Psychopharmacology Update for Clinicians: What’s new in 2017

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Disclaimers

- Some treatments discussed in this presentation have not been systematically reviewed for efficacy.
- Some pharmacological interventions discussed in this presentation have not been indicated by the FDA for the disorder or age group in question.
- This discussion is based on the author’s personal review of the scientific literature and clinical experience and is not meant to guide clinical practice in any individual case.

Three paradoxes

Paradox 1: After decades of trying, we still don’t understand how – or if – most psychotropics work.

Paradox 2: Likewise, after decades of investigation, we still do not understand causality in neurobiological hypotheses of mental disorders.

Paradox 3: In spite of overwhelming evidence that psychopharmacology alone is ineffective, this remains the treatment that most patients receive – and expect to receive.

The central paradox in modern psychopharmacology

- There is a substantial body of evidence to allow us to conclude that
  - Drug treatment without behavioral interventions is ineffective, but that patients are rarely afforded this combined treatment
  - Combined treatments for common emotional conditions, even severe ones, yield better outcomes in primary care.

- IN SPITE OF THIS EVIDENCE, WE CONTINUE TO PROVIDE INEFFECTIVE TREATMENT
A not-so-sobering thought: How far have we advanced?

- Opium use was probably described in the 9th century BCE by Homer.
- Used medicinally by Sumerians in 3rd millennium BCE.
- Opium named "gil" (joy) and opium plant "hulgil" (plant of joy).
- Likely spread from Sumeria (present-day Iraq) to western world and China.

Slide source: www.decodog.com

Disease versus Drug Centered models of Drug Action
(Moncrieff & Cohen, 2009)

- Disease centered models (the “antibiotic” model): Psychotropics work on specific physiological mechanisms that have gone awry, their action corrects problems and leads to improvements in health.
- Drug centered models: Psychotropics induce complex, global effects, the response to which yields a sense of subjective improvement by patients.
- Examples: Benzodiazepines induce a general sense of calm and wellbeing. It is this nonspecific effect that produces patient response.
- Antipsychotics induce a general sense of emotional indifference and calm: This, rather than any specific neuroreceptor target, results in patient improvement.


A world of nonspecificity

- Nonspecificity, then may not only be a hallmark of psychological interventions, it may be a hallmark of psychopharmacological interventions as well.
- Assumptions of nonspecificity are buttressed by the absence of clear mechanisms of action for almost any class of psychotropic drugs: If serotonin were the “phlogiston of the 20th century” (Hacker), then only serotonergic antidepressants would work.
Repent – the end is near (apologies to Belmaker, The Future of Depression Pharmacology, 2009)

<table>
<thead>
<tr>
<th>TABLE A. Future Directions in Psychopharmacology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked reduction in the rate of new, expensive 'me-too' compounds and stereomere reruns</td>
</tr>
<tr>
<td>Increased therapeutic efficacy as a part of clinicoser: reduction in promises as per STARS®</td>
</tr>
<tr>
<td>Decrease in clinical trials by private cistousers and increase in clinical trials for all patients, including methadone, individualized psychopharmacology and psychotherapy</td>
</tr>
<tr>
<td>Training in basic unbiased questions of psychopharmacology, such as the mechanism of action of chlorpromazine, imipramine, ECT, lithium, and diazepam, and less on 'new' thing</td>
</tr>
</tbody>
</table>

STARS®-Supported Treatment Alternatives to Relieve Depression Study (CTR-electroconvulsive therapy).
Belauner RN. CNS Spectr. Vol 13, No 2, 2008

Whither big PHRMA?

- Numerous pharmacopundits now singing more or less the same tune (on key)
- Fibinger (2012) sums it up:
  - "Not a single mechanistically novel drug has reached the market in the past 30 years"
  - Most big PHRMA companies moving away from neurosciences.
  - No good modeling for genetic bases of most psychiatric disease “…there will never be a coherent biology of schizophrenia…”
  - No good modeling for receptor dysfunction as a basis of disease.
  - Diagnostic taxonomy based on syndromic descriptions of disease "a barrier to progress”


What's happening in mental health drug development?
Alzheimer's is the major target.
Source: Eli Lilly Regulatory Pipeline as of 1/2017

Antidepressants: Whither Ghost®?
(*Apologies to Richard Armour)

- As we shall see, Ketamine is emerging as the Hamlet's Father of antidepressant pharmacology.
- (You see him here, you see him there, but is he really anywhere?)
- Recall the MOA: NMDA (N-methyl d-aspartate) glutamatergic receptor (may as well get it over with early in the show) and the excitatory neurotransmitter GLUTAMATE as putative interventions.
- Glycine (another excitatory NT) and GluN2B receptor subtypes may be implicated in depression.
- Ketamine is antagonist at NMDA receptor:
  - Ketamine exists in isomeric form: R-ketamine may have more ADP action than S-ketamine
  - Metabolites of K may have specific ADP action (2R,6R hydroxynorketamine) (Chaki, 2017; Beyond Ketamine...Ann. Pharmacother., 51(4), 315-322); BUT:
  - Ketamine is a dissociative anesthetic and (rather frightening) drug of abuse.

