Self-Assessment 2: Treatment-Resistant Mood and Anxiety Disorders
Learning Objective

• Apply evidence-based strategies to the treatment of patients with treatment-resistant mood and anxiety disorders
DEPRESSION
A 48-year-old woman with a history of treatment-resistant depression is currently taking duloxetine 60 mg/day with partial response as well as trazodone 50 mg/day for insomnia. She states that she feels empty and useless, and she admits to having thoughts of death. She states that she does not have plans to kill herself because it would harm her family and pets. Her clinician decides to try tranylcypromine, a monoamine oxidase inhibitor (MAOI) and one of the few agents that she has not yet tried. Which of the patient's current medications would you discontinue BEFORE initiating tranylcypromine?

1. Duloxetine
2. Trazodone
3. Both duloxetine and trazodone
4. Neither duloxetine nor trazodone
1. Duloxetine

Because of the risk of serotonin toxicity, complete washout of duloxetine is necessary before starting an MAOI.

*5-7 days for most drugs; 5 weeks for fluoxetine

**Titration schedule for MAOI may differ depending on the individual agent.

2. Trazodone

Although trazodone does have serotonin reuptake inhibition at antidepressant doses (150 mg or higher), this property is not clinically relevant at the low doses used for insomnia.

Trazodone as an Antidepressant
(150–600 mg)

Trazodone as a Hypnotic
(25–150 mg)

In fact, because there is a required gap in antidepressant treatment when switching to or from an MAO inhibitor, low-dose trazodone can be useful as a bridging agent when switching.

**Bridging Agents (With Cautious Monitoring)**
- Benzodiazepines
- Z-drug sedative-hypnotics
- Trazodone (low dose)
- Lamotrigine, valproate, topiramate
- Oxcarbazepine, carbamazepine
- Gabapentin, pregabalin
- Stimulants
- Atypical antipsychotics (except perhaps ziprasidone)

Which medication must be discontinued BEFORE initiating tranylcypromine?

3. Both duloxetine and trazodone

4. Neither duloxetine nor trazodone
A 52-year-old man presents to the emergency room with symptoms of hypertensive crisis after an evening dining out with friends. He is currently taking an MAO inhibitor. Which of the following foods must be avoided by patients taking MAO inhibitors?

1. Fresh fish
2. Aged cheese
3. Bottled beer
4. All of these must be avoided
5. None of these must be avoided
no vasoconstriction
no ↑ BP

= high (40-mg) tyramine meal
no vasoconstriction and hypertension

Tyramine meal = high (40-mg) tyramine meal

1. MAO-A inhibitor stops the enzyme from destroying NE

2. Vasoconstriction and hypertension

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Hypertensive Crisis

- Defined by diastolic blood pressure > 120 mmHg
- Potentially fatal reaction characterized by:
  - Occipital headache that may radiate frontally
  - Palpitation
  - Neck stiffness or soreness
  - Nausea
  - Vomiting
  - Sweating (sometimes with fever)
  - Dilated pupils, photophobia
  - Tachycardia or bradycardia, which can be associated with constricting chest pain
How Much Tyramine Is Dangerous With Irreversible MAO-A Inhibitors?

- **BRAIN**
  - tranylcypromine and phenelzine
  - high-dose transdermal selegiline
  - low-dose transdermal selegiline
  - oral low-dose selegiline
  - oral tyramine alone, fasting

- **GUT**
  - 10 mg
  - 80 mg
  - 250 mg
  - 400 mg
  - 400 mg+

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Which of the following foods must be avoided by patients taking MAO inhibitors?

