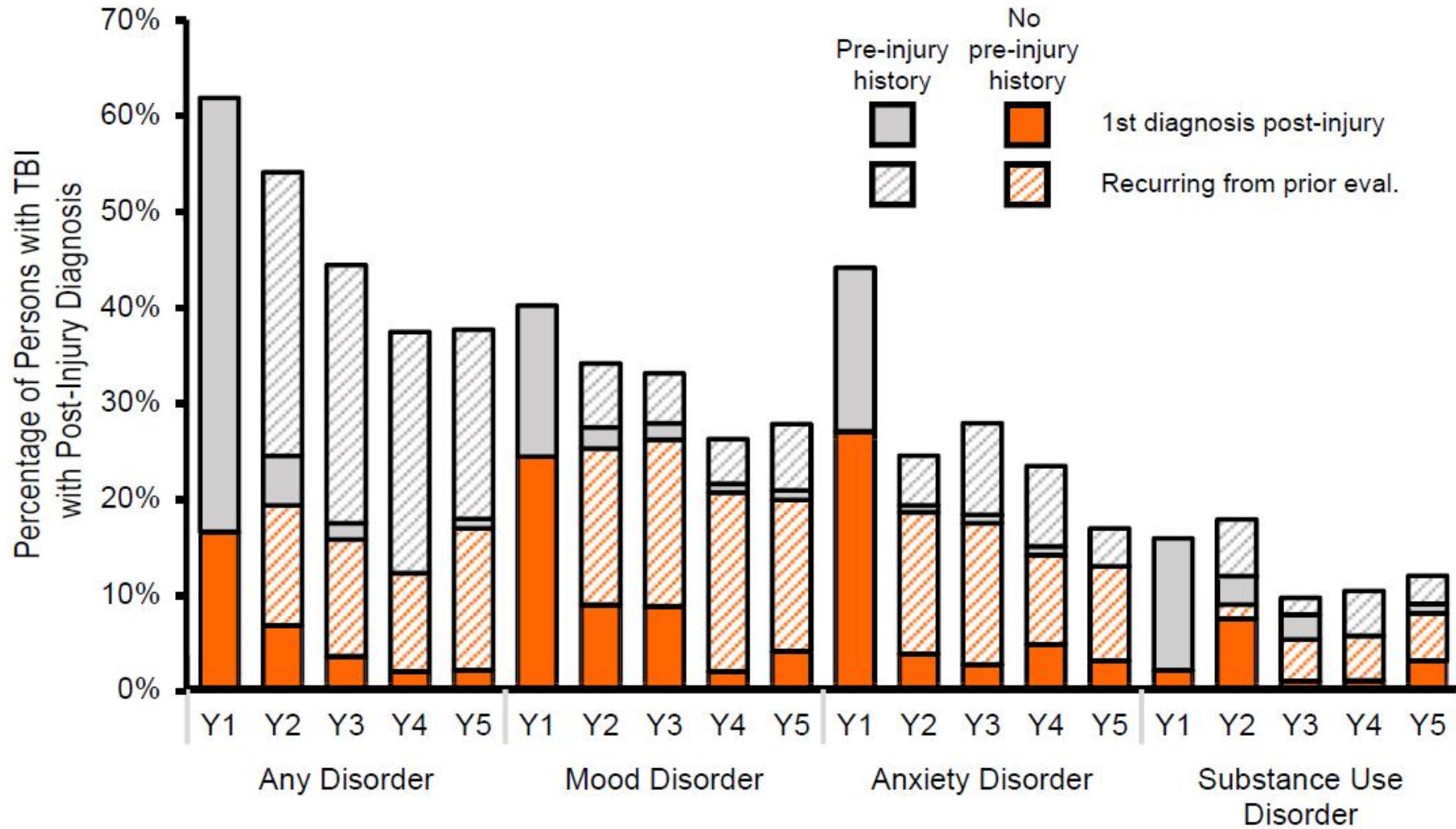


Figure 1. Annual prevalence of different classes of psychiatric disorder in the prospective study of moderate to severe traumatic brain injury (TBI) from Alway *et al.* (54). DSM-IV Axis I diagnoses were determined via Structured Clinical Interview. Mood, anxiety (anx.), and substance use disorders (SUD)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