- Pluses as ADP: Very rapid acting, lacks side effects of standard ADPs
- Minuses as ADP: Dissociative anesthetic, and (rather frightening) drug of abuse.
- Duration of ADP effects uncertain; place in tx uncertain.
Psychopharmacology Epidemiological Snapshot
(from Morrison, T. J., Mattison, D. R., Adult Utilization of Psychiatric Drugs.....Annals of Internal Medicine, Feb. 2017)

- 2013 Medical Expenditure Panel Survey data of adults 18-65
- Survey of use of antidepressants, antipsychotics, and sedative hypnotics
- 16.7% with ≥ 1 Rx for psychotropic
  - 12% using antidepressants
  - 8.3% using sedative hypnotics
  - 1.6% using antipsychotics
- Significant ethnic differences found:
  - 20% Rx use by European-Americans
  - 8.7% of Hispanics
  - African-American, Asian-American slightly lower, not sig different from Hispanics.

Trends in antidepressant utilization
- MEPS data 200-2011 re antidepressants
  - Annual brand name ADP use declined from 51.47M to 7.52M Rx/yr
  - Generic ADP Rx increased from 0 to 88.83M Rx/yr.
  - In same period, payment for brand Rx went up 25%, payment for generics decreased 70%.
- In general, generics decrease cost.
- In general, absence of marketing initiatives decreases overall utilization of any drug class.


The heart of the matter

- The biological fallacy: Misattribution of drug effects on neuronal function as etiological mechanisms for mental illness
  - If, however, the biological fallacy were correct, then
  - Drugs of different classes and different receptor profiles would have differential therapeutic effects (in general, they don’t)
  - All patients with a particular condition would show similar deficits in neurological function (they don’t)
  - Biological and nonbiological interventions would not be shown to have roughly equivalent effects, both behaviorally and in terms of neuronal activity (they often do).
  - Patients without a mental disorder would not respond positively to psychotropics (everybody does better with a little ritalin on board, not just those with ADHD).

Implications for drug development

- Far fewer psychotropic drugs today than there were 50 years ago
  - many nonspecific sedative agents then available have vanished
- This resulted, in part, from consolidation in industry, increased regulatory (FDA) oversight, and effects of DSM-induced tautologies (i.e., ”we have described a disorder with increasing specificity, therefore its treatments must be increasingly specific”)
- Inaccurate or incomplete neurobiological hypotheses have led to pretty much a dead-end. Few new compounds are being synthesized, most marketing consists of tweaks of existing molecules.
This would be just like laughing gas except it’s not very funny.

- Priestley synthesized nitrous oxide in 1722.
- Its anaesthetic properties were quickly recognized.
- But not used in surgery for over 120 years (first use 1844) because:
  - Surgeons prided themselves on speed to minimize pain;
  - Anaesthetics challenged this basic training precept, and;
  - It was commonly accepted that pain was an unavoidable accompaniment of surgery.

Why, then, use psychotropics

- To relieve psychic distress (people indifferent to deprecatory auditory hallucinations are, by definition, less likely to be bothered by them)
- To reduce the severity, but not the time course, of acute psychotic episodes
- To reduce generalized anxiety or agitation by inducing a state of euthymia or eutonia (mostly) or to
- Utilize a drug to counteract the physiological and cognitive effects of a disorder (e.g. counteract the neurovegetative symptoms of depression; assist in sleep induction) or
- Induce a specific drug effect that is judged to be beneficial (enhance attention and concentration with use of psychostimulants)

How, then, to use psychotropics

- Premise #1. All psychotropics are adjunctive, not primary, treatments
  - Exceptions: Psychotic agitation, catatonia, and other acute anxiety states (why the Creator gave us endogenous benzodiazepine receptors)
- Premise #2. Most polypharmacy is mostly irrational when targeting the same symptom complex
  - Exceptions: Psychotic agitation or depression (but these are really two symptom complexes)
- Premise #3. The dose-response curve in clinical psychopharmacology, unlike the world, is more or less flat. Generally, more is not better.

Improvement and side effects as a function of dose increases

Source: Bollini et al., British Journal of Psychiatry, 1999
Combining, Sequencing, Augmenting

- Psychotherapy plus medications yield superior outcomes...but only for conditions where pharmacotherapy is warranted.
- 1. Pharmacology provides more immediate, symptomatic relief, psychotherapy has a longer time of onset but effects more durable.
- 2. Before augmenting meds, assess the adequacy of the treatment plan, including psychological and behavioral interventions.
- 3. Optimize the dose of the initial medication before adding another.
- 4. There is no firm rule for augmenting medications with other medications – but there are exceptions, i.e., things NOT to combine. Target symptoms and drug tolerability are key.

