MANAGEMENT OF ANXIETY & DEPRESSION IN THE PRIMARY CARE SETTING: APPROPRIATE USE OF ANTIDEPRESSANTS AND BENZODIAZEPINES

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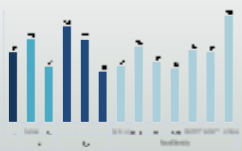
EMOTIONAL EXPERIENCES ARE COMPLEX TO SAY THE LEAST…..

WHO: PREVALENCE OF ANY MENTAL ILLNESS (AMI) 2017



ADDRESSING MENTAL HEALTH IS ESSENTIAL

According to *Science Magazine*, 11 studies have found that "people prefer to do mundane tasks and even mild electric shocks rather than be left alone with their own thoughts."

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

- Anxiety dating back "for as long as I can remember."
- HPI: Presented to clinic 2009 reporting ongoing symptoms of irritable mood, panic attacks (frequency and severity unknown) feeling generally *overwhelmed, excessive worry future events, overly protective of her 2 sons and sister, fearful of catastrophic events involving family and natural disasters, muscle tension, headaches, and general myalgias. Additional symptoms included insomnia, nightmares, fear of public speaking, excessive scrutinization of her own behaviors, and excessive time spent cleaning.* She denied physical ritualistic behaviors and patient denied that her obsessive patterns interfered with her daily functioning or personal relationships. Denied hypervigilance and flashbacks. Patient had calorie restricted and purge with laxatives x 4 as a teen. BMI was low normal and never lost menses. No behaviors suggestive, psychosis, or mania were noted on initial exam.

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

- Past Psychiatric History:
  - Treatment since 2006
  - Past trials of paroxetine, sertraline, alprazolam, escitalopram, and bupropion
  - Some success with citalopram
  - Had discontinued medication and relapsed, noting anxiety and increased irritability.
  - No history of psychiatric hospitalizations, self –harm and suicide attempts
  - C/o sexual side effects from all antidepressants.

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

- Social History/Family History:
  - Multiple family members with similar anxiety symptoms.
  - Son has tic disorder and anxiety
  - Father had alcohol use disorder
  - Patient married for 20+ years and works as community liaison.
  - History of mental abuse in marriage, husband reported to be controlling, verbally abusive, and against psych meds.
  - Husband also complained about her "low" sex drive.
- Substance Use History: Negative
- Contributory Medical History:
  - Hypothyroidism treated with 75 mg of levothyroxine daily
  - Fibromyalgia

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

- Clinical Course:
  - Transferred care to this provider in 2014 after several attempts at the behest of her husband to stop her citalopram.
  - Continued ruminative thinking, isolated panic symptoms, and mild depressive symptoms which included depressed mood, anhedonia, increased appetite, insomnia, and low energy.
  - Due to sexual side effects, opted for re-trial of sertraline which was titrated to 50 mg daily which was changed to duloxetine due to agitation, also to target anxiety, depression, and muscle pains.
  - Poor effect for duloxetine, so citalopram was restarted.
  - Patient frequently self adjusted meds, and eventually returned to 40 mg daily of citalopram.
  - Alprazolam and gabapentin were added as adjunctive therapy with moderate success.

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

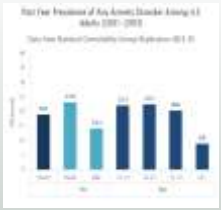
- Family problems intensified in 2017 and she was placed in IOP and then codependency group.
- Stabilized and asked to try another SNRI for her FMS pain which failed.
- Over the course of the next 18 months patient was placed back on citalopram, 40 mg daily, but this time, continued to decompensate
- Failed trials of several other adjunctive medications for worsening panic attacks, general anxiety and agitation, and depression
- Trials included mirtazapine, aripiprazole, trazodone, quetiapine, lamotrigine, topiramate, buspirone, and bupropion.
- Patient was placed off work.

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

- Ah-Ha! Moment:
  - F/u in clinic in June 2019 after 2 ED visits for anxiety, numerous emails, urgent office visits, medication adjustments, and therapy
  - Declined inpatient psychiatric hospitalization and never met criteria for a 5150 hold.
  - This writer inquired as to her menopausal state, she stated that she had been previously been diagnosed with menopause.
  - FSH level was 30.0 (increased) in March of 2018, seemingly around the time her anxiety and depression intensified.

CASE STUDY: 53 YEAR OLD FEMALE WITH ANXIETY

- Treatment changed to paroxetine to address menopausal symptoms, titrated to 30 mg daily with good effect.
- Alprazolam was changed to 0.5 mg of clonazepam twice daily
- Also recommend that she go back to GYN for possible HRT.
- Did very well on estradiol 0.1 mg patch/week
- Has returned to work
- Current plan to is to wean clonazepam to infrequent PRN use within the next 3 months.



