The Versatile “Antidepressant”
A review of the evidence for on and off label uses

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Introductions

• Mark Aksamit – Nothing to disclose
  • Assistant Professor UNMC PA Program
  • Co-Director Psychiatry Department Treatment Resistant Depression Subspecialty
  • Transplant Psychiatry

• Kelly Gassman – Nothing to disclose
  • Addiction Psychiatry Subspecialty
  • Treatment Resistant Depression Subspecialty
Objectives

- Describe the hypothesized roles of specific neurotransmitters and receptors (antidepressants) in treating various psychiatric and medical conditions.
- Explain hypothesized mechanisms of action for various psychotropic medications.
- Evaluate the evidence for on and off-label usage of various psychotropic medications within the context of medical comorbidity.

Overview

Today's Topics

1. Introduction to "antidepressants"
2. Proposed MOAs of various antidepressants
3. Different conditions antidepressants are proposed to help with
4. Review of evidence for & against complementary use in comorbid conditions
"Antidepressants"

- Commonly known to help with various psychiatric conditions
- What is depression?
- Polypharmacy a growing problem

### SSRIs & SNRIs

<table>
<thead>
<tr>
<th>Selective Serotonin Reuptake Inhibitors</th>
<th>Serotonin-Norepinephrine Reuptake Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Desvenlafaxine</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Levomilnacipran</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Milnacipran</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
</tr>
</tbody>
</table>
TCAs

Tricyclic Antidepressants

- Amitriptyline
- Amitriptylineoxide
- Clomipramine
- Desipramine
- Dibenzepin
- Dimetacrine
- Dosulepin
- Doxepin
- Imipramine

- Lofepramine
- Melitracen
- Nitroxazepine
- Nortriptyline
- Noxiptiline
- Opipramol
- Pipofezine
- Protriptyline
- Trimipramine

Other “Antidepressants” of Note

- Bupropion (Norepinephrine-Dopamine Reuptake Inhibitor)
- Mirtazipine (Tetracyclic)
- Vortioxetine (Serotonin Modulator and Stimulator)
- Vilazodone (Serotonin Modulator and Stimulator)
- Esketamine (NMDA antagonist)
- Transcranial Magnetic Stimulation (TMS)
Overview of Medical Conditions

That antidepressants have been proposed to help with

- Migraines
- Neuropathic Pain
- Fibromyalgia
- IBS
- PMS
- Menopause
- Substance Use Disorders

Migraines

Just The Facts

- Affects 15% of the US Population
- Women more than men (2:1)
- More than 4 days per month and functional impairment warrants preventative treatment or combo versus solely abortive therapy (reasonable cut off)
- Goal of prevention is to reduce headache frequency, severity and duration as well as reduce need for and response to acute treatment

- NO FDA APPROVED ANTIDEPRESSANTS
Migraines

Classes of Medications Proposed to Help in Migraine Prevention

- Beta Blockers (Metoprolol, Propranolol, Timolol)
- Antidepressants (Amitriptyline, Venlafaxine)
- Anticonvulsants (Valproate, Topiramate)
- CGRP Antagonists (Erenumab, Fremanezumab, Galcanezumab)

Migraines

Nociceptive Mechanism of Antidepressants in Migraine Prevention

- Serotonergic & Noradrenergic systems are both involved in neuropathic pain and likely migraine pain as well
- Nociceptive properties may be largely related to these effects (NE)
- Better efficacy for drugs that inhibit both NE and 5-HT
- TCAs & SNRIs > SSRIs

NO FDA APPROVED ANTIDEPRESSANTS
Migraines

Antidepressants with Proposed Efficacy in Migraine Prevention

- TCAs
- SSRIs
- SNRIs
- Others

Migraines

**TCAs**

- Complex MOA
  - Prevent re-uptake of 5-HT and NE
  - Anticholinergic & Antihistaminergic activity
  - Degree of monoamine reuptake blockade varies by specific TCA