CBT as effective as Rx in preventing relapse

- 8 wks of 2 hour group mindfulness based CBT (nonjudgmental awareness, self-compassion, relapse action plan) following 8 months remission (Rx 20-60 mg citalopram, maintenance venlafaxine up to 375mg/d).
- MCBT relapse equivalent to that mediated by venlafaxine monotherapy.
- Segal, ZV, Beiling, P, Young, T, MacQueen G, Covic, R, et al (2010). ADP monotherapy vs sequential pharmacotherapy and MCBT, or placebo, for relapse prophylaxis. Arch Gen Psychiatry. 67, 1256-1264

Use of Antidepressants more common, psychotherapy less

- Offson and Marcus (2009) data abstracted from Medical Expenditure Panel Survey.
- 20% of US population has sought MH tx (2003), compared to 12% in early-1990’s. Rate of use of ADPs doubled from 13-23M people yearly.
- Most got Rx, not psychotherapy. Less than 20% of those getting an ADP for depression got psychotherapy, compared to 30% a decade ago, but length of psychotherapy remained the same (~8 visits).
- Rate of use of antipsychotics among depressed pts also increased significantly.

The answers are clear: Will we demand that the question be asked?

- Evidence is clear that current use of psychotropics is inadequate and not science informed.
- Evidence equally clear that there are not, and will not ever be, sufficient specialty trained MH prescribers if we rely on the psychiatric pipeline.
- Evidence again clear that psychologists, when given the opportunity, prescribe well, unprescribe well, and yield positive outcomes.
- Will we ask our legislators to take this important step for improving mental health care in each jurisdiction?
Psychotherapy v. Pharmacotherapy?

- Recent major review (Huhn, et al, 2014) of 61 meta-analyses of 21 disorders (852 trials, >137K subjects).
- "Effect sizes of psychotherapies v. placebo tended to be higher than those of medication, but direct comparisons, albeit usually based on few trials, did not reveal consistent differences".
- Individual pharm trials had larger samples, better controls; psychotherapy trials had lower dropout rates and more followup.
- "Effective medication and psychotherapy are available for most of the psychiatric disorders examined...medium effect sizes...direct comparisons of drug therapy and psychotherapy did not show consistent differences...their combinations were often superior."
  

When assessing need for intervention, keep in mind the power of time

- Remember your Cook and Campbell and threats to internal validity: people change as time passes, and regress to the mean.
- In a general medical (not a mental health) sample (n=4009, in 12 cohorts), at followups of 3-49 years, with at least one episode of ‘observer-assessed’ depression:
  - Between 35-60% of participants experienced stable recovery with no further recurrence.
  - Between 75-85% recovered at least once during followup.
  - Recurrence rates varied between 7-65%.
  - 10-17% had a chronic course of depression.
  

Medication, psychotherapy or both in the prevention of depressive relapse in elders: Cochrane Review

- Review of 7 (n=803) studies of continuation and maintenance treatment of depression with Rx, psychotherapy or both in patients > 60 years.
- Only two were head on comparitors, 6 compared Rx with placebo, 2 involved psychotherapy.
- At 6 months, ADP=PLA (placebo)
  - 12 months, ADP>PLA
  - 36 months, ADP=PLA, except that TCAs>PLA
- Psychotherapy = ADP; Combination = ADP alone at 12, 24, 36 months.
- Conclusions: Long term benefits of continuing ADPs in elders unclear, limited evidentiary base.
  

The Really really big question: Pharmacotherapy, Psychotherapy, or Both?

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The really really big question: Pharmacotherapy, psychotherapy or both?

• So, the answer is truly obscure:
  • Effect sizes not great for either treatment
  • Study design suboptimal, in drug tx often designed to favor drug
    » A ‘wait-list’ placebo in psychotherapy does good things to ‘active treatment’ effect size!
  • Uncertain pharmacotherapy literature even after clinical trial registration
    » But publication bias exists for psychotherapy studies too!
  • With these caveats, combined treatment is usually superior


Drugs in pregnancy: FDA safety classification

• Caveat: Most classifications have more to do with how little a drug is studied, not how much.
• Antidepressants
  • Category A: None
  • Category B: Tetracyclic ADPs (maprotiline)
  • Category C: SRI (except paroxetine), SNRAs, TCAs, MAOIs, hypoproin, MIR, NEE, TRAZ, VILAZ, VOR.
  • Category D: BII, NOH, PAR
  • Category X: None
• Sedatives
  » GRAs: Category C: Zolpidem
  » Benzodiazepines
    • Category D: Diazepam, chlordiazepoxide, alprazolam
• Antipsychotics (many FGAs are simply N (not classified)
  • Category B: Lurasidone
  • Category C: Risperidone, olanzapine; quetiapine, paliperidone, haloperidol, pimozide


Changes to FDA pregnancy labels

• Prior categories of A, B, C, D, X removed.
• New system based largely on human, not animal data
• New drug label section
  • 8. Use in specific populations
  • 8.1 Pregnancy
  • 8.2 Lactation

• Fetal risk summary
• Absorption
• If human data are sufficient
  • “Do not indicate risk of…”
  • “Increase risk of [specific developmental abnormality]…”