OVERVIEW OF ANXIETY DISORDERS

- Anxiety disorders are the most prevalent psychiatric disorders
- Worldwide prevalence 7.3%
- 15% of children have anxiety prone genetic trait
- ⅓ of those will develop an anxiety disorder
- ½ persons will suffer from an anxiety disorder at some time in their life

Temperamental traits of shyness or behavioral inhibition in childhood

Exposure to stressful and negative life or environmental events in early childhood or adulthood

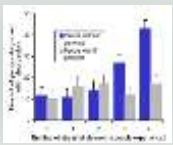
A history of anxiety or other mental illnesses in biological relatives

Some physical health conditions, such as thyroid problems or heart arrhythmias, or caffeine or other substances/medications, can produce or aggravate anxiety symptoms; a physical health examination is helpful in the evaluation of a possible anxiety disorder

NIMH 7/2018

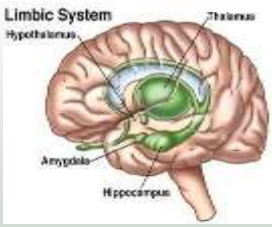
RISK FACTORS FOR ANXIETY

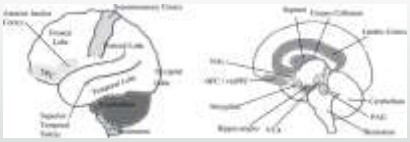
- Complex relationship between genetics, hormones, brain structures, environment, and stressors
- Some studies suggest heritability of 30-45%
- Serotonin Transporter Gene (SERT) allele polymorphism
  - S Allele = thought to be associated with more anxiety
  - L Allele = less anxiety



AMYGDALA

The amygdala processes what is salient, how to feel about it, and what to do about it based on current info and past experiences.

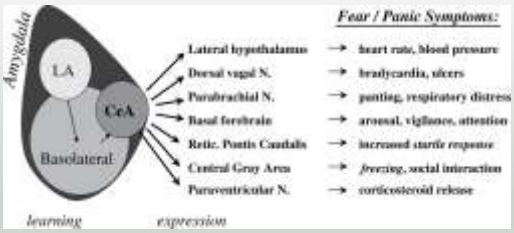




- Amygdala is hyperactive and R side is larger
- Poor communication between amygdala and cortex
- Decreased cortical blood flow
- Smaller/damaged hippocampus
  - More vulnerable to cortisol elevations during stress
  - Oxidative stress
  - Apoptosis
  - Less neuroplasticity

NEUROBIOLOGY OF ANXIETY: THE LIMBIC SYSTEM

NEUROBIOLOGY OF ANXIETY: THE LIMBIC SYSTEM



NEUROTRANSMITTERS

- Cortisol: CCK increases cortisol, cortisol receptors are altered, and stress response is prolonged or exaggerated
- Neuropeptide Y: Stress induced feeding behaviors
- Galanine: depressogenic
- GABA: is inhibitory, but decreased levels in anxious brain
- Glutamate: is excitatory, but hyperactive in anxious brain
- BDNF: Assists with healthy, long lived neurons → neuroplasticity and growth
- Supersensitive norepinephrine receptors
- Dopamine: decreased transmission and concentration
- Serotonin dysregulation

SOCIAL ANXIETY DISORDER

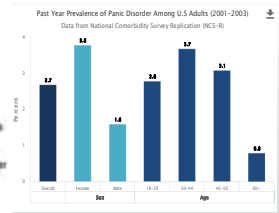
- Marked fear or anxiety in social situations in which an individual may be exposed to the scrutiny of others
  - Eating, writing, performing, socializing
- Fear of humiliation, rejection, or embarrassment
- Avoidance is common
- Out of proportion to the actual threat
- Fear, anxiety, avoidance last 6 mos. or more and causes significant distress
- Performance only specifier
- 12% lifetime prevalence

PANIC DISORDER

- Panic attack: Abrupt surge of intense fear or discomfort that reaches a peak within minutes
- Surge can occur in a calm or anxious state
- Surges are recurrent and unexpected in Panic Disorder
- At least 4 specific symptoms (including culture specific) must be present
- At least one attack followed by at least 1 month or more of persistent fear of panic recurring, or maladaptive patterns designed to avoid further panic attacks
- Panic attack specifier: "…With panic attacks" can be added to other diagnoses such as PTSD or GAD, but other criteria are NOT met

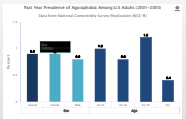
Panic Disorder symptoms:

- Chest burns or pains and discomfort in the torso
- A shaking or trembling feeling, and at times this is heightened when you experience the feeling but can not see it physically
- Sense of unreality or dreamlike feelings
- Choking sensation and difficulty to catch your breath
- Heart palpitations, but again this can be heightened as it is not always noticeable to others
- Excessive sweating with hot and cold flashes
- Fear of dying and loss of control, this can stretch to the fear of others being harmed also
- Nausea and/or numbness



4.7 % lifetime prevalence

PANIC DISORDER



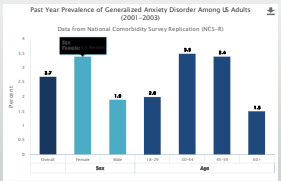
AGORAPHOBIA

Marked fear or anxiety about at least 2 of the following situations:

- Public transit
- Open spaces
- Enclosed public spaces
- Standing in line or crowds
- Being outside of the home alone

- Patient is afraid that escape might be difficult
- Panic symptoms may develop
- Public places are avoided or endured with intense anxiety
- The fear is disproportionate to the actual danger posed
- 1.3 % lifetime prevalence

GENERALIZED ANXIETY DISORDER



Lifetime prevalence 5.7 %

GENERALIZED ANXIETY DISORDER

- Excessive and poorly controlled worry about a number of situations and events
- Somatic symptoms
- Tension
- Restlessness
- Fatigue
- Insomnia
- Irritability
- For at least 6 months, more days than not

