

**Regional Osteopathic Medical Education  
 (“ROME”) Meeting – 2011**

**“Psychopharmacology Review and Update  
 for the PCP”**

**Fri., August 19<sup>th</sup>, 2011  
 5:00 pm – 6:00 pm**

**by Ryan M. Smith, D.O.  
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 Ryan.M.Smith@hitchcock.org**

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**A “Blurb” about the speaker:** Dr Smith is a 2010 graduate of the University of New England College of Osteopathic Medicine (UNECOM) in Biddeford, Maine. He is presently in his second-year of residency training (PGY-2) in psychiatry at Dartmouth-Hitchcock Medical Center (Lebanon, NH), after having completed his intern year (PGY-1) in psychiatry at Harvard Medical School (Boston, MA). He is presently very active in the osteopathic profession, serving on UNECOM’s Alumni Association Board of Trustees, the Board of Directors of the Massachusetts Osteopathic Society, the AOA’s Bureau of Hospital Facilities Accreditation, is an AOA Ambassador to the Council of Interns and Residents, etc. Dr Smith is also an Item Writer for NBOME’s COMLEX Levels 1 & 2, as well as COMAT examinations. He is also pursuing his Master’s degree in Medical Education at UNECOM. He is presently a Clinical Lecturer in Psychiatry at UNECOM, and in that role teaches psychopharmacology to the second-year medical students. Future goals/aspirations are university/college mental health, and academic administration/teaching at a College of Osteopathic Medicine. He lives in the Green Mountains of Vermont.

**Overall Goal of this One Hour Lecture:** To present information about (1) how the student or clinician selects pharmacotherapy for patients suffering from various disorders of the psychiatric system, including but not limited to depression, psychosis, schizophrenia, bipolar disorder (aka manic-depressive disorder), anxiety, attention-issues, and drug abuse, and to (2) introduce the most common drugs used for these applications, including indications, mechanisms of action, side effects, efficacy and information relating to patient compliance. A brief discussion on ECT (and when to refer) will be included. The information will be covered to the depth that a PCP must understand in order to treat his patients with mild-to-moderate co-morbid psychiatric issues effectively. We will also cover some recently-introduced agents that may be encountered by the PCP. Keep in mind we have but one hour, so we will cover as much as we can in that time; that which we do not cover will be provided in your handout for reference at a later date.

**Recommended Reading:** The *Medical Letter* is an excellent resource I encourage you all to look into. Most medical centers and academic institutions provide subscriptions for free to its physicians.

**Learning Objectives:** At the end of this one-hour lecture, the physician should be able to:

- a. List the medications that fall into the classes of antidepressants, antipsychotics, antimanic (bipolar) drugs, sedative-hypnotic drugs, stimulants, and pharmacotherapy for drug abuse;
- b. Understand common side-effects of psychiatric medications, and how to avoid or deal with them;
- c. Understand, in a general sense, when to prescribe a certain medication for a certain indication (i.e., a patient with reactive sadness or bereavement need not necessarily be given medication, but one with MDD should be);
- d. Note key points that the patient should be told when being given a psychiatric medication (i.e., do not stop taking an SSRI after a week if no response);
- e. Choose a “key drug” for a patient, taking into consideration therapeutic benefit, cost, and other social factors.

**Outcomes Measures** (90 days post program):

After attending this lecture, the physician should feel more comfortable both interviewing and prescribing medication to medical patients who have co-morbid psychiatric pathology. PCPs often are not well-versed in psychotropic medication; the main focus of this lecture is to provide an update and some basic guidelines from which the PCP can use to deduce proper treatment, and also understand when to refer to a psychiatrist if the patient is out of the comfort zone of care of that PCP.

Please feel free to send any comments (or corrections/errors) you may find in this handout to [RSmith8@une.edu](mailto:RSmith8@une.edu).

**TASK: COUNT HOW MANY OF THE LETTER "F" APPEAR IN THE FOLLOWING SENTENCE.**

**Count them ONLY ONCE!**

**You have 10 seconds...**

**FINISHED FILES ARE THE RE-  
SULT OF YEARS OF SCIENTIF-  
IC STUDY COMBINED WITH  
THE EXPERIENCE OF YEARS.**

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ANSWER: There are six F's in the sentence...

FINISHED FILES ARE THE RE-  
SULT OF YEARS OF SCIENTIF-  
IC STUDY COMBINED WITH  
THE EXPERIENCE OF YEARS.

There are six F's in the sentence.

A person of average intelligence finds three of them.

If you spotted four, you're above average.

If you got five, you can turn your nose at most anybody.

If you caught six, you are a genius.

## Psychopharmacology Review and Update for the PCP

### I. Introduction

- A. There are several different classes of drugs within the purview of psychopharmacology:
  1. Antidepressant drugs;
  2. Antipsychotic drugs;
  3. Sedative-hypnotic drugs (anxiolytics);
  4. Antimanic drugs;
  5. Alzheimer disorder drugs;
  6. Attention-deficit disorder drugs;
  7. Drugs combating drug abuse.
- B. We will discuss each of the above categories of drugs in-turn, including drug classification, indications, side-effects, toxicities; doses will not be covered due to time limitations
  1. Some discussions will be briefer than others based on the principle of commonality and criticality; also, we must fit this discussion into the confines of one hour!
- C. We will discuss most of the drugs in each class; however, please do not consider this list all-inclusive. The purpose of this handout is to discuss the most commonly-encountered medications you, as a PCP, will encounter