1. Fresh fish  
2. Aged cheese  
3. Bottled beer  
4. All of these must be avoided  
5. None of these must be avoided

- Fresh fish: low tyramine content
- Bottled beer: low tyramine content
Dietary Guidelines for Patients Taking MAO Inhibitors

<table>
<thead>
<tr>
<th>Foods to Avoid*</th>
<th>Foods Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish</td>
<td>Fresh or processed fish, meat, and poultry; properly stored pickled or smoked fish</td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese</td>
</tr>
<tr>
<td>Tap and unpasteurized beer</td>
<td>Canned or bottled beer and alcohol</td>
</tr>
<tr>
<td>Marmite</td>
<td>Brewer’s and baker’s yeast</td>
</tr>
<tr>
<td>Soy products/tofu</td>
<td>Peanuts</td>
</tr>
<tr>
<td>Sauerkraut, kimchee</td>
<td>Bananas, avocados, raspberries</td>
</tr>
<tr>
<td>Banana peel</td>
<td></td>
</tr>
<tr>
<td>Tyramine-containing nutritional supplement</td>
<td></td>
</tr>
</tbody>
</table>

*Not necessary for 6-mg transdermal or low-dose oral selegiline.
After being treated with sertraline for over a year, a 23-year-old man continues to suffer from significant symptoms of depressed mood and intermittent anxiety. He has recently been admitted to a substance dependence treatment program for alcohol use (up to 15 drinks per day for the last 2 years) and has been sober for 2 weeks. Psychotherapy within the program reveals that his depressed mood predated the start of his heavy drinking. There is no current suicidal ideation and no history of attempted suicide. At this point, the patient has discontinued sertraline by choice. Is he a reasonable candidate for transcranial magnetic stimulation (TMS)?

1. No; he has only had 1 medication trial, and at least 2 failed trials are required before considering TMS
2. No; there is possible alteration of consciousness due to the need of anesthesia, which would interfere with his psychotherapy
3. No; his recent alcohol dependence is a contraindication for TMS
4. Yes; he fulfills criteria to qualify for a trial of TMS
1. No; he has only had 1 medication trial, and at least 2 failed trials are required before considering TMS

- Approved for treatment-resistant depression
  - Failed at least 1 pharmacological trial in current episode
  - Based on a multisite, sham-controlled, randomized trial of high-frequency TMS over left DLPFC

- Meta-analyses show small to moderate benefit
  - Include earlier studies; later studies have better sham

- Low-frequency right-sided stimulation also shows efficacy

- Bi- vs. unilateral stimulation shows no difference

- Positive unpublished study of an FDA-approved coil that can stimulate deeper regions of the cortex

2. No; there is possible alteration of consciousness due to the need of anesthesia, which would interfere with his psychotherapy.

1. Electromagnetic coil on scalp: magnetic field penetrates skull by a few cm

2. Depolarizes neurons in superficial cortex

3. Through neural pathways, this local stimulation causes functional changes in other brain regions

2. No; there is possible alteration of consciousness due to the need of anesthesia, which would interfere with his psychotherapy.

- Generally done on an outpatient basis
- No anesthesia, no loss of consciousness
- Pulses of the magnetic field are delivered in 30-s intervals
  - 4 s each, 26-s rest intervals, 10 pulses/s
  - Feels/sounds like light tapping on the scalp (patient and staff should wear protective earplugs)
- Side effects
  - Headache, discomfort at site of stimulation
  - Rare risk of generalized seizure
- Session length: typically 30–50 min
- Treatment duration: typically 5 treatments/week for 4–6 weeks
3. No; his recent alcohol dependence is a contraindication for TMS

Contraindications
Patients with ferromagnetic metal within 30 cm of the coil

Caution
Patients with an implantable device controlled by physiological signs

4. Yes; he fulfills criteria to qualify for a trial of TMS
A 34-year-old woman with a current major depressive episode has failed to respond to an adequate trial of an SSRI. She and her clinician have decided to try transcranial magnetic stimulation (TMS). What is an appropriate therapeutic dose?

1. <30% of motor threshold
2. 30–60% of motor threshold
3. 60–90% of motor threshold
4. 90–120% of motor threshold
TMS: Therapeutic Dose

1. <30% of motor threshold
2. 30–60% of motor threshold
3. 60–90% of motor threshold
4. 90–120% of motor threshold

Motor Threshold = Magnetic field strength that results in movement of right thumb
A 36-year-old woman is suffering from her third major depressive episode. She has not experienced improvement despite adequate trials of several antidepressants, and she is now undergoing electroconvulsive therapy (ECT). She did not respond until the ninth session, but she has shown progressive improvement following the tenth, eleventh, and twelfth sessions. What would be the recommended next step for this patient?

