Depression and Anxiety: Latest in treatment recommendations

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Disclosure
• No real or potential conflict of interest to disclose.
• Select medications will be mentioned that are off-label use for mood disorders, including most second generation antipsychotics and antiepileptic drugs. Nutritional supplements mentioned are not FDA-approved for any disease state.

Objectives
• At the conclusion of this presentation the attendee will be able to:
  – Explain the mechanism of action of commonly prescribed psychotropic medications used in the treatment of mood disorders including depression and anxiety.

Objectives (continued)
• At the conclusion of this presentation the attendee will be able to: (cont.)
  – Describe factors influencing the choice of a psychotropic medication for the treatment of common mood disorders.
  – Identify common adverse effects and therapeutic advantages of the above-mentioned medications.

Are depression, anxiety brain diseases? Neurohumoral disease? Other?

Anxiety and Depression
Common Pathology?
• “...the major mediators of the symptoms of anxiety disorders appear to be norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA).”
Anxiety and Depression
Common Pathology?
(continued)
• “...suggest a disturbance in central nervous system serotonin (5-HT) activity as an important factor. Other neurotransmitters implicated include norepinephrine (NE), dopamine (DA), glutamate, and brain-derived neurotrophic factor (BDNF).”

What does what in the maintenance of mood?
• Serotonin
  – AKA 5-hydroxytryptamine or 5-HT
  – Similar in structure to norepinephrine and dopamine
  – Modulates mood, emotion, sleep, appetite, keeps the motor of life running smoothly
  – Source: www.biopsychiatry.com/serotonin.htm

What does what in the maintenance of mood?
(continued)
• Norepinephrine
  – Associated with focused attention, elevated energy, motivation to win a reward or move towards a goal

What does what in the maintenance of mood?
(continued)
• Dopamine
  – In part, helps with the joy of life, attention, pleasure

Glutamate and GABA
• “Yin and yang” of neurotransmitters
  – Present in nearly all brain synaptic function

Glutamate and GABA
(continued)
• Glutamate
  – Excitatory capacity
  – Stress modulating when working right

• GABA
  – Inhibitory role
  – Select receptor site activity regulate excitability as well as anxiety, panic, and stress
### Hormone Effects

**Presence of Estrogen**

- ↑ Catecholamines*
- ↑ Serotonin function and transport†
- ↓ Monoamine oxidase‡

‡Luine et al. Brain Res. 1975;86:293.

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### Neurotransmitter balance is key.

Most psychotropic medications work through manipulation of serotonin, norepinephrine and/or dopamine.

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### Choosing a Therapeutic Agent in Mood Disorder

**Practice Guideline for the Treatment of Patients With Major Depressive Disorder**


**Clinical Practice Review:**

**Generalized Anxiety Disorder**

Available at www.adaa.org/resources-professionals/practice-guidelines-gad

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### Making the Diagnosis of Depression/Generalized Anxiety Disorder

- **Diagnosis and Treatment of Generalized Anxiety and Panic Disorder**
- **Diagnose and Characterize Major Depression/Persistent Depressive Disorder with Clinical Interview**
  - Source: https://www.icsi.org/guideline_sub-pages/depression/diagnose_and_characterize_major_depression_persistent_depressive_disorder_with_clinical_interview/

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### What are the clinical and cost considerations?

- What does what?
  - What does the patient need for a clinical response?
    - Vegetative or anxious?
  - Will a given medication provide that help?
  - What depression, anxiety symptoms respond best to a given medication?

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### What are the clinical considerations?

- What is the drug’s adverse effect profile?
- What is the risk of the medication in overdose?
- What medication is affordable and accessible?
What are the clinical and cost considerations?

- How is the patient sleeping?
- What is the patient’s energy level?
- Chronic pain?
- Appetite?

How to Choose a Therapeutic Agent for the Treatment of Mood Disorders

- What has worked in the past?
  - Use the tried and true if safe and reasonable
- What has worked for relatives?
  - Might be related to similar action of receptor sites, neurotransmitter activity

Commonly Prescribed Psychotropic Medications

- **SSRIs (selective serotonin or serotonin specific reuptake inhibitors)**
  - Inhibit reuptake of serotonin (5-HT)
  - Net result is more serotonin at synaptic cleft
    - Citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluvoxamine (Luvox®), paroxetine (Paxil®), sertraline (Zoloft®)
    - Source: Stringer (2011)

SSRI: Nuances of Prescribing

Most sedating?