- Amitriptyline (best evidence for efficacy)
  - Dosing 25-50mg daily, but may increase to 100mg as tolerated/needed
  - Action at alpha1 adrenergic receptor in addition to muscarinic acetylcholine receptors and histamine H1 and H2 receptors. It also blocks Na, Ca, and K channels
  - Level B evidence from American Academy of Neurology/American Academy of Neurology guideline for preventive treatment of episodic migraine in 2012 (probably effective)
    - Drop out rates greater than 20% in these trials (no Level A)
Migraines

TCAs Continued

• Use adjunctively in Mood Disorders (MDD) and Insomnia
• Comorbid Neuropathy/Migraine
• Poor tolerability secondary to SE profile
• Nortriptyline, Doxepin and Protriptyline commonly used, but lack proven efficacy
• Amitriptyline metabolizes to Nortriptyline
• NO FDA APPROVED ANTIDEPRESSANTS

Migraines

SSRIs

• Altered serotonergic function is thought to be an important component in migraine pathophysiology
  • Decreased serotonin levels may lower threshold for internal and external stimuli to trigger migraines
• SSRIs increase serotonin levels at the synaptic cleft
  • 5-HT2C uniquely important
• Fluoxetine most well studied and lacks efficacy
  • Studies too small or significant methodological flaws
  • Fluvoxamine, Sertraline, Escitalopram also studied and negative results
  • Some may benefit, but many cases of migraine/headache worsening
Migraines

SNRIs

- Venlafaxine (75mg-150mg)
  - 1 placebo RCT for migraine prevention: 150mg daily showed statistically significant reduction in headache days per month
  - Comparative study with Amitriptyline showed both were effective (no statistical difference between the two)

- Consider other SNRIs as alternatives if comorbid mood/anxiety disorder, but lack proven efficacy of Venlafaxine

- More SEs including headache worsening and potential for withdrawal in comparison to SSRI, but more evidence to support use

- NO FDA APPROVED ANTIDEPRESSANTS

Migraines

Psychiatric Comorbidity

- Psychiatric Comorbidities are highly prevalent in migraine

- Best suggestion is to limit polypharmacy that is a known problem in this population
  - Utilize treatments with proven efficacy in comorbid conditions

- 2006 FDA black box warning for triptans and SSRI/SNRI used in combo (serotonin syndrome)
  - Review of cases that informed FDA warning found that none met modern criteria of serotonin syndrome
  - Further reviews showed relative risk is extremely low

- Tachyphylaxis
Migraines

Clinical Practice

- Amitriptyline has most evidence to support use
  - If useful in patients with comorbid insomnia/depression
  - Caution if SI as TCAs are toxic in OD
  - Helpful in comorbid neuropathy and musculoskeletal pain
  - Avoid in overweight/obese patient and glaucoma
  - Nortriptyline is reasonable if response, but can’t tolerate (elderly, urinary retention or constipation)

- Venlafaxine usually utilized after 1st line Tx is failed
  - Weight neutral overall, better SE profile, but withdrawal symptoms
  - Easier to use in comorbid depression
  - Other SNRIs make sense although they lack evidence (minimal data)

- Other antidepressants lack proven efficacy

Migraines

Other “Antidepressant” with Potential for Migraine Prevention

- rTMS is an FDA approved Tx modality for Treatment Resistant Depression

- Promising trials and some approved device for treating “pain caused by migraine headache with aura” (sTMS device).

- Current data is lacking
  - rTMS is most promising with moderate evidence that it contributes to reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment
  - Even these studies were not consistent
  - Need better data including more RCTs with standardized protocols
Polling Question!

Which antidepressant has the most evidence to support its (off-label) use for migraine headache prophylaxis?