1. Discontinue ECT and switch to a medication treatment
2. Continue ECT until she reaches a plateau of improvement, then initiate medication treatment
3. Continue ECT indefinitely (barring any significant side effects) to prevent relapse
1. Discontinue ECT and switch to a medication treatment

- Typical acute course is 6–12 treatments
- However, due to her progressive improvement, it would not be recommended to stop yet
- Relapse rates are higher if ECT is discontinued prematurely

2. Continue ECT until she reaches a plateau of improvement, then initiate medication treatment

- Yes; treatment should continue until symptoms remit or plateau
- High relapse rates following remission
- No clear evidence to support any particular medicine for maintaining response after ECT
  - Best research suggests nortriptyline, lithium, venlafaxine
Maximum recommended sessions:

20 (generally)

ECT in Practice

• Frequency can affect memory effects; patients may not have sufficient time to recover prior to the next session

• Right unilateral may have fewer memory effects than bilateral

• Urgent situations (eg, suicidality): bitemporal ECT

• Less severe situations: high-dose right unilateral ECT

A 36-year-old woman with longstanding depression is currently experiencing a severe episode characterized by depressed mood, hypersomnia, lack of pleasure, and suicidality. She has not responded to multiple medication trials, including first-line agents, augmentation strategies, and a monoamine oxidase inhibitor. She has also failed to respond to electroconvulsive therapy. Her treatment team is now considering ketamine based on a current leading hypothesis that posits that depression may be related to:

1. Glutamate hypoactivity
2. Glutamate hyperactivity
3. NMDA receptor hypofunctioning
4. NMDA receptor hyperfunctioning
A current leading hypothesis posits that depression may be related to:

1. **Glutamate hypoactivity**  
   [Crossed out]

2. **Glutamate hyperactivity**  
   [Tick]

The depressed brain shows signs of inadequate neuroplasticity and excessive glutamate

---

Beyond Monoamines: The Neuroplasticity Hypothesis of Depression

Acting on monoaminergic systems, current antidepressants may lead to downstream improvement in neuroplasticity and glutamatergic neurotransmission.
Activation of cAMP response element binding protein (CREB)

Genes turned on or off
- Increased expression of AMPA receptor subunits
- Increased proteins involved in neuroplasticity (e.g., BDNF)
- Downregulation of NMDA receptors
- Decreased release of glutamate

Increased neuroplasticity and reduced glutamatergic neurotransmission
Directly targeting glutamatergic neurotransmission or neuroplasticity may lead to faster treatment response and improve response and remission rates.
Ketamine Increases Synaptic Plasticity

AMPA receptor blocked by ketamine

ERK, AKT

mTOR

NMDA receptor

glu
Ketamine Rapidly Increases the Density and Function of the Dendritic Spines of Layer V Pyramidal Neurons in the Prefrontal Cortex

Bottom slide shows regeneration of synaptic connections in group receiving ketamine compared to control group (Courtesy of Yale University)
A current leading hypothesis posits that depression may be related to:

3. NMDA receptor hypofunctioning

4. NMDA receptor hyperfunctioning

Ketamine is an NMDA blocker; however, many other anti-glutamatergic agents being investigated in treatment-resistant depression have different mechanisms of action than NMDA blockade.
PANIC DISORDER
A 24-year-old man was diagnosed with panic disorder 1 year ago. He was initially treated with paroxetine but did not respond. He then received sertraline, but he experienced intolerable activation and chose to discontinue before a full therapeutic trial had been completed. For the last 6 months, he has been maintained on alprazolam XR with good control of his panic attacks. At last month's appointment, he complained for the first time of depressed mood and lack of energy, but these symptoms were assessed to be mild, and the patient was not interested in attempting another antidepressant. He now presents complaining of breakthrough anxiety, including 2 full panic attacks in the last week, 1 of which occurred while he was driving. He also admits that he began taking St. John's wort for his mood symptoms soon after his last appointment. Could the patient's apparent breakthrough symptoms be due to his use of St. John's wort?

