Drug Effects and Depression Severity: A Patient-Level Meta-analysis: JAMA 2010
Fournier et al:
Antidepressant medications represent the best established treatment for major depressive disorder, but there is little evidence that they have a specific pharmacological effect relative to pill placebo for patients with less severe depression.

Date from 6 studies, 718 patients
Paroxetine and imipramine only medication studied
Hamilton used as outcome instrument

Efficacy of antidepressants: a re-analysis and re-interpretation of the Kirsch data: Fountoulakis and Moller 2010

Overall the results suggest that although a large percentage of the placebo response is due to expectancy this is not true for the active drug and effects are not additive. The drug effect is always present and is unrelated to depression severity, while this is not true for placebo.

Interaction between Genes and Experience
5-HTT Polymorphism and MDD

Interaction between Genes and Experience
Antidepressant Medications: Indications

- Depression
  - Major depressive disorder
  - Depressed phase of bipolar disorder
  - Dysthymia
  - Depression associated with axis II disorder
  - Adjustment disorder
  - Grief
  - Post cocaine depression
  - Illness Vs enhancement
  - How to combine with other therapy

Antidepressant Medications: Other Indications

- Anxiety
  - Generalized Anxiety GAD
  - Panic
  - OCD
  - PTSD
  - Social Phobia
  - Bulimia
  - Fibromyalgia
  - Neurogenic pain
  - Migraine headaches
  - Smoking cessation
  - Insomnia

Antidepressants and manic switch

- Adding antidepressant to mood stabilizer may not help with depression
- Risk of switch to mania
  - tricyclics
  - SNRIs: [venlafaxine [Effexor]]
  - SSRIs [sertraline [Zoloft]] > bupropion [Wellbutrin]
Antidepressant Medication and Suicide Ideation [and suicide risk]

- Increase in suicide ideation and behavior
  - Epidemiological associations in children
  - Some epidemiological association in adults
  - Reports of increased in obsessive thinking of suicide
- No clear increase in suicides
  - Increased period of use associated with decrease in completed suicides
- Activation/obsession/coming out of depression

Drug-Drug interactions

Pharmacokinetic: raises or lowers serum level of another medication, ex fluvoxamine (Luvox) can increase clozapine levels or fluoxetine (Prozac) can increase amitriptyline levels

Phamacokinetic: interactions in action, ex tramadol (Ultram) has major risk for serotonin syndrome when given with MAOI, and some risk when given with SSRI or SNRI

Treatment Goals for Patients With MDD


STAR-D Remission Data:

The Overall Remission Rate in Level 1 Was 32.9% (N=943/2876), Based on the QIDS-SR

Fava et al Am J Psychiat 2008; 165: 342-351
Classes of antidepressant medications

- SSRI/SNRI
- Presynaptic agonists
- Bupropion
- Tricyclic antidepressants
- MAOI
- other

SSRI (Selective Serotonin Re-uptake Inhibitor)

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Paxil)
- fluvoxamine (Luvox)
- citalopram (Celexa)
- escitalopram (Lexapro)

SSRIs: Relatively Selective, Not Completely Selective

Different SSRIs have different receptor bindings

SSRI

Clearly work through mechanisms other than just blocking serotonin reuptake
- Time course is too long
- Dose requirement is too high
- Differences in response to different medications
SSRI side effects
- Generally very safe, and very well tolerated
  - Transient but common
    - Headache, nausea
    - Agitation, sleep disturbance, nightmares
    - EPS (extra pyramidal [motor] side effects)
  - Excessive Sweating
  - Sexual side effects
  - Weight gain—more over time
  - Drug-Drug interactions
    - More with some SSRIs than others
    - Serotonin syndrome
  - Withdrawal syndrome from SSRIs
  - Increased tendency to bruise/bleed

SSRI/SNRI and sexual side effects
- 40% of patients have some sexual dysfunction, (\(\delta\) desire, \(\delta\) lubrication/erection, \(\delta\) orgasm)
  - Antidotes without proven efficacy:
    - Mianserin, cyproheptadine, Ginkgo biloba, amantadine, loratadine
  - Antidotes with very limited research support
    - Buproprion, buspirone
  - Selective phosphodiesterase-5 inhibitors
    - Sildenafil (Viagra)