### II. ANTIDEPRESSANTS

- A. Most widely prescribed psychotropic agents
- B. These drugs have both anxiolytic and antidepressant properties
- C. These drugs can be classified into four main groups, as well as a fifth “catchment” category:
  1. Tricyclic antidepressants (TCAs);
  2. Selective serotonin reuptake inhibitors (SSRIs);
  3. Heterocyclic antidepressants, which includes serotonin-norepinephrine reuptake inhibitors (SNRIs);
  4. MAOIs;
  5. Other – bupropion, trazodone, nefazodone.
- D. **Tricyclic Antidepressants** (developed - 1950s)
  1. **MOA:** Block the reuptake of both norepinephrine and serotonin at the presynaptic neuron.
  2. **Clinical Use:** Major depression, bedwetting (imipramine) and OCD (clomipramine), chronic pain syndromes with or without depression (trigeminal neuralgia and RSD).
  3. **Side effects:** TCAs are associated with **troublesome anticholinergic** (think atropine-*urinary retention, constipation, tachycardia, dry mouth, & blurred vision*), **sedative, sexual dysfunction and orthostatic hypotensive** (alpha-blocking) side effects.
    - a. 25-30% of pts discontinue due to side effects.
  4. **Toxicity:** Their side effects limit their use by most physicians, but these drugs are still widely prescribed.
    - a. Quite **cardiotoxic** when taken in overdose – death can result by **arrhythmia** (look for QRS prolongation). So do **BASELINE EKG** on all patients.
    - b. 3 C's: coma, convulsions, cardiotoxicity. Can also see hyperpyrexia (fever over 104F). Confusion and hallucination in the elderly.
    - c. Can also induce **serotonin syndrome** (see discussion under SSRIs).
  5. **Contraindications:** Immediate post-MI, epileptics, pts with glaucoma, pregnant women.
  6. **Generation:** Tertiary generation – more sedation/ACH effects than secondary generation (see list below). Reasonable to take advantage of their side effects [amitriptyline (tertiary), which is sedating, given to a depressed patient who also suffers from insomnia; chronic pain patient who is depressed can be given a TCA].
  7. Often used in patients who have failed to respond to other antidepressants- typically 3rd-line after SSRI/SNRI, and heterocyclic trials.
  8. Blood levels can be obtained which are helpful to guide clinical management. Useful in patients with absorption issues, such as short gut/bowel syndromes.

9. Prominent TCA examples include – in brackets: degree of [sedation/ACH effects (generation)]:

Amitriptyline (Elavil)	[high/high (3')]	Doxepin (Sinequan)	[high/mid (3')]
Clomipramine (Anafranil)	[high/high (3')]	Imipramine (Tofranil)	[mid/mid (3')]
Nortriptyline (Pamelor)	[mid/mid (2')]	Desipramine (Norpramin)	[low/low (2')]

E. **Selective Serotonin Reuptake Inhibitors (SSRIs)** (developed - 1980s)

1. **MOA:** Selectively inhibit the reuptake of serotonin at the presynaptic neuron.
2. **Clinical Use:** Major depression, OCD, bulimia, PTSD, GAD, situational anxiety disorder, panic disorder, social anxiety disorder, trichotillomania, PMDD, dysthymia. Often used in Borderline Personality Disorder (off-label).
3. **Side-effects:** few compared to the TCAs and are not nearly as toxic in overdose.
  - a. OK to prescribe to a patient prone to suicidal ideation.
  - b. Side effects: tension headaches, transient GI sx's, insomnia (co-administer trazodone to Rx), sweating, as well as sexual dysfunction (decreased libido, anorgasmia and 'retarded ejaculation'- yes, this is a real medical term; give Viagra, or co-administer bupropion, or cyproheptadine to Rx this) and decreased spontaneity/apathy, both not transient. 10-15% of pts discontinue due to side effects.
4. Have “**black-box warning**” for increasing suicidality in children – most psychiatrists feel these drugs are safe to use in children/adolescents and in fact their use has led to LOWER suicide rates!
5. **Serotonin syndrome = hypertensive crisis** (delirium, hyperpyrexia, convulsions, hypertension) can result if combined with MAOIs!
6. Citalopram, fluoxetine, paroxetine and sertraline are all generic and CHEAP!
7. These are **popular and useful** agents. **Although the SSRIs are similar to each other in effectiveness, patients who fail to respond to one may respond to another [1].**
  - a. Choice of agent is often based on side effects, drug interaction potential, and cost. All SSRIs are, essentially, equally effective.
8. There are six SSRIs; brief notes for each of these important agents are below (\*=DOC by most clinicians.):
  - a. *Fluvoxamine (Luvox)* - approved ONLY for OCD.
  - b. *Fluoxetine (Prozac)* – approved for depression, PMDD, bulimia. Few withdrawal side effects, long half-life (“Prozac Weekly” formulation). Does inhibit CYP2D6 so has drug-drug interactions.
  - c. *\*Citalopram (Celexa)* and *\*Escitalopram (Lexapro)*, which is citalopram's S isomer, approved for major depression (and GAD-escitalopram). Modest liver effects so few drug-drug interactions. LEAST problematic for sexual side effects. Note: Lexapro is very expensive!
  - d. *Paroxetine (Paxil)* – approved for depression, panic disorder, OCD, social phobia, PTSD, GAD. Hits anxiety hard initially more than the other SSRIs. Several disadvantages – short half-life, frequent sexual dysfunction, weight gain, and severe withdrawal (dizziness, anxiety, irritability, insomnia; takes several months to slowly taper off Paxil). Affects CYP2D6 so has drug-drug interactions.
  - e. *\*Sertraline (Zoloft)* – depression, panic disorder, PTSD, social phobia and social anxiety disorder, PMDD, and OCD in adults and children. SHORT half-life, many withdrawal side effects from rapid discontinuation. Less liver enzyme metabolism so less drug-drug interaction.

F. **Hererocyclic Antidepressants**, including SNRIs (developed - 1990s)

1. **Serotonin-norepinephrine reuptake inhibitors (SNRIs)**
  - a. *Venlafaxine (Effexor and Effexor XR)* – essentially an SSRI at low doses, but SNRI at higher doses.
    - i. **MOA:** potent inhibitor of the reuptake of both serotonin and norepinephrine (as well as dopamine to a smaller extent).