Sigh: Boring but necessary

Principles of Drug Action

<table>
<thead>
<tr>
<th>Molecular Action</th>
<th>Function</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonist</td>
<td>Activates cellular process by binding fully to receptor</td>
<td>May competitively inhibit activity of full agonist</td>
</tr>
<tr>
<td>Partial Agonist</td>
<td>Binds fully to receptor, but elicits a weaker response</td>
<td></td>
</tr>
<tr>
<td>Inverse Agonist</td>
<td>Binds fully to receptor, but produces opposite effects of agonist</td>
<td></td>
</tr>
<tr>
<td>Antagonist</td>
<td>Binds to receptor but does NOT activate cellular processes</td>
<td></td>
</tr>
<tr>
<td>Competitive (reversible) Antagonist</td>
<td>Competes with agonist for cell binding, higher competitive antagonist levels result in less agonist action</td>
<td></td>
</tr>
<tr>
<td>Noncompetitive (Irreversible) antagonist</td>
<td>Binds tightly and permanently (covalent bond) to receptor; prevents cellular agonist activity</td>
<td></td>
</tr>
<tr>
<td>Allosteric Modulator</td>
<td>Modifies agonist action by binding to separate receptor subunit than agonist</td>
<td>Can enhance or diminish agonist induced activity</td>
</tr>
</tbody>
</table>
General precautions with ADPs (mostly SRIs and SNRIs)
- Increased risk of bleeding due to inhibition of platelet aggregation.
- Serotonin syndrome and Neuroleptic Malignant Syndrome (NMS).
- Lowering of seizure threshold.
- General contraindication in pregnancy and nursing mothers.
- Concerns regarding activation of suicidal behavior or ideation.
- Activation of mania/hypomania.

- Increasingly, drug drug interactions (3A4, 2D6) or metabolic concerns.
- Coadministration with MAOIs.
- Initiation and discontinuation syndromes.
- Angle closure glaucoma.
### SRIs

<table>
<thead>
<tr>
<th>Drug (Trade)</th>
<th>Generic</th>
<th>Indication</th>
<th>Dose</th>
<th>Action</th>
<th>Concerns, Cautions, Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brintillex, no... Trintillex (2013, 2016)</td>
<td>Vortioxetine</td>
<td>MDD, Trintillex</td>
<td>5 mg/d then 10-20 mg/d</td>
<td>SHT1a agonist SHT3 antagonist</td>
<td>Cautions with 2D6 poor metabolisers &amp; coadmin with CYP inducers; Name confusion with Brilinta (ticagrelor; platelet P2Y12 receptor antagonist approved NAME CHANGE in 2016.</td>
</tr>
<tr>
<td>Celexa</td>
<td>Citalopram</td>
<td>Depression</td>
<td>10-40 mg/d</td>
<td></td>
<td>Max dose reduced from 50 to 40 mg due to ECG (long QT)</td>
</tr>
<tr>
<td>Lexapro</td>
<td>Escitalopram</td>
<td>MDD, GAD</td>
<td>5-30 mg/d, also as oral solution</td>
<td></td>
<td>SHT1a agonist SHT3 antagonist</td>
</tr>
<tr>
<td>Luvox</td>
<td>Fluvoxamine</td>
<td>OCD</td>
<td>50-300 (adults) 25-200 (peds)</td>
<td></td>
<td>Indicated for OCD only 8-17 years</td>
</tr>
<tr>
<td>Paxil, Paxil CR, Pexeva</td>
<td>Paroxetine</td>
<td>MDD, GAD, PTSD (OCD)</td>
<td>20-50 mg/d 20-40 mg (OCD)</td>
<td></td>
<td>Very sedating, best given at night, note 1st trimester cardiac defect risk, unusual discontinuation syndrome. Max dose 60 mg/d.</td>
</tr>
</tbody>
</table>

### SNDRI, SARIs

<table>
<thead>
<tr>
<th>Drug (Trade)</th>
<th>Drug (Generic)</th>
<th>Indication</th>
<th>Dose</th>
<th>Action</th>
<th>Concerns, cautions, pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serzone* Serzone* unavailable; only as generic</td>
<td>Nefazodone</td>
<td>Depression</td>
<td>100-300 mg twice daily Max 600 mg/d</td>
<td>Serzone sales in US halted in 2004 due to fatalities associated with acute hepatic failure</td>
<td></td>
</tr>
<tr>
<td>*contraindicated with: Carbamazepine Pimozide Terfenadine Cisapride Astemizole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desyrel</td>
<td>Trazodone</td>
<td>MDD</td>
<td>50-400 mg daily</td>
<td>SHT antagonist and reuptake inhibitor (SARI)</td>
<td>Strongly sedating, mostly used as sleep aid (50-100 mg/d) priapism</td>
</tr>
<tr>
<td>Oleptro (2010, withdrawn?)</td>
<td>Trazodone</td>
<td>MDD</td>
<td>Start 75 x2/d, then 150, up to 375 mg/d.</td>
<td></td>
<td>Somnolence, Priapism, prolonged QT interval, orthostasis.</td>
</tr>
</tbody>
</table>