A. Duloxetine
B. Nortriptyline
C. Amitriptyline
D. Fluoxetine
E. Doxepin
Neuropathic Pain

Just The Facts

- Chronic pain is one of the leading cost burdens to the US Healthcare system
  - Estimates exceed $100 billion annually
- Pain caused by a lesion or disease of the somatosensory nervous system (neuropathic pain)
  - Somatosensory pathways in the peripheral or central nervous system
- Chronic pain and Depression are frequently comorbid
- Pain NT signaling involves 5-HT and NE
  - Dysfunction in signaling helps to clarify comorbidity

Inhibition of monoamine reuptake in the CNS leads to increased amounts of monoamines available in the synaptic cleft

Increased monoamines leads to increased activity of the descending pathways and their antinociceptive effects on pain homeostasis

Analgesic effects that are independent of depression
  - Doses used to treat pain are lower than depression doses
  - Differences in effectiveness amongst classes of antidepressants
  - Analgesic effects appear before mood improvement

Antidepressant classes with proposed effectiveness
  - TCAs
  - SNRIs
  - SSRIs
  - Others (Bupropion)

Nociceptive Mechanism of Action of Antidepressants in Neuropathic Pain
Neuropathic Pain

Antidepressants Proposed to Help in Neuropathic Pain

- **TCAs**
  - Amitriptyline, Clomipramine, Imipramine Nortriptyline, Desipramine

- **SNRIs**
  - Duloxetine, Venlafaxine, Milnaciprin (FM pain)

- **SSRIs**
  - escitalopram, citalopram, fluvoxamine, sertraline, paroxetine, and fluoxetine.
Neuropathic Pain

Antidepressants Proposed to Help in Neuropathic Pain: Tricyclic Antidepressants

• Action at many receptors outside of 5-HT & NE
  • Antagonist at Alpha, NMDA, Histamine & Muscarinic receptors
  • Potent inhibitors of Na and Ca channels

• Reduced use because of SE profile
  • Mostly related to antimuscarinic effects (dry mouth, tachycardia, urinary retention)
  • Alpha blocking leads to hypotensive effects
  • Significant risk of overdose
  • Restricted in elderly (anticholinergic SEs)

• Unknown MOA
  • Likely suppresses the noradrenergic descending inhibitory system producing an antihyperalgesic effect

Neuropathic Pain

Antidepressants Proposed to Help in Neuropathic Pain: Tricyclic Antidepressants

• No TCAs have FDA indication for pain management

• Amitriptyline remains first line for neuropathic pain
  • Has failed to demonstrate consistent benefits in multiple studies
  • Significant bias in many of the studies
  • However, given it’s historical success in real world practice it remains first line

• Nortriptyline
  • Minimal hard evidence to support first line usage, but anecdotal evidence for all TCAs.
  • Studies have varied and not shown consistent efficacy despite use

• Take Home Message
  • TCAs lack robust evidence for use, but supported clinically
  • As always weigh risk versus benefits and individualize plan
Neuropathic Pain

Antidepressants Proposed to Help in Neuropathic Pain: SNRIs

- Suppress neuropathic pain by altering the recovery of noradrenergic descending inhibitory system in the spinal cord
- Common SEs include nausea, dry mouth, insomnia, constipation, fatigue, and increased blood pressure.
- Take time to achieve efficacy & significant risk for W/D symptoms
- Duloxetine has strongest evidence to support use in neuropathic pain, but evidence for use in other etiologies of pain as well
- Venlafaxine possibly effective, but not as much data to support use in comparison to alternatives

Neuropathic Pain

Antidepressants Proposed to Help in Neuropathic Pain: SSRIs

- Poorly defined role in the management of chronic pain
- Inconclusive & inconsistent results
  - Reviewed studies showed significant bias and flaws in methodology
- Not recommended at this time
Table 1: Recommended pharmacotherapy for neuropathic pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>NNT for ≥50% pain relief and ≥95% confidence interval</th>
<th>Adverse effects</th>
<th>Precautions, contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Serotonin reuptake inhibitor; reduce nerve blockage</td>
<td>9.0 (0.4-9.8)</td>
<td>Somnolence, akathisia, constipation</td>
<td>Use of tricyclics</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Voltage-gated calcium channels, which decreases central sensitization</td>
<td>6.3 (0.4-6.6)</td>
<td>Seizures, dizziness, peripheral edema and weight gain</td>
<td>Use of tricyclics</td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Voltage-gated sodium channels, which reduces central sensitization</td>
<td>6.3 (0.4-6.6)</td>
<td>Seizures, dizziness, peripheral edema and weight gain</td>
<td>Use of tricyclics</td>
</tr>
</tbody>
</table>