- ii. **Indication:** depression and GAD.
  - iii. **Side effects:** similar to SSRIs, but more initial anxiety and insomnia/sedation, nausea, constipation, and fewer sexual side effects and weight gain issues. Due to its tendency to **increase blood pressure** and its modulative effects on the ANS, it is often used to treat orthostatic intolerance.
    - a) Monitor BP when on this drug and when discontinuing.
  - iv. **Withdrawal: Problematic**, comparable to that of paroxetine; often takes months to d/c this drug.
  - v. Note that there is now a new formulation of this, *desvenlafaxine (Pristiq)*
  - b. Duloxetine (Cymbalta)
    - i. **MOA:** See venlafaxine, above.
    - ii. **Indications:** See venlafaxine, above, but also has indications for treating **chronic pain**, such as fibromyalgia and diabetic neuropathy (as do the TCAs; it is the NE effect that accounts for this).
    - iii. **Side effects:** See venlafaxine, above; however, contraindicated in glaucoma, and serious hepatotoxicity has been reported. Metabolized by CYP2D6 – so use with caution in polypharmacy!
2. “Others”
- a. Bupropion (Wellbutrin)
    - i. **MOA:** Weak NE and S reuptake inhibitor; decreases neuronal dopamine reuptake
    - ii. **Indications:** Depression, atypical depression (symptoms such as hypersomnia, increased appetite and weight, mood reactivity, and excessive fatigue), leaden paralysis
    - iii. **Side effects:** Insomnia, irritability, anxiety, headaches, but **NO** sexual or weight gain side-effects!
      - a) Editorial comment (RS): I have seen patients become extremely hypersexual on Wellbutrin
      - b) Bupropion does not cause the initial calming of the SSRIs – may intensify affects actually [good drug to use in a patient presenting with a flat (numb) affect].
    - iv. **KEY: Avoid in patients with a history of seizure or eating disorder! Decreases seizure threshold!**
    - v. Also marketed as an aid to smoking cessation (Zyban)
    - vi. Used to treat erectile dysfunction in patients already taking an SSRI. Also effective when combining therapy to augment patients already on another antidepressant.
    - vii. This is the \*only\* FDA-approved Rx for prophylaxis of SAD
  - b. Trazodone (Desyrel) and Nefazodone (Serzone)
    - i. **MOA:** Decreases reuptake of serotonin and norepinephrine.
    - ii. **Indications:** Depression; hypnotic.
    - iii. **Side effects:** Sedation, orthostasis/postural hypotension (use with care in elderly). PRIAPISM (sustained erection > 4 hrs – ouch! Surgical emergency!)
    - iv. Clinical note on nefazodone (RS): Rarely used today due to increased liver function tests (LFTs) and risk of hepatotoxicity and liver failure (risk is 1/250000 patient years). Some who have good response choose to use it even knowing the potential toxicity – get informed consent first! \*STOP the medication if LFTs are > 3x Upper Limit of Normal!\*
  - c. Mirtazipine (Remeron)
    - i. **MOA:** Alpha-2 antagonist, increasing the release of norepinephrine and serotonin; also potent 5HT-2 and 5HT-3 antagonist (a tetracyclic antidepressant); more rapid onset than other antidepressants.

- ii. **Indications:** Depression (only).
- iii. **Side effects:** Sedation and increased appetite/weight gain (often good for insomniac and anorexic depressed patients – remember, take advantage of side effects whenever possible!). Can also see increased cholesterol and rarely agranulocytosis.
- d. Note that *atomoxetine (Asendin)* is also an antidepressant – see under Drugs for ADD, later.

G. **Monoamine oxidase inhibitors** (MAOIs) (developed - 1950s)

1. **MOA:** Nonselective MAO inhibition, leading to increased levels of all neurotransmitters (serotonin, dopamine and norepinephrine), and in addition, “tyramine” accumulation (which is natural product of bacterial fermentation processes).
2. **Indications:** Severe depression; atypical depression; hyperchondriasis.
3. Hypertensive crisis = serotonin syndrome (see under SSRI for description). A buildup of tyramine can lead to a hypertensive crisis if excess tyramine is ingested (in cheese, beer, yeast, beans, chopped liver, snails (yum!), chocolate, etc.). Sympathomimetic drugs (TCAs, ephedrine, L-dopa, decongestants, isoniazide, tramadol) may potentiate the MAO inhibitor hypertensive effects. This can be FATAL!
4. **Contraindications:** Meperidine (an opioid), SSRIs, beta-blockers.
5. We are not saying to avoid them – simply use with caution and under the direction of a psychiatrist! If dietary restrictions are respected, they actually are safer and have fewer side effects than the TCAs. They also work in patients who have failed TCA/SSRI/SNRI, etc., trials.
6. Examples of key MAOIs are as follows:

Phenylzine (Nardil)

Tranlycypromine (Parnate)

Isocarboxazide (Marplan)

Selegiline (Emsam) (new- PATCH formulation)

III. **ANTIPSYCHOTICS** (aka “Neuroleptics” or “Major Tranquilizers”)

A. There are TWO major classes of antipsychotics:

1. “Typical,” or “first-generation” and,
2. “Atypical,” or “second-generation.”

B. **Schizophrenia and psychosis linked to excess dopamine in the brain.**

1. Therefore, blocking the activity of dopamine (aka, dopamine antagonism) is the main MOA of all antipsychotic medication
2. *Black Box Warning:* “May cause increased risk of stroke or death in the elderly.”

C. **TYPICAL Antipsychotics** [3] – the Phenothiazines (developed 1960s/1970s)

1. **MOA: Antagonists at the dopamine receptor (D<sub>2</sub>>D<sub>1</sub>)** at the postsynaptic mesolimbic dopaminergic brain receptors (as well as in the nigrostriatal pathway).
2. **Indications:** Schizophrenia and psychosis, as well as in bipolar disorder (manic phase), paranoia, irritability/agitation, Tourette Syndrome, Huntington’s. Note that these affect positive psychotic symptoms ONLY (e.g., hallucinations, delusions, etc.)!
3. **Side effects:** The typical antipsychotics share the same side effects as the TCAs (but not the cardiac toxicity) in addition to having the ability to induce the following:
  - a. **Anticholinergic (muscarinic) side effects** - think atropine-like – examples include urinary retention, constipation, tachycardia, dry mouth, confusion, and blurred vision;
  - b. **Extrapyramidal side effects (EPS)** – there are four classes:
    - i. **Parkinsonian-like effects:** muscular rigidity, flat affect (aka mask-like facies), tremor, and bradykinesia (slowed motor responses).
      - a) Treat with anticholinergic agents, such as benztropine (Cogentin), trihexylphenidyl (Artane), or amantadine;
    - ii. **Akathisia** – uncontrolled sense of inner restlessness.
      - a) Treatment partially controlled with anticholinergic agents (see above), but more successful are drugs like diphenhydramine (Benadryl), propranolol (Inderal), and lorazepam (Ativan);
    - iii. **Acute dystonias** – muscle spasms and prolonged muscular

contractions, usually of the head and neck.

a) Treatment: Anticholinergic agents (see above).