Antidepressant induced sodium reduction (Hyponatremia)
- \(<135\) (mild) headache, decreased concentration, cramps, confusion, weakness, nausea
- \(<130\) (moderate)
- \(<125\) (severe) delirium, seizures, coma, decerebrate posture, death

Reported with all antidepressants, usually early (one report 17% in elderly)

Serotonin Syndrome
- Increased risk with two or more antidepressants
- Clinical symptoms typically begin within 24 hrs of starting or increasing dose—often within 2 hours
  1) cognitive or mental-status changes (e.g., agitation, confusion, delirium, hallucinations,
  2) neuromuscular abnormalities (clonus, hyperreflexia, increased muscle tone, rigidity, shivering, tremor)
  3) autonomic hyperactivity symptoms (diaphoresis, diarrhea, fever, flushing, hypotension or hypertension, mydriasis, increased respiratory rate, tachycardia

SSNRI: selective serotonin and norepinephrine re-uptake blocker
- Venlafaxine (Effexor) \([5HT>>NE]\)
- Duloxetine (Cymbalta)
- Desvenlafaxine (Pristiq)
- Levomilnacipran (FETZIMA) \([NE>5HT]\)
  - May be more effective (probably not)
  - Higher incidence of high blood pressure
  - SSNRI probably more effective than SSRI in pain

Adverse Events: Duloxetine and Fluoxetine

<table>
<thead>
<tr>
<th>Most Frequent Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine (n = 77)</td>
</tr>
<tr>
<td>Fluoxetine 20 mg/day (n = 33)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

*The duloxetine dosage protocol involved a fixed-dose regimen, starting with 40 mgiday and increased at weekly intervals to a maximum of 120 mg/day in 2 weeks. 10% 20 mg placebo.
Dual action medications
indirect or pre-synaptic mechanism

- **Trazodone:**
  - Very short acting—Very sedating
  - Rare risk of priapism [1:8000 men]
  - Commonly used as sleep aid
  - Dry mouth, weight gain
- **Nefazadone (Serzone):**
  - Rare but very serious liver problems
  - Well tolerated: some sedation, some weight gain
  - Few sexual side effects
  - Twice a day, start low, increase dose over time
  - Significant drug-drug interactions

Newer Antidepressants

- **Vilaxodone (Vybrid):** SSRI and 5 HT1A agonist
- **Vortioxetine (Brintellix):** SSRI + HT1A agonist +
- **Levomilnacipran (Fetzima):** SNRI

Bupropion (Wellbutrin)
Mechanism of action unclear: no significant effect on dopamine serotonin or norepinephrine reuptake blockade:

- No sexual side effects (and may reverse sexual side effects of other medications)
- Activating, not sedating
- May be less helpful in anxiety disorders
- Useful to decrease nicotine (?) and other addictive craving
- Slight increase risk of seizures

Tricyclic Antidepressants

- **Amitriptyline (Elavil):**
- **Imipramine (Tofranil):**
- **Nortriptyline (Pamelor):**
- **Desipramine (Norpramin):**
- **Doxepin (Sinequan):**
- **Clomipramine (Anafranil):** [OCD]

### SSRIs vs TCAs

<table>
<thead>
<tr>
<th></th>
<th>Relative Effect Size</th>
<th>N (Patients)</th>
<th>Favors TCAs</th>
<th>Favors SSRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td></td>
<td>101 (10,496)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatients</td>
<td></td>
<td>25 (1377)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatients</td>
<td></td>
<td>56 (7834)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High HAM-D score</td>
<td></td>
<td>38 (3336)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HAM-D score</td>
<td></td>
<td>39 (4645)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonergic TCAs</td>
<td></td>
<td>48 (5317)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenergic TCAs</td>
<td></td>
<td>53 (5179)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAM-D = Hamilton Depression Scale.
Tricyclic Antidepressant Receptor Activity

Sedating Antidepressants for Insomnia
- trazodone
- doxepine (in VERY low dose)
- amitriptyline

MAOIs: Monoamine Oxidase Inhibitors
Action on Serotonin, Norepinephrine and Dopamine
Phenelzine (Nardil)
Tranylcypromine (Parnate)
- May may work when other medications do not
- Many many food and drug interactions
  - Can cause high blood pressure crisis if a
    tyramine containing food is eaten
  - Risk of serotonin syndrome with drug-drug interaction
- Orthostatic BP drop, weight gain, sexual side effects