Most energizing?

Commonly Prescribed Psychotropic Medications

- Venlafaxine (Effexor®), duloxetine (Cymbalta®), desvenlafaxine (Pristiq®), others
  - Inhibits reuptake of serotonin, NE
- Particularly well suited when mood disorder associated with chronic pain, depression resistant to SSRI therapy, anxious depression

Vortioxetine (Trintellix®, was Brintellix®)

- What is it?
  - "Multi-modal” antidepressant or a “serotonin modulator and stimulator”
    - Selective serotonin reuptake inhibitor (SSRI)
    - Serotonin receptor agonist (5-HT1A)
    - Partial agonist (5-HT1B)
    - Antagonist (5-HT3A, 5HT7, 5-HT1D)
  - ~$400 per 30 tabs (goodrx.com)
Levomilnacipran (Fetzima®)

- **Mechanism of action**
  - Serotonin and norepinephrine reuptake inhibitor
  - Relatively more selective for norepinephrine reuptake inhibition (NRI) compared with serotonin reuptake inhibition (SRI)
    - >10-fold greater selectivity for NRI than SRI compared with duloxetine or venlafaxine

- Could offer more targeted treatment of NE deficiency MDD symptoms (e.g., concentration, physical slowing, decreased self-care)
- Could be considered a NSRI
- Cost = ~$400 per 30 tabs

Commonly Prescribed Psychotropic Medications

- **Bupropion (Wellbutrin®)**
  - Inhibits reuptake of dopamine, lesser degree, norepinephrine
  - Typically energizing with lower risk of adverse sexual AE when compared to SSRI, SNRI
    - Potentially well suited for person who is low energy, hx of sexual AE with SSRI, SNRI

- **Nefazodone (Serzone®), trazodone (Desyrel®), vilazodone (Viibryd®)**
  - Inhibits reuptake of 5-HT; blocks 5-HT2A (anxiety receptor site)
  - Vilazodone=~$250 per 30 tabs

Commonly Prescribed Psychotropic Medications (continued)

- **Issues with use**
  - Nefazodone- Seldom used due to liver toxicity
  - Trazodone- Non habituating sleep aid
  - Vilazodone- Low rate sexual AE

Vilazodone (Viibryd®)

- Taking on vilazodone on an empty stomach can decrease the drug’s bioavailability by 50–60%.
Clinical question | Comment | Medication characteristic
--- | --- | ---
What is the given medication’s profile? | Include T ½, potential drug interactions, adverse effect profile, others. | See tables below.

### Rx for older adult?

<table>
<thead>
<tr>
<th>SSRI</th>
<th>T ½</th>
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<tbody>
<tr>
<td>Paroxetine</td>
<td>21 h</td>
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<td>33 h</td>
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<td>84 h, metabolite= 7–15 days</td>
</tr>
</tbody>
</table>

### CYP450 Isoenzyme Inhibition by SSRIs

<table>
<thead>
<tr>
<th>CYP Isoenzymes</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
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</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Citalopram</td>
<td>+</td>
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<td>Fluoxetine</td>
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<tr>
<td>Paroxetine</td>
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<tr>
<td>Sertraline</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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</tbody>
</table>

0=Minimal or weak inhibition; +, ++, +++ =mild, moderate, or strong inhibition*.
n von Moltke et al., 2001; Greenblatt et al., 2002; Greenblatt et al., 1998

### Evaluating Nonresponder

- **Has there been an adequate medication trial?**
  - Adequate dose
  - Adequate length of therapy
  - Adherence

### Which is best SSRI with multiple other medications? Which is worst SSRI with multiple meds, warfarin use?

### Evaluating Nonresponder (continued)

- **Consider coexisting health issues**
  - Medications
    - Clonidine, beta blockers, HCTZ
  - Metabolic issues
    - Optimize DM, thyroid treatment
  - Substance abuse
  - Stress, life events
Antidepressant Use in Adjustment Disorder with Depressed Mood

• If depression is with stressor
  – Agent will work well initially.
  – Less well as time goes on if stressor continues
• If stressor stops, drug will resume its initial efficacy.