- Anxiety or panic is a predominant feature
- Evidence of development of symptoms during or soon after
  - Intoxication
  - Withdrawal
  - Medication change
  - (Provided the substance can produce those symptoms)
- Codes for:
  - *ETOH*
  - *Caffeine*
  - *Cannabis*
  - *PCP*
  - *Other Hallucinogen*
  - *Inhalant*
  - *Opioid*
  - *Sedative/hypnotic or anxiolytic*
  - *Cocaine*
  - *Other (or unknown) substance*

SUBSTANCE INDUCED ANXIETY DISORDER

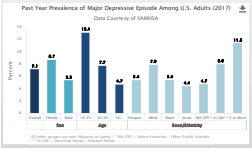
- Anxiety or panic are predominant
- Evidence of direct pathophysiologic consequence of another medical condition
- Not due to delirium or another medical condition
- Examples: pheochromocytoma, hyperthyroidism, respiratory disease

ANXIETY D/O DUE TO ANOTHER MEDICAL CONDITION

ANXIETY: OTHER SPECIFIED AND UNSPECIFIED

- Anxiety causes significant distress, but does not meet criteria for another psychiatric disorder, and is not better explained by a medical condition
  - Limited symptom attacks
  - Ataque de nervios
  - General anxiety occurring more days than not
  - Khyal cap (wind attacks)

OVERVIEW OF DEPRESSIVE DISORDERS



- Globally 350 million people suffer from depression
- CDC : By 2020 Depression will be 2nd only to cardiovascular disease in disease burden, by 2030 expected to be largest contributor to disease burden
- Lifetime prevalence for DSM -5 MDD and its specifiers is 20.6 %
- ~17.3 million adults in the US had at least one Major Depressive episode = 7.1% of all U.S. adults.
- The prevalence of major depressive episode was twice for females > males
- The prevalence greatest in 18-25 population
- The prevalence greatest in adults reporting two or more races

RISK FACTORS FOR DEPRESSION

- *One twin study suggests depression ~37% heritable*

Experiencing traumatic or stressful events, such as physical or sexual abuse, the death of a loved one
Going through a major life change, planned or not
Having a medical problem, such as cancer, stroke, or chronic pain
Heritability is unclear, but having a 1st degree relatives with depression is a risk factor
Certain medications
Substance Abuse
Poverty
Social and educational disadvantages
Separation or divorce

NIMH July, 2018

NEUROBIOLOGY OF DEPRESSION

NEUROINFLAMMATION

- Increased inflammatory cytokines

MONOAMINE HYPOTHESIS

- Serotonin regulates mood, appetite, sleep, sex, pain, body temperature, circadian rhythm
- NE helps us access emotionally arousing memories, modulates working memory, behavior and attention, in the prefrontal cortex
- Dopamine modulates reward, decision making, motivation, and focus
- Transport proteins facilitate presynaptic reuptake of neurotransmitters, decreasing their degradation by monoamine oxidase enzymes
- Alterations to affinity for serotonin receptor
- Super-sensitivity to NE

ENDOCRINE FACTORS

- Blunting of GH
- Thyroid hormone may be a NE co-transmitter and deficiency may produce symptoms of depression
- Hypercortisolism (increased CRF)

GENETICS

- MDD susceptibility genes: APOE 2 and 4, guanine nucleotide binding (GND3,) methylenetetrahydrofolate reductase (MTHFR,) dopamine transporter (SLC6A3,) serotonin transporter, dopamine receptor gene (DRD 4)

MAJOR DEPRESSIVE DISORDER

- **At least 5/9 symptoms for at least 2 weeks.** Must include depressed mood or anhedonia as primary symptom. Symptoms must be most of the day, nearly every day, not better explained by another disorder, no history of manic symptoms.
- Depressed mood (children can be irritable)
- Anhedonia
- > 5% change in body weight and increased or decreased appetite
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or low energy
- Poor concentration or indecisiveness
- Recurrent thoughts of death or suicide

MAJOR DEPRESSIVE DISORDER

Mild
Moderate
Severe
With Psychotic Features
In Partial Remission
In Full Remission
Unspecified

With Anxious distress
With Mixed Features
With Melancholic Features
With Atypical Features
With Mood-Congruent Psychotic Features
With Mood-Incongruent Psychotic Features
With Catatonia
With Peripartum Onset
With Seasonal Pattern

PERSISTENT DEPRESSIVE DISORDER

- **At least 2/6 symptoms for at least 2 years (1 year for pediatric patients.) Patient has never been without symptoms for more than 2 months at time. No history of manic symptoms.**
- Depressed mood (children can be irritable)
- Increased or decreased appetite
- Insomnia or hypersomnia
- Fatigue or low energy
- Poor concentration or indecisiveness
- Feeling hopeless

PERSISTENT DEPRESSIVE DISORDER

Mild
Moderate
Severe
In Partial Remission
In Full Remission

Early Onset (before age 21)
Late onset

With Anxious distress
With Mixed Features
With Melancholic Features
With Atypical Features
With Mood-Congruent Psychotic Features
With Mood-Incongruent Psychotic Features-
With Catatonia
With Peripartum Onset
With Seasonal Pattern

With Pure Dysthymic Syndrome
With Persistent Major Depressive Disorder
With Intermittent Major Depressive Episodes, with Current Episode
With Intermittent Major Depressive Episodes, without Current Episode

PREMENSTRUAL DYSPHORIC DISORDER

Symptoms present for majority of menstrual cycles

- Present in week prior to menses
- Symptoms improve within a few days of starting menses
- Symptoms are minimal or absent in the week postmenses

1 out of 4 symptoms

- Marked affective lability
- Marked irritability, anger, or interpersonal conflicts
- Marked depressive symptoms
- Marked anxiety, tension, feeling on edge

1 out of 7 symptoms

Anhedonia, poor concentration, low energy, increased appetite, hypersomnia or insomnia, sense of being overwhelmed or out of control, physical symptoms such as weight gain, bloating, pain

SUBSTANCE/MEDICATION INDUCED DEPRESSIVE DISORDER

- Marked depression or anhedonia
- Physical evidence of symptoms developing soon after intoxication with, withdrawal from, or exposure to a medication or substance (provided that substance can produce those symptoms)
- Symptoms are not better explained by another depressive disorder or delirium
- Also code "With (mild, moderate, severe) use disorder" or "without use disorder"
- Specify "with onset during intoxication" or "with onset during withdrawal."