1. Yes; St. John's wort frequently causes short-term activation as a side effect
2. Yes; St. John's wort reduces blood levels of alprazolam and thus may reduce its efficacy
3. No; St. John's wort neither typically causes activation nor interacts with alprazolam
2. Yes; St. John's wort reduces blood levels of alprazolam and thus may reduce its efficacy
St. John's Wort: Active Compounds

Hypericin

- Basis for formulation standardization*
- Unclear what amount is necessary

Hyperforin

- Unclear therapeutic effects
- Responsible for drug interactions
- Content often not disclosed*

*Hyperforin is unstable and degrades rapidly under ambient conditions.
Butterweck V. In: Botanical Medicine: From Bench to Bedside. 2009;
## Drug Interactions Between St. John's Wort and Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on levels</th>
<th>Mechanism</th>
<th>Possible clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENZODIAZEPINES</td>
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<tr>
<td>Alprazolam</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Midazolam</td>
<td>↓</td>
<td>3A4</td>
<td>Drug failure due to NTI</td>
</tr>
<tr>
<td>Quazepam</td>
<td>↓</td>
<td>3A4, 2C19</td>
<td>Reduced efficacy</td>
</tr>
</tbody>
</table>

St. John's Wort and Concomitant Drug Recommendations

Do not take

• With immunosuppressants
• With anti-HIV drugs
• With anticancer drugs
• With digoxin
• With anticoagulants
• For 2–3 weeks before surgery

Other cautions

• With other drugs metabolized by 3A4, P-glycoprotein, 1A2
• With SSRIs or MAOIs
Could the patient's breakthrough symptoms be due to St. John's wort?

1. Yes; St. John's wort frequently causes short-term activation as a side effect
   Side effects are mild and include nausea, constipation, dry mouth, headache, restlessness, tiredness, dizziness

3. No; St. John's wort neither typically causes activation nor interacts with alprazolam
POSTTRAUMATIC STRESS DISORDER
A 38-year-old man with a history of treatment-resistant PTSD has now experienced improvement on quetiapine 300 mg/day, duloxetine 90 mg/day, and zolpidem 10 mg at bedtime. However, he complains of ongoing nightmares and difficulty staying asleep. He was previously initiated on prazosin 3 mg at bedtime, but he experienced intolerable dizziness, and it was discontinued. Can this patient be rechallenged with prazosin? If so, at what dose?

1. Yes; dose should be initiated at 1 mg at bedtime
2. Yes; dose should be initiated at 3 mg at bedtime
3. No; prazosin is contraindicated with quetiapine
4. No; prazosin should not be reattempted in patients with previous intolerability
Prazosin and Contraindications

3. No; prazosin is contraindicated with quetiapine

4. No; prazosin should not be reattempted in patients with previous intolerability

Contraindications

Proven allergy to quinazolines or prazosin
(cancer: eg, gefitinib, erlotinib;
prostatic hyperplasia: eg, alfuzosin, bunazosin)

Noradrenergic Hyperactivity During Sleep May Activate Traumatic Memories

Blocking Alpha-1 Adrenergic Receptors May Reduce Noradrenergic Hyperactivation

Prazosin and Dosing

1. Yes; dose should be initiated at 1 mg at bedtime

2. Yes; dose should be initiated at 3 mg at bedtime

**Initial dose: 1 mg at bedtime**

Risk of "first dose effect" syncope with sudden loss of consciousness (1%) with an initial dose of at least 2 mg

Slow titration (1 mg every 2–3 days) also decreases risk of syncope

Prazosin in Practice

• Therapeutic dose
  – No formal guidelines
  – 1–16 mg/day (divided)
  – Several ongoing high-dose clinical trials
  – Increase until nightmares resolve
  – Smaller dose during the day for persistent hyperarousal and reexperiencing

• Side effects
  – Dizziness, headache, drowsiness, lack of energy, weakness, palpitations, nausea
  – Generally decrease with time