Mental Health Disorders after TBI



Axis I Psychiatric Disorder Class and Time Since Injury (Years 1-5)

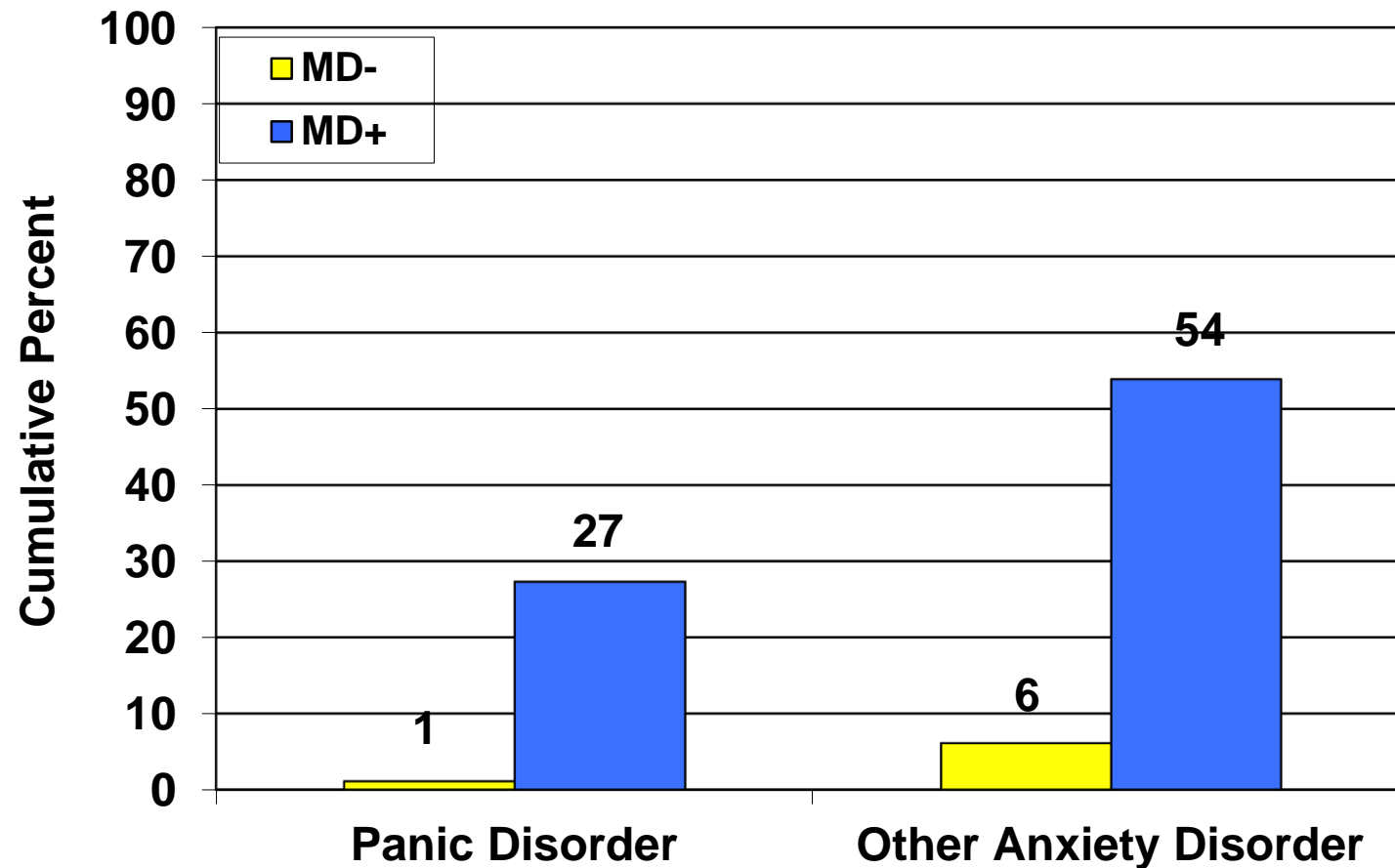
Rates after TBI

(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

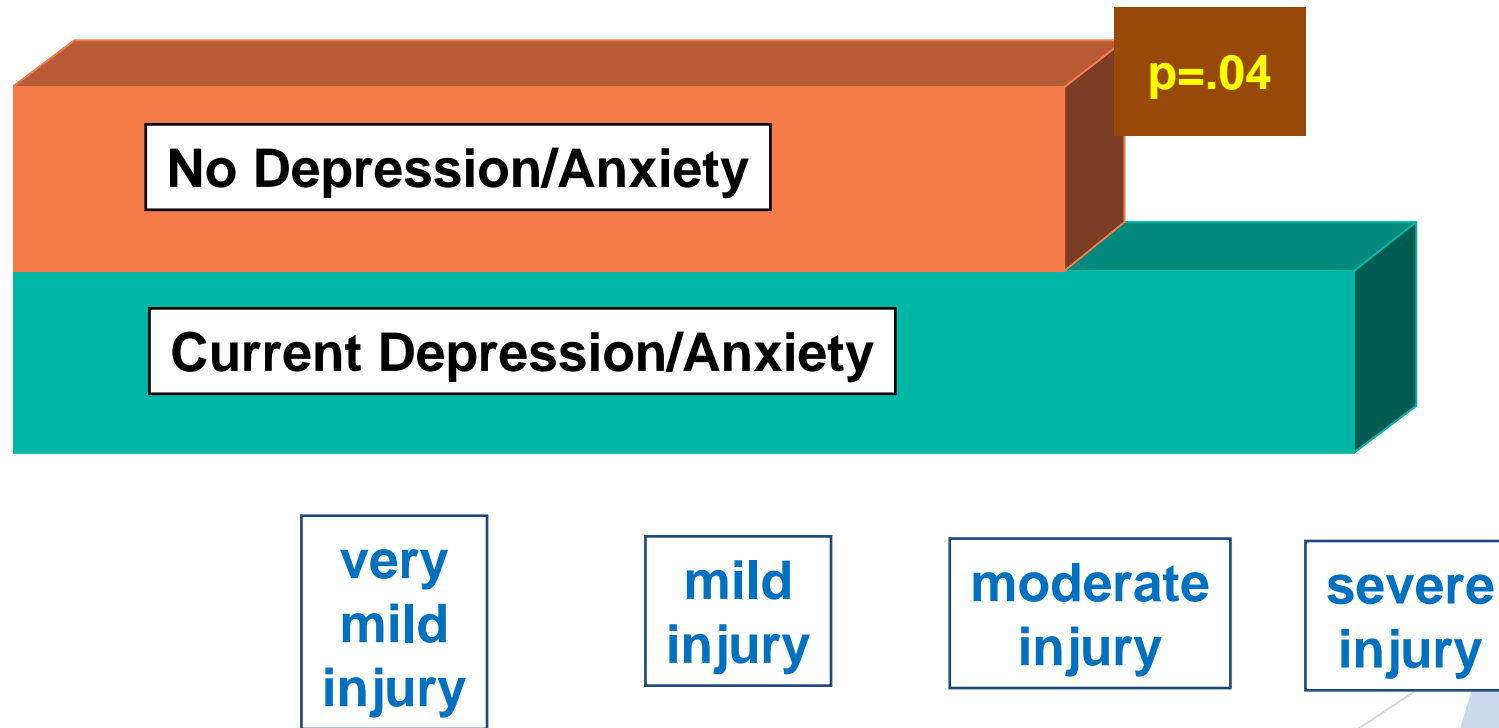


Any comorbid anxiety disorder in MDD+ vs. MDD-
(60% vs. 7%; RR, 8.77; CI, 5.56-13.83)

Bombardier, Fann, Temkin, et al, JAMA 2010



Self-Perception of Injury Severity



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

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



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 occurring **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