### Tetracyclic/Noradrenergic and Specific Serotonin Antagonist (NaSSA)

<table>
<thead>
<tr>
<th>Drug (Trade)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Remeron Remeron SolTabs (rapid disintegrating sublingual tablets)</td>
<td>Mirtazapine</td>
<td>MDD (18+) 15-45 mg/day Soltabs: Same Better at bedtime</td>
<td>Tetracyclic SHT3, SHT2 antagonist Histamine antagonist</td>
<td></td>
<td>Highly sedating (SHT1 antagonist?) MIR may be sexually activating. OMRI studies show enhanced sexual response vs. SRIs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SolTabs: Use immediately after removing from blister pack</td>
<td></td>
</tr>
</tbody>
</table>
Serotonin and Norepinephrine reuptake inhibitors (SNRIs)

<table>
<thead>
<tr>
<th>SNRI Drug (Trade)</th>
<th>Generic</th>
<th>Indications</th>
<th>Dose</th>
<th>Cautions, Concerns, Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cymbalta (2004)</td>
<td>Duloxetine</td>
<td>MDD, GAD, diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain</td>
<td>40-60 mg/d, max 120 (7 yrs &amp; up) 30-60 mg/d</td>
<td>Lower dose for pain conditions</td>
</tr>
<tr>
<td>Effexor Effexor ER</td>
<td>Venlafaxine</td>
<td>MDD, GAD, PD, Soc. Anx.</td>
<td>75-225 mg/d Max 225 mg/d 50-100 mg/d 50/100 mg/d</td>
<td>Nausea, BP elev. BP caution Khedezla: &quot;No benefit &gt; 50 mg/d&quot; Pristiq: &quot;No benefit &gt; 50 mg/d&quot;</td>
</tr>
<tr>
<td>Fetzima (2013)</td>
<td>Levomilnacipran</td>
<td>MDD</td>
<td>48-120 mg/d</td>
<td>3A4 interactions (Note: related molecule, milnacipran (Savella) indicated only for fibromyalgia.</td>
</tr>
</tbody>
</table>

Aminoketone

<table>
<thead>
<tr>
<th>Drug (trade)</th>
<th>Drug (generic)</th>
<th>Indication</th>
<th>Dose</th>
<th>Cautions, Concerns, Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wellbutrin</td>
<td>Buproprion</td>
<td>MDD</td>
<td>200-450 mg/d</td>
<td>Insomnia, CX seizure disorders; morning dosing</td>
</tr>
<tr>
<td>Effexor ER</td>
<td>Buproprion ER</td>
<td>MDD, SAD</td>
<td>174 mg to 348 daily; Dose = 150-300 mg buproprion; CX seizure disorders</td>
<td></td>
</tr>
</tbody>
</table>

Agomelatine? (Valdoxan in UK)

- A melatonin based ADP (MT 1/MT 2 receptor agonism)
- Also active at 5HT 2c receptor subtype
- Approved in UK, EU, Australia but not in USA (no current regulatory action)
- Helpful for sleep, as might be expected
- Effect size smaller than with common SRIs, SNRIs
  - Elevated liver function tests not uncommon
  - May be associated with toxic metabolites
  - Common metabolic pathways CYP1A2, 3A4

ADPs in children: FDA warning

- FDA in Mar 2004 issues public health advisory http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm
- Reiterated that only fluoxetine approved for pediatric depression, Prozac, Zoloft, and Luvox approved for pediatric OCD.
- Monitor closely for worsening depression, suicidal behavior and other adverse reactions.
- ADPs mentioned include all SRIs plus Wellbutrin, Effexor, Serzone, Nefazodone.
- Monitor for irritability, agitation, panic, anxiety, suicidal thinking, and other sx.
- Extended in 2007 to young adults (18-24).
Risk of increase in suicidal thinking in children and adolescents is confirmed

- (1) Meta-analysis of 70 trials (18,526 patients).
  - SRIs and SNRIs (duloxetine, fluoxetine, paroxetine, sertraline, venlafaxine)
  - Missing data re: suicidal behavior noted in Lilly trials
  - OR for adult suicidal behavior 0.81 (0.49-1.21; no difference from controls)
  - OR for children/adolescents 2.39 (1.31-4.33)
  - Increased risk of suicidal behavior, aggressive behavior, akathisia
- (2) Medicaid data suggest 1.52x risk of suicidal thinking or completed suicide in 6-18 year olds, finding not replicated in adults
  - SNRIs, TCAs more associated with suicide attempts than other meds

(2) Olfson, et al. (2006). Antidepressant Drug Therapy and Suicide in Severely Depressed Children and Adults A Case-Control Study. Arch Gen Psychiatry, 63, 865-872.