• Notable interactions
  – Diuretics, other antihypertensive drugs

A 54-year-old woman with PTSD has been taking part in exposure therapy but continues to experience troubling symptoms. Adjunct treatment with a selective serotonin reuptake inhibitor (SSRI) has not enhanced her response to exposure therapy. Her clinician is considering enrolling the patient in a clinical trial that will assess the effects of MDMA as an adjunct to psychotherapy. One possible explanation for why MDMA may be beneficial as an adjunct to psychotherapy is because it:

1. Increases norepinephrine and cortisol
2. Decreases norepinephrine and cortisol
Mechanism of MDMA

Increases release of:

- 5HT
- NE
- Cortisol
- Oxytocin

White CM. Ann Pharmacother 2014;Epub ahead of print.
Fear Conditioning vs. Fear Extinction

VMPFC
hippocampus
lateral amygdala

VMPFC
hippocampus
sensory cortex
thalamus

intercalated cell mass
central amygdala

= glutamate
= GABA

fear conditioning

no fear response

fear conditioning

no fear response

fear conditioning

fear response!!!

fear extinction

renewal

fear extinction

no fear response

Exposure and Cognitive Therapy
Strengthen Extinction

MDMA Strengthens Effects of Therapy

- Increases activity in VMPFC, decreases activity in amygdala
- Increases oxytocin
  - Trust, empathy—therapeutic alliance
- Increases NE and cortisol
  - Increased anxiety during extinction is facilitatory, while decreased anxiety can actually interfere with extinction learning

MDMA: Improvement on Clinician-Administered PTSD Scale (CAPS)

A 28-year-old combat veteran with PTSD has not responded to multiple trials of oral medication. He suffers from nightmares, rarely maintains sleep longer than 2 hours, and has lost interest in his family life, which is particularly difficult for his wife given that she is pregnant with their first child. The role of glutamate in traumatic memory formation and extinction suggests that ketamine may be beneficial; however, the potential side effect profile of ketamine could also be concerning for patients with PTSD. In a recent controlled proof-of-concept study in PTSD, ketamine:

1. Did not reduce PTSD symptoms and caused transient worsening of dissociative symptoms
2. Did not reduce PTSD symptoms and caused sustained worsening of dissociative symptoms
3. Reduced PTSD symptoms and caused transient worsening of dissociative symptoms
4. Reduced PTSD symptoms and caused sustained worsening of dissociative symptoms
Ketamine Strengthens Extinction?

Ketamine:

1. Did not reduce PTSD symptoms and caused transient worsening of dissociative symptoms
2. Did not reduce PTSD symptoms and caused sustained worsening of dissociative symptoms
3. Reduced PTSD symptoms and caused transient worsening of dissociative symptoms
4. Reduced PTSD symptoms and caused sustained worsening of dissociative symptoms
Ketamine Reduced PTSD Symptom Severity

IES-R Total Score

Baseline Day 1 Day 2 Day 3 Day 7

IES-R: Impact of Event Scale-Revised (primary endpoint).
Feder A et al. JAMA Psychiatry 2014;Epub ahead of print;
Ketamine:

3. Reduced PTSD symptoms and caused transient worsening of dissociative symptoms

4. Reduced PTSD symptoms and caused sustained worsening of dissociative symptoms
Ketamine Did Not Cause Sustained Worsening of Dissociative Symptoms

CADDS: Clinician-Administered Dissociative States Scale.
Feder A et al. JAMA Psychiatry 2014;Epub ahead of print;
OBSESSIVE COMPULSIVE DISORDER
Pretest Question

A 57-year-old man presents with depression and a history of obsessive compulsive symptoms that began in his twenties and are mostly religious in nature. He has not responded to numerous previous trials of serotonergic medications at typical depression doses. He fairly recently began cognitive behavioral therapy and has responded well to it; however, he continues to experience significant symptoms of OCD, rating his symptoms a 7/10 in severity. His current medications include fluoxetine 80 mg/day and trazodone 50 mg/night. Which of the following is true regarding the appropriate dosing of SSRIs in OCD?

1. Doses are typically lower than those in depression
2. Doses are typically the same as those in depression
3. Doses are typically higher than those in depression
Which of the following is true regarding the appropriate dosing of SSRIs in OCD?