MAOIs: drug-drug interactions
Can be used with trazodone, antipsychotics, benzodiazepines, other hypnotics
Medications formally contra-indicated, but data suggests risk may be less
- Sympathomimetics (pseudoed, cold meds)
- Decongestant nasal sprays
- Carbamazepine/oxcarbazepine (similar to tricylics)
- Bupropion may be worth cautiously considering in
  special cases: other antidepressants more dangerous

Augmentation Strategies: the art beyond the science
- Two (or more) antidepressants
  - Bupropion or mirtazapine + SSRI or SSNI
- Antipsychotic + antidepressant
  - Good data in psychotic depression
  - Fair data in refractory depression and OCD
- Lithium
- Other mood stabilizers
- Misc: buspirone (buspar), pindolol (Viskin),
  stimulants, atomoxetine (Strattera)

Other things that might be worth trying
- Folic acid
- Omega 3 fatty acids
- Folic acid
- St. John’s wort
Pregnancy and Antidepressants

- Slight increased risk of cardiac malformations with paroxetine (Paxil) exposure.
- Slight increased risk of permanent pulmonary hypertension in newborn with exposure to SSRIs after 20th week of pregnancy. From 2:1000 baseline to 12:1000.
- Withdrawal symptoms common in newborns of women taking SSRI at birth.
- Paroxetine and fluoxetine may carry more risk than other SSRIs.

Other Biological Treatment for Depression

- Sleep deprivation: effective but not practical.
- ECT: effective, safe, probably underused.
  - Problem with politics and stigma.
  - Problem with relapse.
  - Maintenance ECT an outpatient option.
- VNS: Vagal Nerve Stimulation.
  - Now FDA approved.
  - Surgical procedure.
  - Takes months to be effective, up to 30% of very treatment resistant patients.

Transcranial Magnetic Stimulation (TMS)

- Meta analysis with outcome data from 25 studies.
- Total N = 1317.

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active TMS: 699</td>
<td>250 (36%)</td>
</tr>
<tr>
<td>Sham TMS: 618</td>
<td>93 (15%)</td>
</tr>
</tbody>
</table>

670 Studies would be needed to bring p value to 0.05.

Allan et al: Neuropsychobiology 2011: 64 164-169

Ketamine:


Other possible medications for depression (NOT FDA approved)

- Botox
  - Facial nerves connected to brain regions controlling mood and emotion.
- Diclofenac and Minocycline
  - Both with anti-inflammatory effects.

’Tis better to hunt in fields for health unbought,
Than fee the doctor for nauseous draught.
God never meant his works for man to mend.
The wise for cure on exercise depend.

Dryden
Unadjusted mean scores (with 95% confidence intervals) on the Hamilton Rating Scale for Depression (HRSD) over time.

M. Belvederi Murri et al. BJPsych 2015;207:235-242

Other Biological Treatment for Depression

- Exercise: effective for mild to moderate depression
  - Few side effects
  - Low cost
  - Compliance an issue
- St John’s Wort: [most prescribed antidepressant in Germany]
  - Recent controlled trials did not support use
  - Many drug-drug interactions
- Stimulants: amphetamines, modafanil, etc
- Light therapy (for seasonal affective disorder)

Light Vs Fluoxetine Vs Placebo for Adults with Non-seasonal Major Depression

Mean Ham-D 22
CGI severity 4.5

Lam et al JAMA Psychiatry Nov 18, 2015

Augmentation of antidepressants with 2nd generation antipsychotics

- Risperidone (not FDA approved)
- Olanzapine (only approved in combination with fluoxetine)
- Quetiapine (only XR form is FDA approved)
- Aripiprazole
- Lurasidone

Citalopram Response in STAR*D: Remission in Only One-Third

Depressive Symptoms (QIDS-SR Score) After up to 12 Weeks of Antidepressant Treatment

Michael Thase 2011

Meta-Analysis of Response Rates in Double-Blind, Placebo-Controlled, Atypical Augmentation Trials

Michael Thase 2011
When treatment does not work, THINK
• Alcohol and other substance abuse
• Medical Illness
• Other prescribed or OTC medication
• Non-adherence with prescribed medication

Treatment of Anxiety and Sleep Problems
Ronald J Diamond M.D.