- iv. **Tardive dyskinesia (TD)** – a late-onset EPS. This is very serious and sometimes irreversible. Affects 1/25 pts at 1 year of antipsychotic use, and ¼ after 7 years. Involves involuntary sucking and smacking of the lips and mouth, and can include chorea in the trunk and extremities.

a) Treatment: stop medication. The dyskinesia will worsen initially as it is unmasked; often takes MONTHS for TD to remit.

- v. **Timeline:** Rule of thumb is: 4 hours acute dystonia → 4 days akinesia → 4 weeks akathisia → 4 months tardive dyskinesia. Keep this in mind!

- c. **Neuroleptic Malignant Syndrome (NMS)** – hyperpyrexia (temp > 104F), extrapyramidal rigidity, severe ANS dysfunction, myoglobinuria, lead-pipe rigidity, and sometimes death.

i. Treatment: dantrolene and dopamine agonists

- d. **Endocrine side effects** – dopamine receptor antagonism (at tubuloinfundibular pathway) → hyperprolactinemia → gynecomastia and milk expulsion from the breasts, and amenorrhea

e. There are also **alpha (hypotensive)** and **histaminic (sedative)** properties

- f. **Agranulocytosis** and impaired temperature regulation (thus risk of heat stroke or hypothermia) are rare but do occur.

4. These are often *second-line drugs* over atypicals because of their side-effect profile; they would seldom be used now in initiating Rx by a non-psychiatrist.

- 5. **Potency.** Low potency typicals often have a high (“↑”) rate of ACH side effects, but a low (“↓”) rate of EPS; conversely, high-potency typicals often have a low (“↓”) rate of ACH side effects, but a high (“↑”) rate of EPS. 72-80% dopamine receptor occupancy is required for treatment effect; any higher results in severe side effects.

a. See below for examples of the most commonly encountered typical antipsychotics as well as a handy schema to use to quickly ID side effects of this difficult-to-learn class of meds

**SCHEMA FOR REMEMBERING SIDE-EFFECT PROFILE OF TYPICALS**

Haloperidol (Haldol)	Fluphenazine (Prolixin)	Thiothixine (Navane)	<b>High Potency</b>	<b>High EPS</b>	<b>Low ACH</b>
Perphenazine (Trilafon)	Molindone (Moban)*	Loxitane (Loxapine)	<b>Medium Potency</b>	<b>---</b>	<b>Medium ---</b>
Chlorpromazine (Thorazine)	Trifluoperazine (Stelazine)	Thioridazine (Mellaril)	<b>Low Potency</b>	<b>Low EPS</b>	<b>High ACH</b>

\*Discontinued in 2010

D. **ATYPICAL Antipsychotics** [3] (developed 1990-2000s)

1. **MOA:** Antagonists at both dopamine (D2 and D4) and serotonin receptor (5-HT2A) as well as other receptors (less alpha and histaminic activity than typicals).
2. **Indication:** Same as above for typical antipsychotics. These drugs affect both positive and negative symptoms (blunted affect, poverty of thought, etc) of schizophrenia! In general, atypical antipsychotics are preferred because they are safer, adherence is better, and the risk of tardive dyskinesia is lower [1].
  - a. Also FDA approved for acute mania or mixed bipolar episodes, and for bipolar maintenance treatment.
3. **Side effects:** better side effect profile than the typical antipsychotics and are less likely to induce EPS/tardive dyskinesia especially at lower doses. They may cause NMS.
4. The atypicals are implicated in the “metabolic syndrome,” with **obesity, hyperglycemia, and hyperlipidemia [6].** Hyperglycemia, **sometimes extreme, can occur with these atypical agents.** These agents must be used with caution, and careful monitoring in diabetic patients. **Type II diabetes can result!**
5. Note: atypical are used more frequently than the typical – however there is question as to whether they are more effective overall or even for the Tx of negative symptoms (exception=clozapine, see later).

6. Examples of atypical antipsychotics:
- a. Quetiapine (Seroquel)
    - i. **Indication:** Acute exacerbation of schizophrenia. Often preferred agent in pt with co-morbid depression\*.
    - ii. Association with the development of **cataracts** in dogs – but disproven in humans – for historical interest.
    - iii. Used for patients with Parkinson’s (Lewy Body) Dementia, and in the treatment of anxiety and insomnia by primary care physicians. Commonly used off-label as a **sedative**.
    - iv. **Side-effects:** *Minor QTc prolongation*, possible TD and NMS, weight gain, orthostatic changes.
  - b. \*Olanzapine (Zyprexa)
    - i. **Indications:** Schizophrenia, bipolar mania, psychotic disorders, acute agitation.
    - ii. **Side effect** (most significant): **weight gain**, which can be severe (20-40lbs+, >7% body weight!). Use with caution in obese and diabetic populations! Also **sedating**, so often given QHS. Seizures also reported.
      - a) Raises triglycerides and HbA1c higher than any other atypical. See fat buildup and insulin resistance.
      - b) Smoking increases clearance significantly, and female gender increases clearance by 30%
  - c. \*Risperidone (Risperdal)
    - i. **Indications:** Schizophrenia, dementia of the elderly, bipolar disorder, mania, Tourette disorder, autism.
    - ii. More **activating** and likely weight-neutral. At higher doses, behaves as a typical (similar parkinsonian SE), and can increase prolactin levels! Akathisia and EPS common at high doses.
    - iii. There is a long-acting depo injection formulation, which is expensive (Risperidone CONSTA).
    - iv. Both Zyprexa and Risperdal come in dissolvable formulations (Zydis and Risperdal M-tabs) useful to treat a pt that “cheeks” their medication or when forced administration is required.
  - d. Clozapine (Clozaril)
    - i. **Indication:** Refractory, severe treatment-resistant schizophrenia.
    - ii. Eldest atypical & it may be the most effective agent. It is as effective as haloperidol for positive symptoms and superior to it for negative symptoms, and is effective in decreasing risk for suicide.
    - iii. **Side effects:** Its routine use is limited since it causes **granulocytopenia** or **agranulocytosis** in about 1% of patients. It is used in patients not responding to other drugs (refractory patients); initially weekly, or even twice weekly, blood counts are MANDATORY (WBC & ANC) to monitor the white cell count [1]. If the WBC remains stable on Rx for about 6 months, blood counts may then be done every other week.
      - a) Warning: May cause **myocarditis**, agranulocytosis, **seizures (2-6%, very significant)**, orthostatic BP decrease! Thus contraindicated in epilepsy or leukopenic patients!
  - e. \*Ziprasidone (Geodon)
    - i. **Indications:** Schizophrenia, acute agitation.
    - ii. Most worrisome side effect: QTc prolongation (and possible development of Torsades de Pointes). Contraindicated if QTc > 500 ms and with low pulse.
    - iii. **Contraindicated** in acute post-MI, QRS prolongation, uncompensated HF, meds that increase QTc, and in patients with a history of bulimia or arrhythmias
    - iv. First atypical antipsychotic which is available in an intramuscular (IM)