1. Doses are typically lower than those in depression (X)
2. Doses are typically the same as those in depression (X)
3. Doses are typically higher than those in depression (√)
SSRI Dosing in OCD

• Treatment resistance in OCD ranges from 40–60%

• Approved medications include clomipramine and fluvoxamine; however, all SSRIs (including clomipramine) are generally considered to be comparably effective

• SNRIs (venlafaxine, duloxetine, milnacipran, tricyclic antidepressants) and MAOIs may also be effective but are not well studied in OCD

• Appropriate trial duration is typically at least 12 weeks
SSRI Doses in OCD Are Typically Higher Than Those in Depression

- Higher doses of SSRIs than those used in depression are often needed in OCD, in many cases exceeding the recommended maximum dose.

<table>
<thead>
<tr>
<th>Recommended Daily Doses for OCD</th>
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</thead>
<tbody>
<tr>
<td>citalopram</td>
</tr>
<tr>
<td>clomipramine</td>
</tr>
<tr>
<td>escitalopram</td>
</tr>
<tr>
<td>fluoxetine</td>
</tr>
<tr>
<td>fluvoxamine</td>
</tr>
<tr>
<td>paroxetine</td>
</tr>
<tr>
<td>sertraline</td>
</tr>
</tbody>
</table>

Abudy A et al. CNS Drugs 2011;25(7):585-96.
Pretest Question

A 35-year-old woman with obsessive compulsive disorder has not responded to clomipramine 250 mg/day. Her clinician is considering adding fluvoxamine. Which pharmacokinetic interaction can take place between these 2 agents?

1. Clomipramine can induce metabolism of fluvoxamine
2. Clomipramine can inhibit metabolism of fluvoxamine
3. Fluvoxamine can induce metabolism of clomipramine
4. Fluvoxamine can inhibit metabolism of clomipramine
Which pharmacokinetic interaction can take place between these 2 agents?

1. Clomipramine can induce metabolism of fluvoxamine  **X**
2. Clomipramine can inhibit metabolism of fluvoxamine  **X**
3. Fluvoxamine can induce metabolism of clomipramine  **X**
4. Fluvoxamine can inhibit metabolism of clomipramine  

**Substrate**
- Clomipramine: 1A2, 2D6
- Fluvoxamine: 1A2, 2C19, 3A4

**Inhibitor**
- Clomipramine: --
- Fluvoxamine: 1A2

**Inducer**
- Clomipramine: --
- Fluvoxamine: --

Metabolism of Clomipramine

Inhibition of CYP450 1A2 by Fluvoxamine
Combining Clomipramine With Fluvoxamine

• Rationale: serotoninergic effect of the combination will be greater than with either agent alone

• Risks: 5HT overstimulation, QTc prolongation, seizures, myoclonic jerks

• In practice:
  – Generally use low doses of each drug
  – Monitor plasma levels* of clomipramine and desmethylclomipramine, especially if clomipramine dose is >75 mg/day
  – Consider divided dosing or sustained release of clomipramine to lower peak blood levels