DSM 5: Organization of Anxiety Disorders
Anxiety disorders: fear based
Panic
Phobias, Agoraphobia
Social Phobia
Generalized Anxiety Disorder:
Obsessive-Compulsive Disorder:
Post Traumatic Stress Disorder:
Performance Anxiety:

Anxiety Disorders
• Anxiety: fear based disorders: benzodiazepines, SSRIs
  Panic: benzodiazepines, SSRIs
  Phobias, Agoraphobia, Social Phobia
  Generalized Anxiety Disorder:
  Obsessive-Compulsive Disorder: SSRIs, clomipramine
  Post Traumatic Stress Disorder: PTSD:
    alpha 1 agonists, alpha 2 antagonists
  Dissociative Disorders: ?? No meds clearly effective
  Performance Anxiety: beta-blocker (propranolol)

Common Causes of Anxiety
• Caffeine
• Stimulants
• Alcohol withdrawal
• Prescribed medications

Treatment of Anxiety: when to consider medication
• What is going on in the person’s life?
• What drugs/alcohol is the person now using?
• What is the person doing to try and be less anxious, and how well is it working?
• What does the person do to “self-sooth”
• How good is the person at tolerating anxiety and distress?
• What is the person doing that is making the anxiety worse?
  Do not get overwhelmed by the person’s distress
Anxiolytics: Anti-anxiety Medications
Benzodiazepines [all are potentially addictive]
  • Diazepam (Valium)
  • Chlordiazepoxide (Librium)
  • Lorazepam (Ativan)
  • Clonazepam (Klonopin)
  • Alprazolam (Xanax)
Buspar (buspirone)
SSRI/SNRI "antidepressants" [generally preferred]
Antipsychotic medications [as seen on TV]
Gabapentin and pregabalin (Lyrica)

Benzodiazepines
  • Non-specific: bind to all BZP receptors
  • Specific receptors
    – Sleep
    – Anxiety
    – Anti-convulsant

Benzodiazepines
  • Very effective
  • All work rapidly
  • Most people use them without problem
  • Can be used long term as well as short term
  • All are to some extent "cross tolerant" with each other and with alcohol
  • Safe in overdose UNLESS combined with alcohol or other medication

Benzodiazepines
  • All can cause intoxication, drowsiness, impaired driving
  • May cause "disinhibition" in some people
  • Can cause confusion or memory impairment, especially in older people
  • Use with extreme caution in people who already abuse alcohol or other drugs
  • Must be discontinued slowly. Abruptly stopping can cause medical dangerous withdrawal
  • Increase fall risk in the elderly

Benzodiazepine Kinetics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset</th>
<th>Half-life</th>
<th>Duration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>30 min</td>
<td>12-15 hr</td>
<td>3-4 hr</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>30 min</td>
<td>50-100 hr</td>
<td>4-6 hr</td>
<td>5 mg</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>15-30 min</td>
<td>40-114 hr</td>
<td>10-30 hr</td>
<td>15 mg</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>30-60 min</td>
<td>10-20 hr</td>
<td>4-6 hr</td>
<td>1 mg</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>60 min</td>
<td>18-50 hr</td>
<td>6-8 hr</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>2 hr</td>
<td>24-96 hr</td>
<td>4-6 hr</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

adapted from Drug Information Handbook 2000/2001
Carlat Report July/Aug 2011
**Benzodiazepine Use in the United States**

![Graph showing the percentage of the US population using benzodiazepines by sex and age from 2008.](image)

**Figure Legend:**
- **Buspirone (Buspar):**
  - Completely different mechanism of action
  - [5HT partial agonist]
  - Not addicting, not easily abusable
  - Takes days to weeks to work (like antidepressants)
  - Not useful in panic or phobias when used alone, but *could* be useful to augment other medications

---

**SSRI/SNRI “antidepressants”**

- All have good general anti-anxiety properties
- Effective in panic, general anxiety, OCD
- Not subject to abuse

**BUT**

- Takes a while to work
- May cause initial agitation/increase in anxiety
- Side effects

---

**Antipsychotic Medications for Anxiety**

- They work, but...
- NOT FDA approved
- Quetiapine (Seroquel) most commonly used

---

**Performance Anxiety: Beta-blockers**

**Propranolol (Inderol)**

- **Indications:**
  - Tremor
  - Performance anxiety
  - Rage reactions
  - Askathisia

---

**PTSD:**

decreases nightmares, startle

**Alpha_2-adrenergic receptor agonist**

- Stimulates alpha2 adrenergic receptors
  - Clonidine (Catapress)
  - Guanfacine (Tenex)
  - [alpha2 agonists also help decrease opiate craving/withdrawal]