form. It is not a depot long-acting injection, but a rapid-onset injection marketed as being as effective as haloperidol for rapid sedation but with less side-effect potential.

- v. Do ECG prior to starting this medication! MUST take with food or totally ineffective!
  - f. \*Aripiprazole (Abilify)
    - i. **Indications:** Schizophrenia, bipolar disorder, clinical depression.
    - ii. In general aripiprazole and ziprasidone are not considered potent agents and should not be first line agents for schizophrenia. Many patients with axis II disorders such as borderline personality disorder may be on an antipsychotic.
    - iii. Often a choice drug in **children** as it has few side effects and is not overly potent.
  - g. Iloperidone (Fanapt), Asenapine (Saphris) and \*Paliperidone (Invega) are brand-new medications. Some notes:
    - i. Paliperidone is the major active metabolite of risperidone; has a market in Tx schizoaffective disorder.
    - ii. Iloperidone – high incidence of QTc prolongation
7. **Overall efficacy:**
- a. From Medical Letter: “A meta-analysis of head-to-head comparisons among the other second-generation antipsychotics found a statistical advantage for olanzapine over aripiprazole, quetiapine, risperidone and ziprasidone in reducing psychotic symptoms. Risperidone was also superior to quetiapine and aripiprazole, but quetiapine and ari-piprazole have been found useful for treatment of depressive symptoms. The most recently FDA-approved antipsychotic drugs – paliperidone, asenapine and iloperidone – are effective for some patients, but their advantages relative to other drugs in the class remain to be established.”

#### IV. SEDATIVE-HYPNOTICS AND ANTI-ANXIETY AGENTS

##### A. Benzodiazepines (All are Schedule IV Medications)

1. **MOA:** Bind to benzodiazepine receptors, potentiating the effect of the inhibitory neurotransmitter GABA by increasing the frequency of chloride channel opening at the GABA-A receptor, which leads to decreased neuronal firing (“calming” effect).
2. **Indications:** \*ACUTE\*/short-term anxiety and panic attacks, and as sedatives, hypnotics, anticonvulsants (status epilepticus – use lorazepam and diazepam), detoxification (especially ETOH withdrawal to Rx DTs), skeletal muscle relaxants, night terrors, sleepwalking. We must be judicious in our use!
3. Note that the *Medical Letter* suggests that for most patients with an anxiety disorder, even without concomitant depression, an antidepressant, usually an SSRI, is the drug of first choice.
  - a. Benzodiazepines are also effective for most forms of anxiety, but are potentially addicting & have limited benefit in OCD or PTSD [1]. May use anxiolytics while patients are being titrated on antidepressant as it takes 4-6 weeks before antidepressant effects will be noticed.
4. **Side effects:** Somnolence, interference with psychomotor performance, impaired memory, addiction potential (increased in those with a predisposition to drug or alcohol abuse).
5. Because of these side effects, the above agents are for ACUTE sx's of anxiety & panic attacks; **SSRIs are preferred for long-term Rx.** (*Med Letter* 2005; 47:5).
6. **Toxicity:** Dependence develops rapidly. Also, additive CNS effects with ETOH. Treat OD with flumazenil, a competitive GABA-A antagonist.
7. Examples of drugs in this class include: (note these drugs end in either "-pam" or "-lam")
  - a. *Alprazolam (Xanax)* - high abuse potential due to short half life.

- i. *Editorial Comment (RS)*: Good to Rx acute panic attack/disorder. Good for little else, as it is HIGHLY addicting.
- b. *Clonazepam (Klonopin)* - less abuse potential due to longer half life, more sedating, helpful with sleep, and used often in mania, for seizures, and for panic.
- c. *Diazepam (Valium)* - outdated drug, often abused. Long half life, may be helpful with treating alcohol withdrawal and delirium tremens (DT).
- d. *Lorazepam (Ativan)* - commonly used for anxiety. Intermediate half-life, often used in-patient with respiratory and cardiac dysfunction and in palliative care.
- e. *Midazolam (Versed)* - mostly used as an induction agent for anesthesia.
- f. *Oxazepam (Serax)* – often used for detoxification from alcohol in patients with liver pathology (metabolized elsewhere).
- g. Examples of other benzos you may encounter: *Chlordiazepoxide (Librium)* – often used in uncomplicated alcohol detoxification, *Chlorazepate (Tranxene)*, *Prazepam (Centrax)*, *Fluorazepam (Dalmane)*, *Triazolam (Halcion)*, *Quazepam (Doral)*, *estazolam (Prosom)*, *ramelteon (Rozerem)*.