*See appendix.
## Important Drug Interactions With St. John's Wort

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on levels</th>
<th>Mechanism</th>
<th>Possible clinical effect</th>
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<tbody>
<tr>
<td><strong>IMMUNOSUPPRESSANTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>↓</td>
<td>3A4 P-glycoprotein</td>
<td>Organ rejection</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↓</td>
<td>3A4 P-glycoprotein</td>
<td>Organ rejection</td>
</tr>
<tr>
<td><strong>ANTI-HIV DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>↓</td>
<td>3A4 P-glycoprotein</td>
<td>Drug failure due to NTI</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↓</td>
<td>3A4</td>
<td>Drug failure</td>
</tr>
<tr>
<td><strong>ANTICANCER DRUGS</strong></td>
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<td>Irinotecan</td>
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<td>Imatinib</td>
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<tr>
<td><strong>HORMONE THERAPIES</strong></td>
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<tr>
<td>Oral contraceptives</td>
<td>↓</td>
<td>3A4</td>
<td>Intermenstrual bleeding Reduced efficacy</td>
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<tr>
<td><strong>ANTICOAGULANTS</strong></td>
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<tr>
<td>Warfarin</td>
<td>↓</td>
<td>3A4</td>
<td>Drug failure due to NTI</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↓</td>
<td>3A4 P-glycoprotein</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Apixaban</td>
<td>↓</td>
<td>3A4 P-glycoprotein</td>
<td>Reduced efficacy</td>
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<tr>
<td><strong>ANTIHYPERLIPIDEMICS</strong></td>
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<tr>
<td>Simvastatin</td>
<td>↓</td>
<td>3A4 P-glycoprotein</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>ANESTHETIC</strong></td>
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<td></td>
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<tr>
<td>Fentanyl, propofol, sevoflurane in O2, nitrous oxide</td>
<td></td>
<td>Unknown</td>
<td>Delayed emergence</td>
</tr>
</tbody>
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<tr>
<th>Drug</th>
<th>Effect on levels</th>
<th>Mechanism</th>
<th>Possible clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BENZODIAZEPINES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Midazolam</td>
<td>↓</td>
<td>3A4</td>
<td>Drug failure due to NTI</td>
</tr>
<tr>
<td>Quazepam</td>
<td>↓</td>
<td>3A4, 2C19</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>SEROTONERGIC DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>↓</td>
<td>3A4</td>
<td>Drug failure due to NTI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-glycoprotein</td>
<td></td>
</tr>
<tr>
<td>SRI</td>
<td></td>
<td>Additive</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td>MAOI</td>
<td></td>
<td>Additive</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td><strong>OPIOID WITHDRAWAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>↓</td>
<td>3A4</td>
<td>Withdrawal symptoms</td>
</tr>
</tbody>
</table>
## Important Drug Interactions With St. John's Wort

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on levels</th>
<th>Mechanism</th>
<th>Possible clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CALCIUM CHANNEL BLOCKERS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Verapamil</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>BETA-ADRENERGIC BLOCKERS</strong></td>
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<td>Talinolol</td>
<td>↓</td>
<td>P-glycoprotein</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>ANTIANGINAL</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ivabradine</td>
<td>↓</td>
<td>3A4</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>CARDIAC INOTROPIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>↓</td>
<td>P-glycoprotein</td>
<td>Drug failure due to NTI</td>
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<tr>
<td><strong>ANTIPLATELET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>↓</td>
<td>3A4</td>
<td>Enhanced actions (prodrug)</td>
</tr>
</tbody>
</table>

## Important Drug Interactions With St. John's Wort

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<tr>
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<th>Possible clinical effect</th>
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<tbody>
<tr>
<td><strong>CENTRAL MUSCLE RELAXANT</strong></td>
<td></td>
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<tr>
<td>Chlorzoxazone</td>
<td>↓</td>
<td>2E1</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
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<tr>
<td>Fexofenadine</td>
<td>↓</td>
<td>P-glycoprotein</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>HYPOGLYCEMIC</strong></td>
<td></td>
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</tr>
<tr>
<td>Gliclazide</td>
<td>↓</td>
<td>2C9?</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>ANTIMICROBIC</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Voriconazole</td>
<td>↓</td>
<td>3A4, 2C19</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td><strong>GI DRUGS</strong></td>
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</tr>
<tr>
<td>Omeprazole</td>
<td>↓</td>
<td>3A4, 2C19</td>
<td>Reduced efficacy</td>
</tr>
</tbody>
</table>

# Plasma Levels of Clomipramine and Desmethylclomipramine

<table>
<thead>
<tr>
<th>Author</th>
<th>Clomipramine</th>
<th>Desmethylclomipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhagwagar Z</td>
<td>30–250 ng/mL</td>
<td>150–500 ng/mL</td>
</tr>
<tr>
<td>Baldessarini</td>
<td>150–500 ng/mL</td>
<td>(no breakdown provided)</td>
</tr>
<tr>
<td>Stein DJ</td>
<td>&lt;450 ng/mL combined (trough)</td>
<td></td>
</tr>
</tbody>
</table>

Baldessarini RJ. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. 2001;
Stein DJ, Fineberg NA. Obsessive-Compulsive Disorder. 2007.