DEPRESSIVE DISORDER DUE TO ANOTHER MEDICAL CONDITION

Persistent depression or anhedonia

Physical evidence that symptoms are directly due to pathophysiological consequence of another medical condition

SPECIFY

- With depressive features
- With Major Depressive like symptoms (meeting full criteria for MDD)
- With Mixed Features

OTHER SPECIFIED DEPRESSIVE DISORDER

Symptoms cause significant distress or difficult functioning

Do not meet criteria for another disorder

Recurrent Brief Depression

- Depressed mood + 4 other symptoms for 2-13 days per month (not associated with menses) for at least 12 months

Short Duration Depressive Episode

- Depressed mood and 4 other symptoms for > 4 but less than 14 days

Depressive Episode with Insufficient Symptoms

- Depressed mood and one other symptom for at least 2 weeks

UNSPECIFIED DEPRESSIVE DISORDER

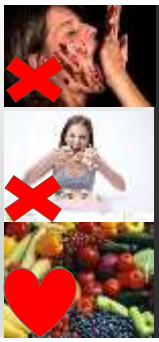
- Clinician chooses not to specific diagnosis
- Insufficient information to make more specific diagnosis

WHOLE-BODY APPROACH

- Complete medical assessment
- Medication and psychotherapy
- Healthy Habits
  - Helps the body utilize it's innate capacity for recovery

NUTRITION

- Stress→cortisol/NPY→ carbs→ central obesity→inflammation→brain injury
- Massachusetts General Hospital suggests that foods rich in magnesium, zinc, B vitamins, probiotics can reduce risk of anxiety and depression
- Gut biome linked to mental health disorders
- Omega 3 fatty acids
  - Decrease inflammation
  - 20% reduction in anxiety



EXERCISE

- CDC recommends 30 min of moderate- to high-intensity exercise, 5 days a week for healthy individuals = 2 to 2.5 hours/week
- Strong evidence
- Yoga is controversial, more data needed
  - Seems to positively affect perceived well being and executive functioning
  - Reduced oxidative and inflammatory stress
  - Active exercise appears to be more effective

EXERCISE

- Brain blood vessels grow
- Less cortisol
- More serotonin
- Endogenous opioid release
- Healthier hippocampus → neuroplasticity and neurogenesis
- Reduces anxiety sensitivity (due to panic like state during aerobic exercise)
- Increased sense of self efficacy
- Distraction
- Less oxidative stress

COGNITIVE APPROACHES

MINDFULNESS

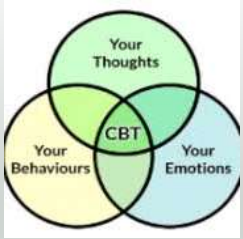
"…A process that leads to a mental state characterized by nonjudgmental awareness of the present moment experience, including the person's sensations, thoughts, bodily states, consciousness, and the environment, while encouraging openness, curiosity, and acceptance."

COGNITIVE APPROACHES

MINDFULNESS

"Moment to moment awareness"

- Derived from Buddhism
- Outperforms health education, relaxation training, and supportive psychotherapy
- Performance comparable to CBT
- Increased self-awareness, attention, and emotion regulation
- *Better cortical and limbic communication means, we are LESS REACTIVE, MORE REFLECTIVE*
- Effective in reducing insomnia



COGNITIVE APPROACHES

- Relaxation Techniques
  - Deep breathing
  - Progressive muscle relaxation
  - Guided imagery
  - Increase brain O2 and Serotonin
- CBT challenges distorted thinking
  - Build evidence for or against a negative thought
  - Discourages catastrophic thoughts and personalization.
  - 50-60% of patients benefit from CBT or medications
- Other psychotherapeutic modalities
  - EMDR
  - DBT
  - ACT

PHARMACOLOGIC TREATMENT STRATEGIES

- Use ½ or less of the maximum dose (if possible)
- Titrate in 2 week intervals
  - Start at 25% of max dose and move to 50% in 6 weeks if needed
- Prepare patients to wait 8-12 weeks for therapeutic effect
- For elderly monitor Na 2-3 weeks after dose adjustments
- Avoid SSRIs/SNRIs if history of significant hyponatremia
- QTc> 500 = If QTc is > 450 in males and > 460 in females, repeat EKG 4-6 weeks after any dose adjustments
- Screen for mania first

QUICK SCREEN FOR MANIA

"DIGFAST"

D-Distractibility
I- Indiscretion (sexual or financial impulsivity, risk taking behaviors)
G-Grandiosity
F- Flight of ideas (racing thoughts)
A- Activity or energy increase
S- Sleep deficit (decreased need for sleep)
T- Talkativeness (pressured speech)