Depression as Part of Bereavement

• Indications
  – Severe acute bereavement (<4 mo post event)
  – Moderate to severe chronic bereavement
• Anticipated effect of medications
  – Improves vegetative symptoms
  – No real effect on normative mood fluctuation of grief

Atypical or Second Generation Antipsychotics (SGA) as Adjunctive Therapy in MDD, GAD

Atypical or Second Generation Antipsychotics (SGA) as Adjunctive Therapy in MDD, GAD

• Typical (AKA 1st generation)
  – Haloperidol, others
• Atypical (AKA 2d generation)
  – Risperidone, olanzapine, others
• Mechanism of action
  – Block selective dopamine receptor sites

Second Generation Antipsychotics (SGA)

• Group of agents with action at a variety of receptor sites
  – Dopamine receptors (D2, D1, D3, and D4 antagonism)
  – Serotonin receptors (5-HT2A, 5-HT2C, 5-HT1A, 5-HT1D, others)
  – Norepinephrine (alpha 1- and alpha 2-adrenergic receptor blockade)

Atypical/Second Generation Antipsychotics and MDD/ GAD

• Best effect on positive symptoms
  – Hallucinations, agitation, confusion
    • Improvement plateaus at 3–6 months
• Less effect on negative symptoms
  – Blunted affect, cognitive dysfunction, inattention
    • Improvement at 2–3 months of treatment, often continue to improve
Atypical/Second Generation Antipsychotics and MDD/ GAD (continued)

• When to consider
  – Inadequate response with monotherapy
  – Particularly with depression is severe
  – Potentially helpful with sleep, sexual function

Second Generation Antipsychotics
Rank Order, Weight Gain

• From greatest to least
  – Clozapine
  – Olanzapine (Zyprexa®)
  – Quetiapine (Seroquel®)
  – Risperidone (Seroquel®)
  – Iloperidone (Fanapt®)

Rank Order, Weight Gain (continued)

• Reported low to no weight gain
  – Ziprasidone (Geodon®)
  – Aripiprazole (Abilify®)
  – Asenapine (Saphris®)
  – Lurasidone (Latuda®)
  – Paliperidone (Invega®)

Recommendations

• Prior to starting medication
  – Fasting plasma glucose
    • Repeat q 3–6 months as indicated
  – Lipid profile
    • Hypertriglyceridemia common
  • Life style changes
    – Diet, exercise, smoking cessation, etc.

Torsades de Ponte Risk with SGA Use
(continued)

• Likely class effect
  – Increasing risk with greater CV disease risk
  – Listed under “Drugs with Possible TdP” in Crediblemeds.org
• Consider baseline ECG with particular attention to QT interval prior to initiation.

- “There are potential safety concerns when using low-dose quetiapine (SGA) for treatment of insomnia. These concerns should be evaluated in further prospective studies. Based on limited data and potential safety concerns, use of low-dose quetiapine for insomnia is not recommended.”

Pharm Phun Phacts

BZD True or false?

- The use of a BZD does not help in decreasing the worry associated with anxiety but is helpful in reducing disease-associated vigilance.
- BZD abuse is rare in the absence of substance abuse.

Antiseizure/Antiepileptic Drugs (AED)

- “Antiseizure drugs were initially used for mood stabilization in mood disorders; however, their anxiolytic properties were quickly noted. Many agents in this drug class are being used in an off-label fashion to treat anxiety, especially gabapentin (Neurontin®, Pfizer) and pregabalin (Lyrica®, Pfizer).”

- Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628173/

Gabapentin

Off-label Use for Anxiety Disorder

- Proposed mechanism of action
  - Structurally similar to GABA
- Dose
  - 300–2400 mg/total daily dose
  - Short T ½=TID dosing, not to be used PRN
- Comorbid conditions
  - Helpful in chronic pain

- Source: http://mentalhealthdaily.com/2015/06/22/gabapentin-for-anxiety-disorders-an-off-label-treatment/

Hydroxyzine

Off-label Use in Anxiety Disorder

- Proposed mechanism of action
  - Inhibiting H1 receptor, serotonin-2a receptor
- Dose
  - Up to 200–400 mg/d divided QID
  - Dose limited to adverse effects including sedation, dry mouth, etc.
  - Potentially helpful sleep aid, possible PRN use
Discontinuing Psychotropic Therapy

- Slowly discontinue psychotropic therapy p 4–6 month maximum improvement
  - 1st episode MDD
  - Family’s 1st depression
- Treated ≥9–12 months
  - Repeat episode
  - Strong family hx depression

Antidepressant Discontinuation Syndrome
FINISH Mnemonic

Typically noted when SSRI, SNRI, TCA taken for ≥6 weeks then rapidly discontinued.
Typically lasts <7 days. Avoided with medication taper over ~6 weeks. Sx quickly resolve with restarting prior med dose. Bothersome but not life-threatening.