## B. Non-Benzodiazepine Sedative-Hypnotics

1. *Bupirone (BuSpar)*
  - a. **MOA:** CNS Serotonin (5HT-1A) receptor agonist.
  - b. **Indications:** Short-term relief of anxiety; occasionally used for GAD\*
  - c. **Side-effects:** Dizziness, headache, nausea (often disappear within a week). Does NOT interact with ETOH.
  - d. It is non-sedating and non-addicting, but it may take up to 4 weeks to act (inform patients of this!) and may be less effective than antidepressants or benzodiazepines for anxiety [1]. Not usually effective at low doses. Don't prescribe for major depression or panic attacks as it is inadequate treatment. Considered by many to be a placebo, as many who have taken benzos state that this drug is ineffective.
    - i. \* More often treated by psychiatrist using SNRIs or SSRIs, but bupirone has a role.
2. *Zolpidem (Ambien)* and *zaleplon (Sonata)* (VERY similar drugs; information below applies to both; Schedule IV Medications)
  - a. **MOA:** See “benzodiazepines,” above. Binds to “specific” benzo receptors.
  - b. **Indication:** Short-term Rx of insomnia.
  - c. **Side-effects:** Same as benzodiazepines (including rare anterograde amnesia). May cause dream like states during the day. Has been associated with driving accidents.
  - d. Has a rapid onset of action and usually little morning residual drowsiness. Tolerance does develop to the drug, so intermittent use is recommended. It has **potential for abuse** & benzodiazepine-like side effects particularly at high doses
3. *Eszopiclone (Lunesta)* (Schedule IV Medication)
  - a. **MOA:** Nonbenzodiazepine hypnotic
  - b. **Indication:** Insomnia.
  - c. **Side effects:** Headache, dizziness, somnolence, hallucinations, unpleasant taste.
  - d. **Important:** High-fat meals decrease absorption and effect!
4. *Hydroxyzine (Vistaril, Atarax)*
  - a. **MOA:** Antihistamine, antianxiety
  - b. **Indication:** Anxiety, sedation. Often used as a sleeping aid.
  - c. **Side effects:** Drowsiness and anticholinergic effects.
5. *Chloral Hydrate (Aquachloral)* (Schedule IV Medication)
  - a. **MOA:** Sedative hypnotic; active metabolite of trichloroethanol
  - b. **Indication:** Short-term nocturnal sedation.
  - c. **Side effects:** GI irritation, drowsiness, ataxia, rash, nightmare
  - d. Note: tolerance can develop after 2 wk of use; use intermittently! Mix in water or fruit juice. AVOID ETOH and CNS Depressants.

- C. **Barbiturates** - These drugs are rarely used in psychiatry now and are often viewed at 3<sup>rd</sup>-line drugs due to abuse and side-effect profiles; these are the eldest group of sedative-hypnotics.
1. **MOA:** Depresses sensory cortex, decreases motor activity, alters cerebellar function, and produces drowsiness, sedation, and hypnosis by facilitation of GABA-A activity through increasing chloride channel opening thus decreasing neuronal firing. Overdose can lead to respiratory depression and coma. (Schedule IV Medications)
  2. **Indications:** Are used as sedatives, hypnotics, as inducers in anesthesia (as for ECT) and occasionally as anticonvulsants.
  3. **Side effects:** Bradycardia, decreased BP, hangover, Stevens Johnson syndrome (rare), blood dyscrasias.
  4. **Toxicity:** Dependence, additive CNS effects with ETOH, respiratory and cardiovascular depression\*\* leading to death, drug interactions due to CYP450.
    - a. Contraindicated in porphyria.

Examples of drugs in this class include:

Phenobarbital (Luminal)

Pentobarbital (Nembutal)

Meprobamate (Equanil)

Secobarbital (Seconal)

Thiopental (Trapanal) – often used in **ECT induction**, along with succinylcholine (Scoline; muscle relaxer)

## V. DRUGS FOR BIPOLAR DISORDER (MANIC-DEPRESSIVE DISORDER)

- A. **Mood stabilizers:** Although lithium continues to be the standard treatment for bipolar disorders in some reviews [1], valproate is also commonly being used [2]. These are the two major agents.
- B. **Lithium (*Eskalith, Lithobid*)**
  1. **MOA:** Alters sodium transport in nerve and muscle cells by inhibiting the phosphoinositol cascade. Its antimanic effects may be the result of increased reuptake of norepinephrine. Some say it “effects shift toward intraneuronal metabolism of catecholamines.”
  2. **Indication:** Classic, euphoric manic episodes of bipolar disorder; blocks relapse into acute mania.
  3. **Side effects:** VERY IMPORTANT – *Learn these, especially **bolded** terms!* Nausea, diarrhea, vomiting, **fine hand tremor**, sedation, muscular weakness, edema, weight gain, dry mouth. Adverse effects from chronic use include **polyuria/polydypsia** leading to **nephrogenic diabetes insipidus** (reversible, as it is an ADH antagonist), **hypothyroidism and goiter**, acne, **leukocytosis** (reversible upon Li discontinuation), **psoriasis, teratogenesis** (first trimester), and kidney damage.
  4. **Toxicity:** Signs include lethargy, ataxia, slurred speech, tinnitus, **severe N/V**, tremor, arrhythmias, hypotension, **seizures**, shock, delirium, coma, and even death.
    - a. Since there is a **narrow therapeutic window** with Li, blood levels and adverse effects must be monitored closely.
    - b. *Clinical Labs of Importance:* **Na+, Ca++, P+, Cr, urinalysis, complete CBC, EKG and thyroid battery with TSH** included. Do **BEFORE** initiating patient on Li, and repeat serially.
    - c. Monitoring lithium levels are important should be between **0.8-1.2 (some say 1.5) mEq/L**. Toxicity seen often in >2 mEq/L levels, but can be seen at much lower doses!
  5. **Li may prevent suicidal risk in bipolar patients in the depressive phase of the illness by up to 82%**
- C. **Valproic acid (*Valproate; Depakote*) and derivatives**
  1. **MOA: Anticonvulsant; increases GABA availability.**
  2. **Indications:** Epilepsy, migraine prophylaxis, and bipolar mania.
  3. **Side effects:** Somnolence, dizziness, GI upset, diplopia, ataxia, rash, **hepatitis, pancreatitis**, prolonged bleeding, alopecia, wt gain, polycystic ovary syndrome (in epileptics).
  4. **Toxicity:** Rare but fatal **hepatotoxicity (monitor LFTs!), neural tube defects in fetus (spina bifida-use birth control!),** tremor, weight gain. Also monitor CBC for potential of **granulocytopenia** and **thrombocytopenia**. Must also monitor **valproate levels** serially (should be between 40 and 150 mcg/mL).