Severity of Illness	Medication?	Psychotherapy Only?	Both
Mild to Moderate	Yes***	Yes	Yes
Severe without Psychosis	Yes	No	Yes
Severe with Psychosis	Yes (antidepressant AND antipsychotic)	No	Yes

Adapted from APA Practice Guidelines, 2010

APA GENERAL TREATMENT GUIDELINES

****** Consider medication in the following cases:***

- ***Prior positive response to an antidepressant***
- ***Moderate to severe symptomatology***
- ***Significant sleep or appetite disturbances or agitation***
- ***Anticipation of need for maintenance therapy***
- ***Patient preference***

GENERAL TREATMENT GUIDELINES

Selective serotonin reuptake inhibitors are more likely than placebo to produce depression remission in the primary care population.
Serotonin-norepinephrine reuptake inhibitors are slightly more likely than selective serotonin reuptake inhibitors to improve depression symptoms, but they are associated with higher rates of adverse effects such as nausea and vomiting.
Treatment for a first episode of major depression should last at least four months. Patients with recurrent depression may benefit from prolonged treatment
Preferred agents for older patients with depression include citalopram, escitalopram , sertraline , mirtazapine ,venlafaxine, and bupropion. Because of higher rates of adverse effects in older adults, paroxetine and fluoxetine should generally be avoided.
Antidepressants are most effective in patients with severe depression.
treatment-naive patients, all second-generation antidepressants are equally effective. Medication choice should be based on patient preferences, with adverse effect profiles, cost, and dosing frequency taken into consideration

Drug/Usual Dose Range	Pros	Cons	Elderly Appropriate? (Na is normal)	Cost	FDA Indication	Appropriate if Hx of Fall?
Sertraline 25-200 mg in the morning	Activating, less weight gain potential, good cardiac safety profile, fewer sexual side effects Useful for atypical depression Less hyperprolactinemia potential No renal dosing	Activating May cause insomnia More GI upset Hepatic dosing needed	Yes	$6-$17	OCD, PD, PTSD, SAD	No
Citalopram 10-20 mg daily	Less activating No renal dosing	QTc prolongation, sedation, sexual side effects Hepatic dosing needed	Yes	$3-$13	MDD	No
Escitalopram 5-20 mg daily	Activating Often well tolerated Less weight gain, sexual side effects No renal dosing	Qtc prolongation Hepatic dose limited to 10 mg/day	Yes	$3-$50	GAD, MDD	No
Fluoxetine 10-60 mg daily	Longer acting if adherence is an issue Well studied in adolescent population Useful for atypical depression No renal dosing, not	Activating due to 5HT2C antagonism Long acting Hepatic dosing needed	No	$3-$20	OCD, PD, MDD, Bulimia, PMDD, Bipolar Depression with olanzapine	No

Drug/Usual Dose Range	Pros	Cons	Elderly Appropriate? (Na is normal)	Appropriate if Hx of Fall?	Cost	FDA Indication
Paroxetine 10-40 mg daily	More sedating Very useful for panic disorders and agitated depression Low doses prescribed for hot flashes	More pronounced withdrawal syndrome Potential VSD/ASD Weight gain potential Sexual side effects Renal and hepatic dosing needed	No	No	$3-$19	GAD, OCD, PD, PTSD, SAD, PMDD, MDD
Venlafaxine XR 75-225 mg daily	Neuropathic pain benefit (higher doses = > NE activity May be activating May be helpful in treating ADHD Combine with mirtazapine	Nausea May be sedating Weight gain not uncommon Need to monitor blood pressure May not be suitable if cardiac disease May cause discontinuation syndrome May assist with hot flashes Not recommended in pregnancy Renal and hepatic dosing required	Yes	No	$6-$28	GAD, PD, SAD, MDD

Drug/Usual Dose Range	Pros	Cons	Elderly Appropriate? (Na is normal)	Appropriate if Hx of Fall?	Cost	FDA Indication
Duloxetine 20-90 mg daily	Neuropathic pain benefit/somatic depressive symptoms May be activating Approved in some countries for stress urinary incontinence Less HTN potential than venlafaxine?	Nausea Sedation Renal and hepatic dosing needed	Yes	No	$6-65	GAD, MDD, Diabetic Peripheral Neuropathic pain, FMS, Chronic MSK Pain
Mirtazapine 7.5-45 mg nightly	Useful for insomnia and decreased appetite May work faster than SSRIs Less sexual dysfunction	Weight gain Sedation May cause photosensitivity May cause lower WBCs Use with caution for renal/hepatic impairment	Yes	Yes	$5-$20	MDD
Buspirone 10-60 mg daily in divided doses	Often combined with another antidepressant Good safety profile May work faster than SSRIs/SNRIs No dependence/tolerance	Sedation Caution in cases of severe renal and hepatic impairment	Yes	Yes	$4-16	ANXIETY (NON-SPECIFIC)
Bupropion SR 75-400 mg daily XL 150-450 mg daily (Extended release 174-522 mg)	Can reverse SSRI induced sexual dysfunction Can augment mood stabilizers Good for atypical depression and weight issues Smoking cessation Do not use if hx of seizures or eating disorders	Can cause activation	Yes	Yes	$18-$30	MDD, Seasonal affective d/o, Nicotine Addiction