Discontinuation Syndrome
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Flu-like symptoms
Insomnia
Nausea
Imbalance (dizziness, difficulty with coordination)
Sensory disturbances (nightmares common)
Hyperarousal (anxiety/agitation), Headache

Which SSRI with usually worst withdrawal syndrome with rapid discontinuation?
Which likely will have little withdrawal syndrome with rapid discontinuation?

Shorter T ½ vs. Longer T ½
Pro and Con

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Nutritional Supplements and the Treatment of Mood Disorders
65-year-old Woman with Depression, HF

- On citalopram
  - Discontinued medication 4 days ago and began St. John’s wort
  - C/O nausea, dizziness, nervousness
- Additional medications
  - Lisinopril, digoxin, furosemide, lovastatin, ASA

St. John’s Wort (Hypericum Perforatum)

- Mechanisms of action
  - Inhibits action of monoamine oxidase and catechol O-methyltransferase, similar to MAOI
  - Interferes with serotonin uptake, similar to SSRI
- Indications
  - Depression, anxiety, ADHD

St. John’s Wort (Hypericum Perforatum) Issues of Efficacy

- Meta-analysis of 23 randomized controlled trials of 1,757 outpatients
  - St. John’s wort extract more effective than placebo, comparable to conventional antidepressants mild to moderate depression
  - Adverse effect profile more favorable than with TCAs, SSRI

CYP450 3A4 Inducer

- St. John’s wort
  - Cyclosporine
    - Result: Transplanted organ rejection
  - Digoxin
    - Decreased digoxin levels by day 10

Folic Acid Deficiency and Mood Disorder

- Indinavir
  - AUC decreased by 57%
  - Extrapolated 8-h trough by 81%
- Result
  - Increased HIV viral load

- Folic acid (FA)
  - Required for neurotransmitter production including serotonin
  - FA deficiency common in depression
  - Low folate status or lower dietary folate intake=Higher risk for depression, less response to antidepressant treatment
Treatment of Folic Acid Deficiency and Mood Disorder

- Folic acid 500 mcg daily vs. placebo
  - All taking SSRI
  - Marked increase in clinical response in women, but not men, in FA arm
  

Folic Acid Deficiency Genetic Contribution

- MTHFR gene action
  - Critical to multistep process folic acid biotransformation, which in turn make proteins and other important compounds including neurotransmitters

MTHFR Gene Mutation Up to 40% of the Population

- Associated disease states
  - Anencephaly, spina bifida
  - Heart disease, stroke, HTN
  - Mood disorder

- Clinical implication
  - Need to supplement with a FA metabolite such as L-methylfolate

Evidence of L-methylfolate Treatment Effect

- Adjunctive L-methylfolate at 15 mg/day can constitute an effective, safe, and relatively well tolerated treatment strategy for patients with major depressive disorder who have a partial response or no response to SSRIs.


L-methylfolate Sources

- Rx only products
  - Considered medical foods, include L-methylfolate (Deplin®), multivitamin with iron (EnLyte®), multivitamin, prenatal (Optinate®)
- OTC
  - Optimized folate

S-adenosylmethionine (SAM-e®)

- What is it?
  - Naturally occurring molecule found throughout body
  - Synthesis closely linked to vitamin B₁₂ and folate metabolism
  - Role in ≥100 biochemical reactions synthesis, activation and/or metabolism of hormones, neurotransmitters, others
S-adenosylmethionine (continued)

- Role in treatment of mood disorders
  - S-adenosylmethionine supplement 400–800 mg BID to conventional treatment increases remission rates by ~14% after 6 weeks

- Possible adverse effect
  - Increased serotonergic effect with given with SSRI, SNRI, TCA, tramadol

S-adenosylmethionine (continued)

Conclusion

- Understanding the science behind prescribing medications in depression will help you and your patients to choose the best treatment option.

End of Presentation

Thank you for your time and attention.

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Torsades de Ponte Risk with SGA Use