Paroxetine

- Distributed by Apotex.
- Available as Pexeva, Paxil, generic, and now...Brisdelle.
  - Brisdelle: very controversial FDA approval, panel voted 14-10 against, but overruled.
  - Brisdelle indicated for menopausal hot flashes; 7.5 mg formulation.
  - Only nonhormonal treatment for hot flashes currently approved.
  - Drug previously categorized as FDA Category X – contraindicated in pregnancy.
  - New FDA categorization unpublished, but do NOT use in pregnancy or breastfeeding.
  - Sedating SRI, long history of reports of severe discontinuation symptoms.
  - See slide on study 359.
  - This is not a recommended drug for any condition.

Do we know less about Study 329 than Area 51?

- Study 329 – infamous 2001 study of Paxil (JAACAP): Findings:
  - Safe in kids!!
  - And it works too!!
  - But......
  - Recent reanalysis suggests
    - Unsafe (high risk of side effects)
    - Suicidal ideation
    - No more efficacious than placebo
- No difference between Paxil, high dose imipramine and placebo.
- High incidence of adverse SE's, incl. suicidal ideation and CV effects in IMI group.
- My take: Don’t use Paxil in either kids or adults.

Antidepressants and pregnancy

- Recent British study: although ADP prescribing increased 4x in past 15 years, only 10% of a British epidemiological sample who received ADPs (mostly SSRIs) prior to becoming pregnant were still taking those drugs at beginning of 3rd trimester.

SRIs in pregnancy and autistic spectrum disorders: More than likely NOT

- Earlier link postulated between use of SRIs in pregnancy and elevated risk of Autistic Spectrum Disorder (ASD) in children.
- Two recent analyses (1 CA, 1 UK) do not support this.
  - CA study: retrospective cohort study of 35,906 single births:
    - 7.9% pregnant moms exposed to ADPs
    - Kids followed for dx after 2 years (4 yr total followup)
    - Non-significant elevation in ASD in ADP exposed kids (adjusted 3.4/1,000 py v. 2.05/1,000 py in non-exposed; HR: 1.60, CI = 0.69-3.74).
    - UK study similarly found no association – multiple confounds likely.

Treatment of depression during pregnancy I

- Evidence conflicting; read beyond the headlines
- Recent newsmaker that SSRIs are safe in pregnancy misleading:
  - Reefhuis, et al. (2015) did NOT find that all SRIs were safe in first trimester
  - Authors found no association between Sertraline and prior reports of 1st 3mester use
  - But, Bayesian analysis found risks of:
    - Atrial septal and other cardiac defects, anencephaly, and intestinal malformations with Paroxetine and Fluoxetine take in 1st trimester.

Treatment of depression in Pregnancy II:


- Other reviews (eg. Epstein, Moore, Bobo):
- Effectiveness of pharmacotherapy in pregnancy unclear
  - Cohen et al found that women previously treated with ADPs had higher rate of relapse during pregnancy if meds stopped, BUT
  - Risk of episode during pregnancy did not differ between those who took ADPs and those who didn’t.
  - Septal defects seem most common in 1st trimester (Paroxetine and Fluoxetine)
  - Persistent Pulmonary Hypertension of Newborn more common in 3rd trimester, but may also occur with earlier exposure.
  - Poor Neonatal Adaptation Syndrome (irritability, agitation, respiratory distress, tremor) more likely associated with 3rd trimester use.
ACOG practice guidelines for pharmacotherapy in depression (2008/2012)

**Antidepressants**
- Paroxetine: AVOID. Fetal ECG for women exposed in 1st trimester.
- Multidisciplinary management (inc. MH provider) during pregnancy
- Use single med at higher doses v. multiple meds
- 'Individualize' doses of SRIs.
- Close monitoring of lithium levels.

  - Source: ACOG (2008/2012) Use of psychiatric medications during pregnancy and lactation; ACOG practice bull. #92

**Mood Stabilizers**
- Lithium – small increase in cardiac defects (1.2-7.7 RR)
- Valproate: AVOID, esp in 1st trimester:
  - risk neural tube defects, neurocog defects, etc.
- Carbamazepine: AVOID, esp. in 1st trimester:
  - Fetal carbamazepine syndrome
- Benzodiazepines:
  - ↑ risk of cleft palate (RR 0.01%) Antenatal use associated with floppy infant syndrome.
- LAMOTRIGINE: potential maintenance during pregnancy for women with bipolar disorder.

Treatment of depression in pregnancy: Summary slide

- Careful evaluation of chronicity & severity of prior depression essential.
- Not all women respond to drugs in pregnancy, and drugs not necessarily proof against relapse.
- Use non pharmacological treatments when possible.
- No dose-response curve for ADPs vis-à-vis fetal defects.
- 1st trimester use low but present association with cardiac, cephalic, GI defects, esp with paroxetine, fluoxetine.
- 3rd trimester use associated with Poor Neonatal Adaptation Syndrome.
- For mania, Lamotrigine least risky.

- My conclusion: Use only if non-drug treatment doesn’t work, careful informed consent; consider referral.