Adapted from refs. 1, 2, 3, 4.
* The number needed to treat (NNT) for ≥50% pain relief in placebo-controlled trials represents the number of patients needed to treat for one to have significant pain relief as compared to placebo. The higher the NNT, the lower the proportion of responders compared to placebo. 5.
1. Not available in this form.
2. This number comes from small low-moderate quality clinical trials and may have been overestimated. One unpublished clinical trial was negative (NNT infinity) and the NNT in a clinical trial positive to the meta-analysis was 73 (95% CI: 16-164).[10]
Polling Question!

Through what pathway are most antidepressants proposed to improve neuropathic pain?

A. Inhibition of ascending pain transmission
B. Activation of ascending pain transmission
C. Facilitation of descending pain modulation
D. Modulation of voltage-gated calcium channels
E. Blocking voltage-dependent sodium channels
Fibromyalgia

Just The Facts

• Chronic widespread musculoskeletal pain disorder that is often accompanied by fatigue and disrupted sleep, cognitive disturbance, and multiple somatic and psychiatric symptoms

• Centralized pain (nociceptive pain) includes any chronic pain disorder with a primary mode of action in the central nervous system
  - Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain

• Significant Psychiatric comorbidity

• Management typically includes both pharmacological and non-pharmacological interventions

• Only 3 FDA approved medications
  - Pregabalin, duloxetine, and milnacipran

Fibromyalgia

Antidepressants with proposed efficacy

• Evidence supports use of Amitriptyline at low doses as first line for pharmacotherapy
  - Multiple systematic reviews and meta-analysis support superiority of Amitriptyline to other agents (Duloxetine, Milnaciprin)
  - Doses used to treat FM usually lower than depression
  - Desipramine likely a reasonable alternative with less anticholinergic SEs

• FDA indicated medications (Duloxetine, Milnaciprin, Pregablin) used as alternative 1st line therapies
  - Select medication based off of patient’s symptoms
  - Utilize SNRI in prominent fatigue/depression
  - 2010 meta-analysis showed superiority of Duloxetine/Pregablin to Milnaciprin
  - Milnaciprin best utilized in patients with severe fatigue (not FDA approved for depression)
Irritable Bowel Syndrome

Antidepressants with proposed efficacy

- Analgesic properties independent of mood improvement

- TCAs slow intestinal transit time which may benefit IBS with predominant diarrhea
  - Caution in patients with constipation
  - Use low doses

- Mainly effective in abdominal pain associated with IBS
  - Amitriptyline, Nortriptyline, Desipramine & Imipramine have demonstrated efficacy

- Less evidence to support use of SSRIs (Citalopram) & SNRIs
  - Results of studies have been inconsistent
  - Not routinely recommended, but could use if depressive symptoms predominate
Premenstrual Symptoms

Premenstrual syndrome and premenstrual dysphoric disorder

- Symptoms of PMS and PMDD must impair functioning and be relieved at the start of menses

- Symptoms include:
  - Depression/anxiety/irritability
  - Breast pain
  - Bloating/swelling
  - Headaches

- Moderate to severe symptoms warrant pharmacotherapy intervention
  - SSRI/SNRI
  - TCA

Premenstrual Symptoms

For women who do not desire contraception

Three possible regimens:
- Continuous daily administration
- Luteal-phase therapy: started on day 14 – onset of menses
- Symptom-onset therapy: onset – first few days of menses
Premenstrual Symptoms
For women who do not desire contraception