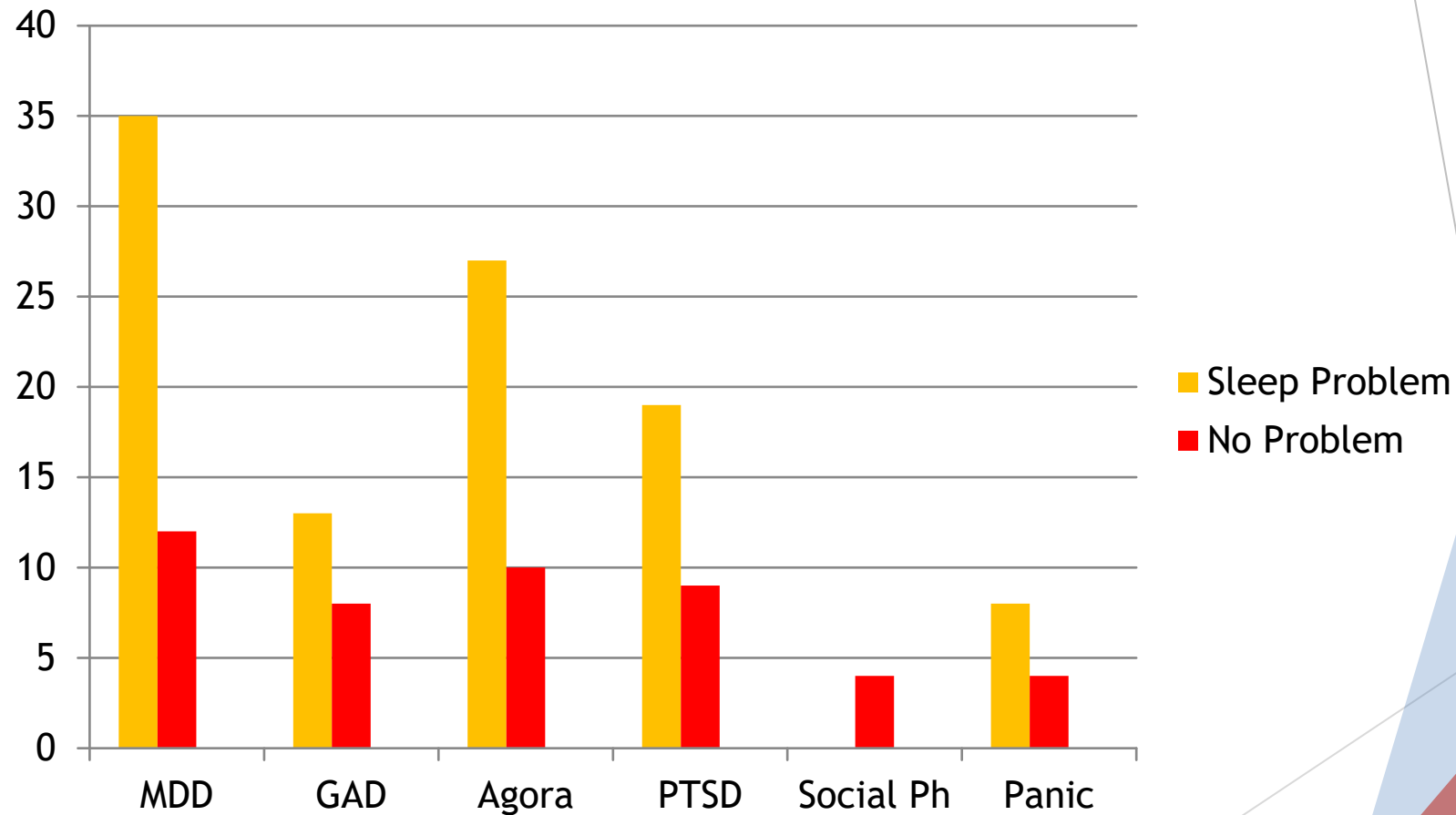
Panic Disorder

- 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 or 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.