5. Valproate may be as effective as lithium for the treatment of mania [1].
- D. Carbamazepine (Tegretol) and Oxcarbamazepine (Trileptal)
1. **MOA:** Epilepsy, trigeminal neuralgia, ETOH withdrawal. OFF LABEL use for Bipolar Disorder!
  2. **Indication:** Mania, and may be helpful for patients intolerant of or nonresponsive to lithium or valproate [1]. It is not as commonly used as either lithium or valproate.
  3. **Side effects:** Drowsiness, dizziness, blurred vision, nausea/vomiting, rash, hyponatremia.
  4. **Toxicity:** Leukopenia and agranulocytosis – monitor CBC and serum levels!
    - a. Note that this drug has been used off label for mania for years but has NOT been demonstrated to be effective!
- E. Lamotrigine (Lamictal)
1. **MOA:** Decreases glutamate, and thus stabilizes the neuronal membrane.
  2. **Indications:** Partial seizures, bipolar disorder, and the ever-popular Lennox-Gastaut Syndrome.
  3. **Side effects:** Photosensitivity, headache, GI upset, dizziness, ataxia (all usually transient), and Stevens - Johnson syndrome rash (1/1200 risk; if slow induction used, rash is unlikely). If rash appears, discontinue drug immediately.
  4. This medication is good for maintenance in bipolar disorder and for the treatment of depressive episodes in bipolar disorder.
- F. Notes
1. Carbamazepine (Tegretol), oxcarbamazepine (Trileptal), gabapentin (Neurontin), topiramate (Topamax), zonisamide (Zonegran), and tiagabine (Gabitril) have all been used for bipolar disorder, and there is little evidence presently to support their use, but you WILL see these used to Rx bipolar disorder!
  2. **An antipsychotic (olanzapine or risperidone, usually) is often paired with a mood stabilizer, often for control of aggression and irritability in the manic phase of bipolar disorder.**
  3. Editorial Comment (RS): If you have an acutely manic patient, most drugs in this antiepileptic category, along with Lithium, will \*take time\* to work. So do start an agent, but also start an antipsychotic, which will effectively deescalate the manic episode while the other agent is building; the antipsychotic can then be stopped or continued once at therapeutic level

## VI. CHOLINESTERASE INHIBITORS

- A. **MOA:** Centrally-acting cholinesterase inhibition, which enhances ACh activity.
- B. **Indications:** Treatment of mild to moderate dementia of the Alzheimer's type.
- C. **Side effects:** GI upset, N/V/D, dizziness, insomnia, fatigue, tremor, diaphoresis, HA.
- D. Drugs in this class include:
 

donepezil (Aricept)	tacrine (Cognex)
rivastigmine (Exelon) (PATCH formulation!)	galantamine (Reminyl)
- E. Studies suggest these drugs have only a modest effect when started in patients with mild dementia.
- F. Patients will ask about using Vitamin E, however studies have been mixed at this point and no clear benefit has been identified.

## VII. DRUGS FOR ATTENTION-DEFICIT DISORDER (with or without hyperactivity)

- A. Stimulants (Stimulants are Schedule II Medications; HIGHLY addictive and abusable!)
  1. **MOA:** CNS stimulant; increases release directly or indirectly of dopamine, serotonin, and/or norepinephrine.
  2. **Indications:** ADHD, narcolepsy, depression.
  3. **Side effects:** CV and CNS stimulation.
  4. **Caution!** These are drugs of abuse. Use with caution in patients with a substance abuse history. However, note that studies of ADHD children, adolescents and adults without a personal or family history of substance abuse show NO tendency to abuse the stimulants!

Stimulant medications used to treat ADHD:

methylphenidate (Ritalin, Metadate, Concerta)  
dexamethylphenidate (Focalin XR)  
dextroamphetamine (Dexedrine)  
amphetamine (Adderall, Adderall XR)

modafinil (Provigil, Sparlon)  
pemoline (Cylert) - discontinued  
lisdexamfetamine (Vyvanse)

B. Notes:

1. Pemoline (Cylert) has been associated with serious hepatotoxicity, so LFTs must be monitored! Though discontinued in 2006, was asked about COMLEX Level I in early summer 2008!
2. Modafinil (Provigil) (Schedule IV Medication)
  - a. **MOA:** Alters dopamine and NE release and decreases GABA transmission
  - b. **Indications:** ADHD and to Rx obstructive sleep apnea; improve wakefulness in narcolepsy.
  - c. **Side effects:** Toxic epidermal necrolysis, Stevens Johnson Syndrome are reported (rare)
3. Lisdexamfetamine (Vyvanse) – this is a prodrug to dextroamphetamine that is inactive until metabolized in the GI tract – developed to discourage abuse, as there is little euphoria associated. Side effects similar to stimulants (see above).