SUGGESTED AUGMENTATION ALGORITHM

	PTSD	Specific Phobia	GAD	SAD	OCD
SSRI	1		1	1	1
SWITCH TO DIFFERENT SSRI/SNRI	2		2	2	2
AUGMENTATIN W/ ADDITIONAL SSRI/SNRI BUSPIRONE/MIRTAZAPINE	3		3	3	3
OTHER ANTIDEPRESSANT	4		2	3	4
TCA	3		3	3	1
ATYPICAL ANTIPSYCHOTIC	4		4	4	4
ANTICONVULSANT			4	4	
BETA BLOCKER		2			
BZD		2	3	4	*J Anxiety Disord. 2012 Dec; 26(8): 833-843.*

STAR*D

- Funded by NIMH
- "Sequenced Treatment Alternatives to Relieve Depression" = (STAR*D)
- Conducted to determine the effectiveness of different treatment for those who responded poorly to initial treatment
- Largest and longest study ever conducted to evaluate depression treatment
- Study from 2001-2009

OTHER OPTIONS TO TREAT ANXIETY

- Hydroxyzine pamoate (Vistaril) is indicated for anxiety and probably achieves anxiolysis by inhibiting the histamine H_1 receptor
- Gabapentin and pregabalin are alpha–delta calcium channel blockers, anticonvulsant.
  - Reduce neuronal excitability
  - Balance between inhibitory and excitatory neuronal activity.
  - Rapid onset of action
  - Superior to placebo in GAD
- Beta blockers are used for performance-related anxiety
  - Reduce peripheral physical symptoms with 30-60 min
  - Do not address cognitive aspects of anxiety

ADJUNCTIVE TREATMENT FOR DEPRESSION

GOOD EVIDENCE TO SUPPORT	LESS SUPPORTING EVIDENCE	TREATMENT RESISTANT DEPRESSION
Add another non-MAOI antidepressant, generally from a different class	Add omega-3 fatty acids	TMS (transcranial magnetic stimulation)
Add lithium	Add folate	ECT (electroconvulsive therapy)
Add thyroid hormone	Add a psychostimulant medication	VNS (vagus nerve stimulation)
Add a second-generation antipsychotic	If anxiety or insomnia are prominent, adding an anxiolytic or sedative-hypnotic medication, including buspirone, a BZD, or a selective gamma-aminobutyric acid (GABA) agonist hypnotic (e.g., zolpidem, eszopiclone)	
	Add an anticonvulsant	*American Psychiatric Association Guidelines , 2010*

POTENTIAL SIDE EFFECTS OF ANTIDEPRESSANTS

- Dizziness
- Muscle tension
- Activation
- Sedation
- White blood cell dysfunction
- Serotonin Syndrome
- Hyponatremia
- Elevated prolactin
- Dry mouth
- Blurry vision
- Suicidal thoughts
  - Ages 18-24, within 1-2 mos of med changes

- GI upset/diarrhea/bleeding
- Changes in weight and appetite
- Insomnia
- Sexual dysfunction
- Changes in pulse and blood pressure
- Increased potential to have seizures
- Abnormal heart rhythms
- Liver toxicity (nefazodone esp)

REVIEW OF SEROTONIN SYNDROME/DDIs

- Use caution when combing **SSRIs, SNRIs, TCAs, Lithium, SMRS, SGAs, St. John's Wort, Anticonvulsants, MAOIs, Buspirone, Mirtazapine, Triptans, meperidine, methadone, oxycodone, and Fentanyl, Ondansetron, Metoclopramide, Linezolid, dextromethorphan, and/or cocaine**
  - CNS depression, increased seizure risk, and serotonin interactions
- **TRAMADOL IS AN SNRI**
  - 2D6 inhibitors (ie bupropion, fluoxetine, paroxetine, sertraline, duloxetine, buprenorphine) inhibit formation of O-demethylated tramadol metabolite causing patient potentially overuse of tramadol

CYTOCHROME P450 CONSIDERATIONS

ENZYME	*METABOLIZER PHENOTYPE*	*POPULATION FREQUENCY (%)* *ASIANS*	*AA*	*CAUCASIAN*
CYP2C9 *Fluoxetine*	Poor	0.4	0.0	1.0
	Intermediate	3.5	13	33
	Ultrarapid	—	—	—
CYP2C19 *Citalopram*	Poor	18 to 23	1.2 to 5.3	2.0 to 5.0
	Intermediate	30	29	18
	Ultrarapid	—	—	—
CYP2D6 *Fluoxetine* *Paroxetine* *Duloxetine ** *Venlafaxine** *Aripiprazole** *Fluvoxamine* *Mirtazapine (Also 1A2 and 3A4)* *Sertraline **	Poor	1.0 to 4.8	1.9 to 7.3	7.0 to 10
	Intermediate	51	30	1.0 to 2.0
	Ultrarapid	0.9 to 21	4.9	1.0 to 5.0

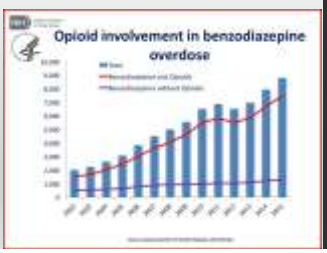
Bupropion is 2D6 inhibitor
Buspirone is metabolized by 3A4
* = both substrate and inhibitor

ANTIDEPRESSANT WITHDRAWAL SYNDROME

- Anxiety
- Insomnia
- Vivid Dreams
- Headaches
- Dizziness
- Fatigue
- Irritability
- Flu-like Symptoms
- Nausea
- Electric Shock Sensations (Dysethesias)
- Recurrence Of Depression/Anxiety Symptoms
- Suicidal Thoughts

BENZODIAZEPINES: AN EPIDEMIC

- Between 1996 and 2013, the number of adults filling a BZD prescription increased by 67%
- Quantity of benzodiazepines filled increased from 1.1 to 3.6 kg lorazepam equivalents/100,000 adults
- The overdose death rate (related to BZD use) increased from 0.58 to 3.07 per 100,000 adults
- JAMA retrospective study found that use of BZDS not prescribed by a psychiatrist *increased* with age and was nearly doubled in the female population
- ¼ were on a long acting BZD



FDA BLACK BOX WARNING

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.1), Drug Interactions (7.X)]. Reserve concomitant prescribing of these drugs for use in patients *for whom alternative treatment options are inadequate**. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation."