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

Phenylpropanolamine

Procarbazine

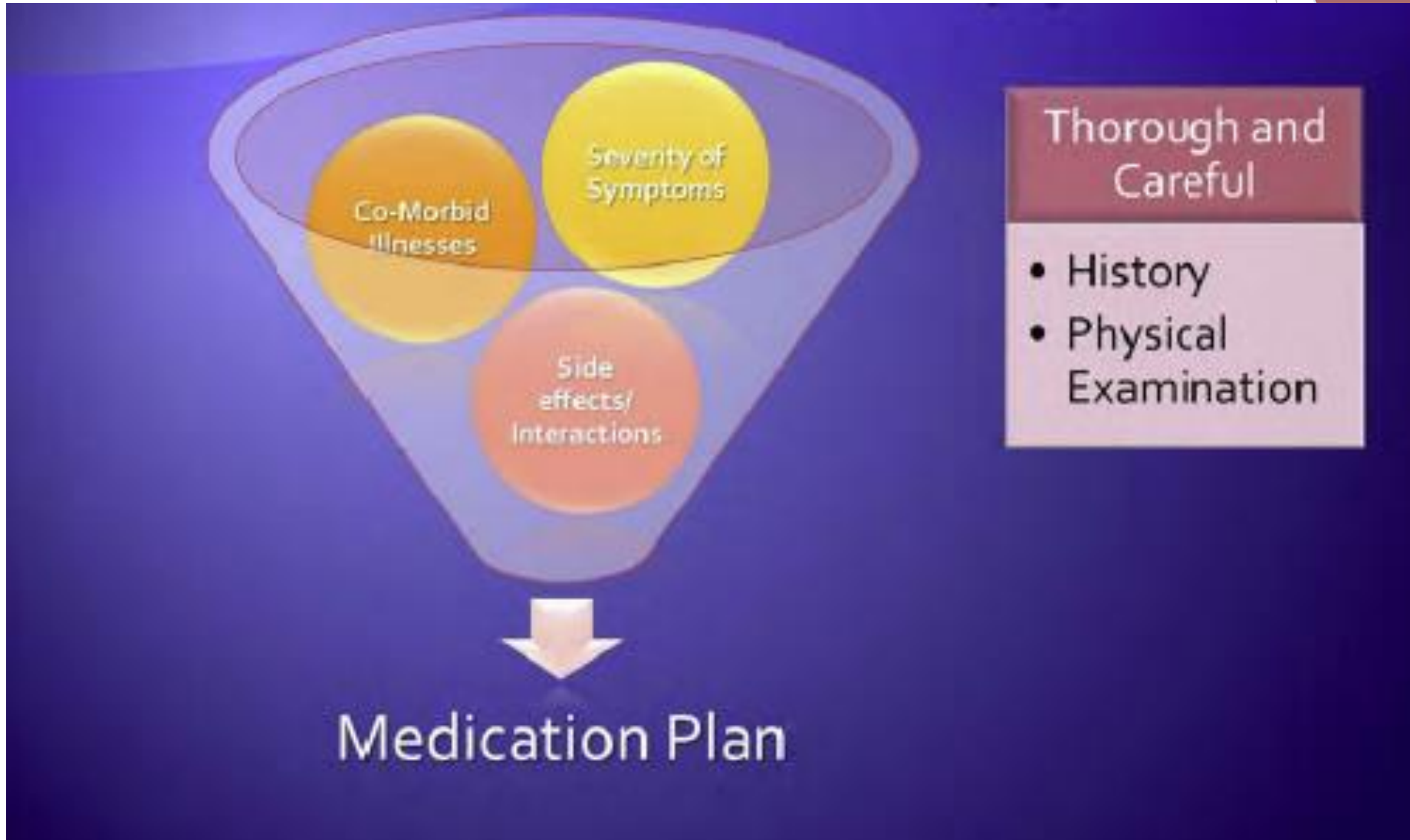
Pseudoephedrine

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

Bupirone - 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



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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.



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



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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



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.



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?