**Alpha_1-adrenergic receptor antagonist**

- Prazosin (Minipress)
**Anxiety: anticonvulsants**

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)

Approved for neuropathic pain
Approved for fibromyalgia (pregabalin)
Not FDA approved for anxiety
Dizziness, sedation and wt gain

**Insomnia and its treatment**

Problems caused by Insomnia:
- Daytime sleepiness
- Fatigue
- Poor concentration
- Dysfunction
- Irritability
- Medical problems/GI/HA

Primary Vs. Secondary Insomnia

"Insomnia is very common. Try not to lose any sleep over it."

**Insomnia:**

<table>
<thead>
<tr>
<th>Depression</th>
<th>Heavy smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Alcohol withdrawal</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Boredom</td>
</tr>
<tr>
<td>PTSD/fear</td>
<td>Caffeine</td>
</tr>
</tbody>
</table>

**Narcolepsy and other specific sleep disorders**

**Restless Legs Syndrome**

- Strong urge to move legs
- Symptoms worse at night
- Symptoms worse with inactivity
- Temporary relief with movement
Insomnia: Medical Causes

<table>
<thead>
<tr>
<th>Medical Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor sleep hygiene</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
</tr>
<tr>
<td>Sleep apnea</td>
</tr>
<tr>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Arthritis and other chronic pain</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>Functional bowel syndrome</td>
</tr>
<tr>
<td>Gastro-esophageal reflux</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Huntington disease</td>
</tr>
<tr>
<td>Menopause</td>
</tr>
<tr>
<td>Nocturia</td>
</tr>
<tr>
<td>Parkinson disease</td>
</tr>
<tr>
<td>Progressive Supranuclear Palsy</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
</tbody>
</table>

Complex Behaviors During Sleep

“You were talking in your sleep again.”

Sleeping pills:

- Benzodiazepines are GABA receptor agonists
- Newer hypnotics are more specific
  - GABA A receptor agonists

Ramelteon (Rozerem) is melatonin receptor agonist
- No abuse potential
- Increases prolactin in women

Suvorexant (Belsomra)
- Blocks orexins—neuropeptides responsible for arousal

Hypnotics (sleeping pills)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Serum half-life</th>
<th>Speed of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem (Ambien)</td>
<td>2.5</td>
<td>+++</td>
</tr>
<tr>
<td>Zolpidem CR (Ambien CR)</td>
<td>2.8</td>
<td>+++</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>1</td>
<td>+++++</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>6</td>
<td>+++++</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>3-25</td>
<td>++</td>
</tr>
<tr>
<td>Estazolam (Prosom)</td>
<td>10-24</td>
<td>+++</td>
</tr>
<tr>
<td>Trazodone</td>
<td>4-9</td>
<td>+++</td>
</tr>
<tr>
<td>(diphenhydramine) Benadryl</td>
<td>1-3</td>
<td>++</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>48-150</td>
<td>+++</td>
</tr>
</tbody>
</table>

Remelteon (Rozerem)

Selective melatonin agonist: 17 times greater affinity for MT1 and MT2 than melatonin
  - MT1 agonism: sleep promoting
  - MT2 agonism: synchronize circadian clock

Half-life 1-2.6 hrs
8 mg single size dose, takes days or longer to work
No effect on COPD or sleep apnea
Take 30 min prior to bed
Remelteon (Rozerem)
4 studies with polysomnography
• Decreased sleep latency 7.5 - 15.7 minutes
• Increased total sleep time 11.6-19.0 minutes

Sedating Antidepressants
• Trazodone
• Doxepin
• Mirtazapine (Remeron)
• Amitriptyline (Elavil)

Other Medications Used as Hypnotics
• Melatonin
• Diphenhyramine (Benadryl)
• Quetiapine (Seroquel)

Antidepressants for insomnia

Advantages
• Inexpensive
• Low abuse potential

Disadvantages
• May be less effective
• Weight gain, daytime sedation, anticholinergic effects
• Risk of bipolar switch into mania

Suvorexant
Orexin antagonist
• Orexin is neuropeptide that binds to orexin receptors 1 and 2 in lateral hypothalamus
• Typical dose 15-20 mg
• Higher doses can cause next day sedation and impairment
• $T_{(\text{max})}$ 2 hr (30-6 hr), half-life approx 12 hrs