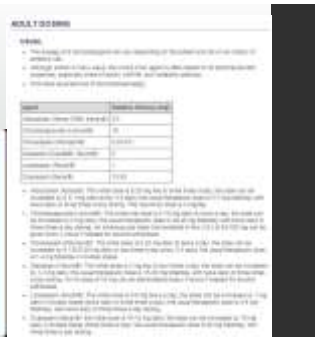
SCPMG REGIONAL GUIDELINES: GENERAL PRACTICE

- Avoid prescribing BZDs/SHs to patients also on opiates
- Avoid prescribing BZDs/SHs to patients >65 years old. They are a "high-risk medication in the elderly" due to increased severe adverse events and are listed in the American Geriatrics Society Beers Criteria List of Drugs to Avoided in the Elderly
- Limit use to 2 weeks for insomnia
- Limit use to 4-6 weeks for anxiety "apart from exceptional circumstances"
- "There is no evidence to support long-term use, for anxiety, insomnia or any mental health indication."
- "For panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and insomnia, BZDs have only demonstrated short-term efficacy and are only recommended for short-term durations (i.e., less than 2–4 weeks) and for treatment-resistant cases (i.e., after failing multiple first-, if not second-, line treatments)."
- "BDZs use may be considered for occasional anticipatory anxiety, e.g. pre-MRI/CT scans, travel, chemotherapy or panic disorder…"
- Local agreement to prescribe no more than 30 day supply at a time

METRIC	SCORED	MONITORED	REGIONAL PRACTICE GUIDELINE
OVERALL BZD/SH UTILIZATION (< 30 TABS/YEAR EXCLUDED)		+	
SH CHRONIC UTILIZATION (65 AND OLDER)		+	
ANY OPIOID+ BZD/SH	+		
BZD/SH HIGH UTILIZATION (> 50 DED/DAY)	+		
BZD/SH NEW STARTS (# OF PILLS TBD)		+	
OVERALL DEPRESCRIBING of BZD/SHs BZD USE LESS THAN 4-6 WEEKS FOR ANXIETY DISORDERS AND 1-2 WEEKS FOR INSOMNIA (2019 REGIONAL PRACTICE GUIDELINES PENDING)			+

BENZODIAZEPINE MANAGEMENT

DOSING CONSIDERATIONS



ACUTE INSOMNIA:

- Give # 12 tabs with no refills
- Limit use to 1-2 weeks
- Write the Sig for occasional use, not daily

CHRONIC INSOMNIA:

- Refer patient to Health Education (Center for Health Living) for insomnia classes and CBT Classes.
- Order the Emmi Insomnia Video for your patient to watch
- Consider melatonin, start with 3 mg and escalate weekly if needed to 5 mg, max of 10 mg 30-60 minutes before sleep
- Consider low dose trazadone, 25 mg nightly, if the patient has no cardiac or other contradictions. May titrate dose slowly by 25 mg every 3-4 days if needed up to 100 mg nightly 30 minutes before bedtime. Higher doses if needed
- Slower titration and lower doses should be used in the elderly.
- CBT with low dose trazodone maybe more effective in some patients.
- Discuss sleep hygiene and provide the Sleep Hygiene Handout
- Refer to KPHC Smart Rx on Anxiety, Insomnia, Neuropathic Pain

REGIONAL GUILDELINES: WHEN AND HOW TO PRESCRIBE

ACUTE ANXIETY:

- Do not prescribe BZDs to the elderly > 65
- Do not prescribe BZDS to use for longer than 6 weeks
- Write the sig for occasional use
- # 12 tabs with no refills only for new starts
- Do not prescribe a BZD if the patient has history of SUD

CHRONIC ANXIETY ("LIFERS")

- See upcoming slides for tapering recommendations
- WE KNOW IT'S DIFFICULT
- "Some patients will feel threatened or frightened about tapering these medications, and their trepidation can be expressed in various ways. "
- "Remember that "bullying" behavior (i.e., attempting to intimidate clinicians into ongoing refills) is commonly an expression of fear. Focus your discussion about tapering on RISKS and BENEFITS of these drugs. "
- "Empathize with the patient's uncertainty and reassure the patient that you will not abandon him or her. "
- " Remind the patient that there are more effective* ways to treat anxiety and insomnia. Patients are expected to remain calm and respectful during these conversations, even if they feel angry."
- " Belligerent behavior (by patients) is an indication for tapering off BDZ or non-BDZSH/Z drugs. Remind the patient that this behavior is not acceptable and will not be tolerated. If it continues, a taper can be initiated."
- Your safety matters too…call security if you detect a threat

REGIONAL GUILDELINES: WHEN AND HOW TO PRESCRIBE

PSYCHIATRY PATIENTS WHO HAVE "FAILED" TAPERING

- These patients will stay in Psychiatry until tapered.
- For a stable patient taking 1-2 BDZ tabs/caps a month, consideration of the transfer of care to the patient's PCP should be considered