SSRI/SNRIs:
- Sertraline*
- Fluoxetine*
- Paroxetine*
- Citalopram
- Escitalopram
- Fluvoxamine
- Venlafaxine

TCA:
- Clomipramine

* FDA approved for PMDD
Menopause

Hot flushes ("hot flashes"):  
- Associated with a rise of central NE both before and during the episode  
- Maintaining serotonin can reduce this rise which would prevent hyperthermia

Sleep disturbance:  
- ¼-½ of menopausal women complain of sleep difficulties  
- Mostly associated with hot flashes

Menopause

SSRI/SNRIs:  
- Medications:  
  - FDA approved - Paroxetine salt 7.5mg/day  
  - Paroxetine or paroxetine ER 10-25mg/day  
  - Escitalopram 10-20mg/day  
  - Citalopram 10-20mg/day  
  - Venlafaxine 37.5-150mg/day  
  - Desvenlafaxine 50-150mg/day

- Paroxetine exhibited greatest statistically significant reduction in hot flushes

- Venlafaxine works more quickly but has greater incidence of adverse effects (nausea, constipation, elevation in BP)

- Some SSRIs can inhibit CYP2D6 which can result in lower than therapeutic levels of tamoxifen
Menopause

Serotonin multimodal – vortioxetine

### TABLE 3
Changes in menopause-specific symptoms

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Final visit</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>29 (27 to 33.5)</td>
<td>7.5 (3.5 to 16)</td>
<td>.001</td>
</tr>
<tr>
<td>GCS VMS</td>
<td>6 (4 to 6)</td>
<td>2 (0 to 2.9)</td>
<td>.001</td>
</tr>
<tr>
<td>MEN-GOL</td>
<td>8.58 (7.48 to 9.28)</td>
<td>6.44 (5.19 to 7.2)</td>
<td>.001</td>
</tr>
</tbody>
</table>

**Note:**
- Frequency and severity of hot flashes were assessed by daily hot flash diaries.
- GCS: General Climate Hemostatic Scale; GCS VMS: General Climatic Hemostatic Scale subscore; VMS: hot flashes; Q1: interquartile range; MEN-GOL: Menopause-Specific Quality of Life Scale; SD: standard deviation.

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Substance Use Disorders

- Highly comorbid with depression:
  - 3.8x higher risk in those with SUD excluding alcohol
  - 3.1x higher risk in those with alcohol use disorder
  - 54% of those with chronic MDD had lifetime history of SUD

- Substance-induced depression vs substance use as a result of depression

- Treating both the SUD and depression have greater outcomes regardless of an antidepressant's direct effects on substance use

- Caution is needed to ensure antidepressants used do not interact with the substance
Table 1  Factors that suggest primary MDD versus substance-induced depressive disorder

<table>
<thead>
<tr>
<th>Primary MDD</th>
<th>Substance-induced disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective history clearly indicates the onset of depressive symptoms preceded onset of substance use disorder</td>
<td>Retrospective history clearly indicates that substance use disorder preceded onset of depressive symptoms</td>
</tr>
<tr>
<td>Retrospective history clearly indicates that depressive symptoms occurred or persisted during periods of abstinence from substance use for at least 4 weeks or longer</td>
<td>Retrospective history clearly indicates that depressive symptoms persisted during periods of sobriety last 4 weeks or longer</td>
</tr>
<tr>
<td>Family history positive for a first-degree relative with primary MDD</td>
<td>Family history negative for first-degree relative with primary MDD</td>
</tr>
</tbody>
</table>

Fig. 1  When to initiate antidepressant medication treatment in a patient with co-occurring disorders.