In post-partum depression, SRIs OK – we think. But so are other treatments

- Qualitative review of 6 RCTs (n=595) using CBT, community based tx, TCA, placebo, and psychodynamic therapy vs. SRI.
- All studies showed some superiority for SRIs, but drop-out rates high, differences did not always meet significance.
- “Available evidence fails to demonstrate clear superiority over other treatments”
- Please recall: All antidepressants are expressed in breast milk.

Psychotropics and kids

- Since introduction of SRIs, antidepressant Rx for children and adolescents has increased >200%
- 2004 FDA black box warning of suicidal behavior slowed trend.
- In 2007, black box extended to young adults (18-24).
- Similar trajectory for antipsychotics (200K Rx in 1993, 1.2M Rx in 2001)
General guidance regarding antidepressants (mostly newer ones)

I. In general, all are equal in terms of efficacy and tolerability (except Paxil)
II. Side effects, past experience, and patient preference drive the train
III. Suicidal behavior, aggression, akathisia, irritability must be monitored during start and stop
   I. No TCAs for suicidal patients
IV. Initiate gradually to lowest effective dose, discontinue gradually
V. General cautions in pregnancy, esp. paxil, fluoxetine
VI. Noradrenergic agents (bupropion, levomilnacipran) may be better for patients with anergia, cognitive slowing

How to choose…..heads or tails?

- Cipriani et al (2009) published a meta-analysis suggesting that:
  - Mirtazapine, escitalopram, venlafaxine, sertraline outperformed Duloxetine, fluoxetine, fluvoxamine, paroxetine, reboxetine

Findings challenged by Del Re et al (2013). Due to measurement errors associated with meta-analyses, no drug outperformed any other, except all did better than reboxetine.

Sources:
Del Re, et al. (2013). Efficacy of new generation antidepressants: differences seem illusory. PLOS One, 8(6);e63509 doi: 10.1371/journal.pone.0063509

Those NICE British folk (National Institutes for Clinical Excellence)

- NICE guidelines on 1st choice antidepressants
- For depression: Generic SSRI
  - Choice depends on side effects, patient preference, and previous response.
- For GAD/Panic disorder: Escitalopram, duloxetine, paroxetine, venlafaxine and sertraline all indicated, but sertraline most cost effective.

NICE (2015). First choice antidepressant use in adults with depression or GAD.
More on clinical trial reporting

- Despite registries in US, most trials not completely reported at clinicaltrials.gov (Anderson, et al., 2015)
- (Maund, et al. (2014):
  - Publication bias remains significant in antidepressant research
  - Newly available European registry data allows comparison of published, unpublished and other trial data.
  - Harms, including serious adverse events, not published
    - May not be assessed (discontinuation syndromes)
    - May be serious but not meet reporting thresholds (suicide)

  - Maund, et al. (2014) Benefits and harms in clinical trials of duloxetine….British Medical Journal, 348:g3510. doi: 10.1136/bmj.g3510

Efficacy of internet-based psychotherapy for mood and anxiety disorders

- Recent Cochrane review: 40 studies of I-CBT for mild-moderate depression and social phobia showed moderate short-term efficacy v. waiting list (i.e., not terribly compelling, but probably as good as Rx)

The TADS Study

- Large multicenter trial involving 327 12-17 year olds treated with fluoxetine, fluoxetine + CBT, and CBT alone
  - CDRS-R and CGI-Improvements were primary outcomes
  - Results favored combination therapy at week 12, slight advantage for combined tx at wk 36
  - Suicidal ideation not uncommon in fluoxetine tx (14.7%), reduced in comb (8.4%), and CBT (6.3%).
  - Fluoxetine or combination tx accelerate response
    - The TADS study: Long term effectiveness and safety outcomes; the TADS team (2007) Arch Gen Psychiat, 64 1132-1143
SSRIs and neonatal pulmonary hypertension

- Persistent pulmonary hypertension in newborns (PPRN) occurs more frequently in newborns of mothers taking SSRIs after wk 20. Risk low (6-12/1,000), but higher than other risk factors (e.g. smoking)
- Association not seen in other ADPs (inc. MFAs)
- Possibly due to accumulation of SRIs in lung tissue, vasoconstrictive effects of SRIs.

Other cautions; special populations

- GSK facing significant lawsuits regarding birth defects (cardiac defects) in children of mothers who took paroxetine while pregnant.
- Paroxetine not approved for use in pregnancy.
- While paroxetine in particular is at issue, other SRIs may also be implicated.
- Smokers: Oliviera et al (2017) showed an association between smoking and induced metabolism of some ADPs (Fluvoxamine, duloxetine, mirtazapine, trazodone).
  - Clinical implications unclear, note that there is no correlation between serum levels and ADP response in general, but perhaps avoid above drugs in smokers)

Antidepressants in elders

I. Like any agent, lowest effective dose is critical
II. Avoid agents that cause unwanted sedation, potential anticholinergic effects (tricyclics, paroxetine)
III. Avoid agents associated with urinary retention (tricyclics, duloxetine)
IV. Avoid agents with extensive hepatic metabolism
V. Avoid agents with long half-lives
VI. Commonly used at low doses: citalopram