- PRIMARY CARE PATIENTS WHO HAVE "FAILED" TAPERING
- For those patients who failed a tapering plan, Dr. Advice or calling Psychiatry (or ADM) is suggested, and the psychiatrist or addiction specialist can evaluate what future steps should be taken
- PLEASE DO NOT abruptly decline a refill and defer to Psychiatry if the patient is not already established in Psychiatry

REGIONAL GUILDELINES: WHEN AND HOW TO PRESCRIBE

BENZODIAZEPINE MANAGEMENT

THE BASICS:

1. Avoid new starts if at all possible
2. If a new start is needed, say it with me "THIS IS TEMPORARY"
3. Whomever starts it owns it
4. Patients need to be seen every 3-6 mos. minimum
5. Avoid prescriptions lasting > 2 weeks. 6 weeks is upper limit
6. Do not start BZDs on patients who are already on opiates or SMRs, esp > 64 y

BENZODIAZEPINE MANAGEMENT

RISKS, BENEFITS, SIDE EFFECTS (AAFP)

- Tolerance/dependence >with short and intermediate acting meds
- Sedation
- Increased risk of falls and mortality

  "Hip fracture: Benzodiazepines increase the risk of hip fracture in older persons by at least 50%. In a study of 43,343 persons, zolpidem increased the risk of hip fracture by 2.55 times in those older than 65 years."
- Risk of temporary of permanent cognitive impairment
- "Cognitive impairment. Benzodiazepines cause acute adverse effects: drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. Additionally, a meta-analysis of studies looking at withdrawal from an average of 17 mg per day of diazepam (Valium) found that long-term use led to substantial cognitive decline that did not resolve three months after discontinuation."
- "Motor vehicle crashes. The risk of driving while on benzodiazepines is about the same as the risk of driving with a blood alcohol level between 0.050% and 0.079% (an alcohol level greater than 0.08% is illegal in all states)."
- Other drug-drug interactions (opiates, SMRs, Etoh, etc)
- May worsen depression

TAPERING CONSIDERATIONS

Notes:

- Alprazolam is shorter acting and withdrawal seizures are more prone to occur. Taper 0.25 mg/week if taper becomes difficult toward the end
- There is a lack of good quality evidence for switching to diazepam.
  Some providers do this due to the long t ½, but sedation and delirium are more likely to occur, so avoid in >64 population
- For Z Drugs:
  Stop -short term low dose usage, no aberrances
  Taper by reducing the # of nights patient takes per week until off
  Switch to lorazepam and taper as below

Long or intermediate acting agent → GRADUAL TAPER
10%/week
or
10% every 2-4 weeks
If function worsens, they are tolerant from long term use, or medical comorbidities are present

Short acting agent (esp >64 y) → SWITCH to Long or Intermediate acting agent

Suspicious UDS is + or aberrant/drug seeking behaviors → RAPID TAPER
25%/week
Refer to ADM and Psych if needed

RECOGNIZE WITHDRAWAL

Benzodiazepines and other sedative/hypnotics	Short-acting: 2 to 4 days Long-acting: 4 to 7 days	Short-acting: 4 to 7 days Long-acting: 7 to 14 days	Increased psychomotor activity, agitation, muscular weakness, tremulousness, hyperpyrexia, diaphoresis, delirium, convulsions, elevated blood pressure, pulse and temperature, tremor of eyelids, tongue and hands	Anxiety, depression, euphoria, incoherent thoughts, hostility, grandiosity, disorientation, tactile, auditory and visual hallucinations, suicidal thoughts

WITHDRAWAL SYMPTOM	MEDICATION	DOSING	CONSIDERATIONS
Seizure Prevention	Carbamazepine Valproic acid Divalproex sodium EC	Start 200 mg twice a daily, adjust dose weekly up to 400 mg twice daily. Continue for 2-4 weeks after stopping benzodiazepine and then taper anticonvulsant. Start 500 mg twice daily, adjust dose weekly o to 2,000 mg daily. Continue for 2-4 week after stopping benzodiazepine and then taper anticonvulsant.	In patients with liver impairment, consider topiramate or gabapentin. Check CBC and liver function tests at baseline Check CBC and liver function tests at baseline and every 3 months during treatment
Tachycardia, Hypertension, Tremors, Sweats, Anxiety, Restlessness	Propranolol	10 mg three times daily as needed for 3 days	
Hypertension, Tremors, Sweats, Anxiety, restlessness	Clonidine	0.1 mg tid for 3 days	
Anxiety and restlessness	Hydroxyzine or Diphenhydramine	25 mg every 6 hours as needed	Not for elder population
Insomnia	Hydroxyzine or Diphenhydramine	25-50 mg qhs prn	Not for elder population
Nausea	Promethazine Metoclopramide	25 mg every 6 hours as needed 10 mg every 6 hours as needed	Not for elder population
Dyspepsia	Calcium Carbonate Mylanta Milk of Magnesia	500 mg 1-2 tabs every 8 hours as needed Follow package instructions	

WHEN/WHERE TO REFER

- Active alcohol or other drug use disorders are present (including opiates or amphetamines)
- High dose benzo use
- History of severe withdrawals or withdrawal seizures

→ ADDICTION MEDICINE

- Significant or Severe Comorbid Mental Illness
- Suicidal Thoughts

(Use appropriate crisis resources if acutely expressing SI)

→ PSYCHIATRY

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