Table 2  Possible/obligatory pharmacologic drug-medication interaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction with</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>MAOIs</td>
<td>• Alcohol does not interact with MAOI. However, tyramine found in some wines and beer can result in hypertensive crisis and/or headache</td>
</tr>
<tr>
<td></td>
<td>TCA</td>
<td>• Excessive CNS depression and impaired psychomotor performance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute alcohol use may inhibit metabolism of tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prolonged use of alcohol may stimulate hepatic metabolism of TCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Detoxified alcohol-dependent individual, elimination of imipramine and desipramine were increased</td>
</tr>
<tr>
<td>Cannabis</td>
<td>SSRIs</td>
<td>• Mania</td>
</tr>
<tr>
<td></td>
<td>TCAs</td>
<td>• Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Delirium</td>
</tr>
<tr>
<td>Cocaine</td>
<td>MAOIs</td>
<td>• Hypertensive crisis</td>
</tr>
<tr>
<td>Heroin</td>
<td>MAOIs</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>MDMA</td>
<td>MAOIs</td>
<td>• Hypertensive crisis</td>
</tr>
<tr>
<td></td>
<td>TCA</td>
<td>• Serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS stimulation</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>TCA</td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS stimulation</td>
</tr>
<tr>
<td></td>
<td>MAOIs</td>
<td>• Hypertensive crisis</td>
</tr>
</tbody>
</table>
**Tobacco Use Disorders**

**First line therapies: nicotine replacement, varenicline, bupropion**

**FDA approved: Bupropion SR:**
- Dosing recommendation: 150mg daily x 3 days, then increase to 150mg BID. Stop smoking 1-2 weeks after initiation.
- MOA: Unsure for smoking cessation
  - Preventing reduction of NE and DA during nicotine withdrawal may play a role\(^1\)
  - Non-competitively blocks nAChR subtypes reducing addictive effects of nicotine\(^2\)
  - Anti-smoking effect is separate from antidepressant effect
    - Efficacy equal in those with and without depression
- Pros:
  - May counter weight gain associated with cessation
  - Safe for use with co-morbid CVD and COPD
- Cons
  - Less effective than varenicline
  - Lowers seizure threshold

**Second line therapy: nortriptyline – tricyclic antidepressant**

**Off-label: Nortriptyline 75mg daily:**
- MOA: Unsure – possibly via noradrenergic and dopaminergic mechanisms\(^2\)
  - Anti-smoking effect is separate from antidepressant effect
- Pros:
  - Possibly similar rates of abstinence as bupropion and NRT (more head to head studies needed) More cost effective
- Cons
  - Possible unpleasant adverse anti-cholinergic effects (dry mouth, sedation)
  - Psychotherapy needed for sustained abstinence in context of depressive symptoms
Tobacco Use Disorders

Other possible therapies -- not FDA approved

- Doxepin 150mg/day – tricyclic antidepressant
  - May decrease withdrawal effects and cravings
  - Larger studies with extended follow-up needed

- SSRIs
  - Fluoxetine 30mg and 60mg – enhanced quit rates but lacks long-term abstinence
    - Could be due to trial structure
    - May improve withdrawal symptoms and weight gain
  - Paroxetine – short term abstinence achieved but high rates of return
  - Sertraline – may lower withdrawal symptoms and act as negative reinforcement
    - Increases of serotonin by sertraline and nicotine result in nausea

Other possible therapies -- not FDA approved

Methamphetamine Use

Mirtazapine (off-label):

Bupropion (off-label):

- May be beneficial for males with light methamphetamine use
- Modulating dopamine neurotransmission may alleviate withdrawal symptoms
Other substances

- Cocaine: no evidence of similar effects from mirtazapine or bupropion
- Alcohol and opioid: other non-antidepressant medications shown more efficacious for treatment of substance use

Polling Question!

Preventing the reduction of which of the following neurotransmitters is hypothesized as bupropion’s mechanism of action for smoking cessation?

A. Norepinephrine and dopamine
B. Dopamine and serotonin
C. Serotonin and norepinephrine
D. Norepinephrine and epinephrine
E. Dopamine and endogenous opioids