C. Non-stimulants

1. Atomoxetine (Strattera)
  - a. **MOA:** Not a stimulant but a selective norepinephrine blocker (an antidepressant).
  - b. **Indication:** ADHD only.
  - c. **Side effects:** Tachycardia, weight loss, sexual dysfunction, **severe liver injury** has been rarely reported (DC with jaundice, increased LFTs, or suicidality).
  - d. The *Medical Letter* recently concluded “there is no convincing evidence that atomoxetine is as effective as or as well tolerated as stimulants such as methylphenidate.” Best “reserved for patients who have not responded to or cannot take stimulants” and for those who do not want or cannot take stimulants.
2. Key Note: *Bupropion (Wellbutrin)*, an antidepressant (see under heterocyclic antidepressants, earlier), as well as *clonidine (Catapres)* and *guanfacine (Tenex)*, both alpha-agonists, are also used to treat ADHD

## VIII. DRUGS OF ABUSE

- A. **MOA:** Addictive properties are thought to be due to the release of dopamine in the limbic forebrain.
- B. Drugs commonly abused: Ethanol; stimulants (amphetamine, cocaine, methamphetamine); opioids (morphine, heroin; hallucinogens (LSD, MDMA-ecstasy, phencyclidine (PCP), ketamine); marijuana.
- C. Know the signs of intoxication and of withdrawal for the major drugs of abuse!
- D. **TREATMENT OF DRUG ABUSE**
  1. Disulfiram (Antabuse)
    - a. **MOA:** Inhibits acetaldehyde dehydrogenase, causing acetaldehyde to accumulate, leading to hangover symptoms.
    - b. **Side-effects** (purpose of drug): Skin flushing, increased pulse, diaphoresis, increased respiration, hypotension, chest pain, nausea, copious vomiting, blurred vision (*sounds fun, huh?!).*
    - c. **Toxicity:** Severe reactions can lead to respiratory depression, cardiovascular collapse, cardiac arrhythmias, CHF, seizures and death.
    - d. Only used in patients who secretly want to stop drinking and may be likely to drink on impulse!
  2. Naltrexone (Revia; Trexan)
    - a. **MOA:** Competitive opioid antagonist at mu receptors.
    - b. **Indication:** ETOH and narcotic addiction.
    - c. **Side effects:** Insomnia, GI upset, joint pain, HA, fatigue, rare hepatotoxicity.
    - d. Contraindicated in acute hepatitis, liver failure, opioid use.

- e. Has been shown to reduce cravings for alcohol; may also decrease the euphoric effects of ETOH, leading to decreased consumption when a patient does drink.
- 3. Buprenorphine (Buprenex)
  - a. **MOA:** Opioid agonist/antagonist.
  - b. **Indication:** Severe pain states.
  - c. **Side effects:** hypotension, respiratory depression and sedation.
  - d. \*\*\*Note that *Suboxone* is buprenorphine : naloxone 4:1 preparation.\*\*\*
- 4. Methadone (Dolophine)
  - a. **MOA:** Narcotic analgesic.
  - b. **Indication:** Severe pain; detoxification and maintenance of narcotic addiction.
  - c. **Side effects:** Respiratory depression, sedation, constipation, urinary retention, ventricular arrhythmias, prolongs QTc.
- 5. Acamprosate (Campral)
  - a. **MOA:** Structurally resembles GABA so decreases glutamatergic transmission and modulates neuronal hyperexcitability during withdrawal from alcohol.
  - b. **Indication:** Maintain abstinence from alcohol
  - c. **Side effects:** Generally safe. Diarrhea is the most common side effect; appears dose related. N/V, depression, anxiety. Suicidal ideation and acute renal failure have occurred.

#### IX. ELECTROCONVULSIVE THERAPY

- A. Electrodes placed on scalp (uni- or bi-temporal), electrical impulse passed through brain, causing a generalized convulsive seizure. Pre-treatment is with a short-acting barbiturate (thiopental), and a short-acting muscle relaxant (succinylcholine), which allows the pt to experience only very short-term anesthesia and a significant diminution of the tonic-clonic movements in the generalized seizure. Therapeutic response is correlated with total seizure time. Post-ictally, the pt is confused, disoriented to time/place, and may have a headache or muscle pains, each of these lasting only up to 1 hr. Short-term memory loss can last from several hrs to several days. 80% or more of pts with severe depression respond to ECT. This modality is often used in refractory depression/psychosis/suicidal/homicidal /catatonic patients.
- B. A good rule of thumb for a PCP is to try an agent or two for a disorder; if there is no effect or the patient decompensates, refer to psychiatry for medication management and possible ECT consultation.

#### X. FURTHER (OPTIONAL) READING and CLINICAL WARD REFERENCES:

[1] The Medical Letter. Drugs for Psychiatric Disorders. Treatment Guidelines from *Med Lett* June, 2006; (46) pp. 35-46. Editorial comment (RS): This is an outstanding clinical resource & highly recommended reading. It is available online. This is an excellent summary for Board review (RR)

[2] Belmaker, R.H. Medical Progress: Bipolar disorder. *New Engl. J. Med.* 2004; 351:476  
This is an excellent review of this topic including pharmacotherapy.

[3] Freedman, R. Drug therapy: Schizophrenia. *N. Engl. J. Med.* 2003; 349:1738.

[4] The Medical Letter. Is effexor more effective for depression than an SSRI? *Med Lett.* 2004; 46:15

[5] The Medical Letter. Atypical antipsychotics in the elderly. *Med Lett* 2005; 47:61

[6] Consensus statement. *Diabetes Care* 2004; 27: 596

[7] The Medical Letter. Acamprosate (Campral) for alcoholism. *Med Lett.* 2005; 47:1

[8] Cipriani, A et al. Comparative efficacy and accessibility of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* Vol 373, February 28, 2009.

Editorial Comment (RS): **I HIGHLY recommend** these books for the RIDICULOUSLY SIMPLE series:

- [9] *Clinical Psychopharmacology Made Ridiculously Simple* (6<sup>th</sup> ed, 2009) (whole book=70pgs!)

- [10] *Psychiatry Made Ridiculously Simple* (4<sup>th</sup> ed, 2005) – “Chapter 13: Treatments” (whole book=90pgs!)

[11] The Medical Letter. Drugs for Psychotic Disorders. *Med Lett* 2010; 96:8.

Stahl’s Essential Psychopharmacology, as well as his Prescriber’s Guide, are both \*excellent\* resources which break this complex topic down and make it fun and manageable. Check them out at your library before buying, as they are quite costly (\$250 for the pair).

If you find any corrections or errors or have suggestions for future drug lists or revisions of this list, please email me (RS) at [RSmith8@une.edu](mailto:RSmith8@une.edu). Thanks!