Other potential developments

- No significant breakthroughs in the pipeline, but
- Glutaminergic agents may hold some promise (this based on small studies of ketamine in major depression….hmmm).
- Edivoxetine (noradrenergic reuptake inhibitor) – possible use in depression and ADHD – under development by Lilly. How different than tomoxetine? (Of course, I mean atomoxetine….or do I?)
Pomeglumetad methionil

- Pomeglumetad (LY404,093) and oral prodrug p. methionil agonize certain GLU receptors (MGlur2, MGlur3).
- Pomeglumetad may also agonize certain D2 receptors.
- Hypothesis: GLUTAMINERGIC HYPOTHESIS OF SCHIZOPHRENIA
  - E.g., dysregulation of glutamate (excitatory) neurotransmission in susceptible cortical areas may lead to psychotic thought processes and behavior.
- Synthesized 2007, investigated by Lilly 2010-2015, licensed to Denovo Pharmaceuticals in 2015.
- No success in clinical trials (a “subset of patients” may improve per Denovo), possibly due to low bioavailability.

Where are we with combined treatments for depression?

- The bag is still mixed.
- PReDICT study (Dunlop, et al., 2017)
  - 344 treatment naïve pts randomized to CBT (16 1 hr), SRI escitalopram (10-20 mg/d), SNRI duloxetine (30-60 mg/d)
  - HAM-D main outcome
  - Patient preference for type of tx moderated adherence but not outcome
  - NSD in mean decreases in HAM-D (CBT = 10.2, SRI = 11.1, SNRI = 11.2)
  - NSD in mean remission rates (CBT = 41.9%, SRI=46.7%,SNRI = 54.7%)

The normal cardiac cycle
(sorry, I can’t find an attribution for this image)

Revised FDA safety warning IRT Citalopram

- Citalopram is not recommended for use at doses greater than 40 mg per day because such doses cause too large an effect on the QT interval and confer no additional benefit.
- Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure.
- Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval.
- The maximum recommended dose of citalopram is 20 mg per day for patients with hepatic impairment, patients who are older than 60 years of age, patients who are CYP 2C19 poor metabolizers, or patients who are taking concomitant cimetidine (Tagamet) or another CYP2C19 inhibitor, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.
SRIs in kids: Cardiac Concerns?

- SRI use in kids without heart disease apparently safe.
- Uchida, et al. (2017) examined ECGs in 49 children taking a variety of non-TCAs (SRIs, bupropion, SNRIs, Remeron) at low or high doses.
- Normalized doses to “CEDs”: citalopram equivalent doses.
- Results: Slight evidence of a prolonged PR interval with citalopram, escitalopram, but such differences vanished when weight-based or age-corrected dosing was used.
- Take-home: Non-TCAs safe in cardionormal pediatrics, but caution with escitalopram and citalopram.


SRI labeling changes in 2011

- Oct 2011 FDA revised labels to note that coadministration of some SRIs (Paxil, Prozac, Cymbalta, Celexa) with certain antibiotics (linezolid) or methylene blue could result in development of serotonin syndrome.
- Citalopram (Celexa) labeling changes revised maximum dose downward from 60 mg to 40 mg/d, due to risk of cardiac arrhythmias at higher doses.
- SRIs and PPHN – first advised in 2006, since then conflicting results. FDA recommends no change in prescribing at this time

- Source: www.fda.gov/safety/medwatch

Neurotoxicity of SSRIs

- Neuroleptic malignant syndrome (NMS: dysregulated core body temperature, delirium/confusion/coma, muscle rigidity, hypertension; rare but often fatal)
- Associated with all antipsychotics, including second-generation antipsychotics.
- SRIs also associated independently with rare NMS, extrapyramidal symptoms (EPS: akathisia, dystonias, dysscoordination, associated with dopamine blockade).
- Coadministration of antipsychotics and serotonergic antidepressants may increase risk of development of NMS, possibly due to antidopaminergic effects of SRIs, or drug interactions increasing levels of antipsychotics.
- Coadministration not contraindicated, but should be performed with caution.
Turmeric as a therapeutic agent

- Turmeric contains curcumin, the putative active agent.
- Long history of use in ayurvedic medicine, herbal pharmacopoeia
- Extensive speculation as to effects as antioxidant, promoter of BDNF
- Many small, open trials to treat cancer, glaucoma, HTN, Alzheimer’s, etc…
- No convincing RCTs for mental disorders; major problem is bioavailability of curcumin.
- Recent good review is:


- BLUF (IMHO) – we cannot safely recommend herbal/alternative remedies to patients.
- Latest (egregious) example: Mei Zi Super Power Fruits Herbal Slimming Formula
  - Active ingredient sibutramine (formerly Meridia, 5HT blocker and psychostimulant removed in 2010)
  - Since Oct, 2015, FDA has issued ≈25 warnings for weight loss/sexual enhancement herbal agents, all contain:
    - Sildenafil (PDE5 inhibitor, active ingredient Viagra)
    - Sibutramine (banned stimulant)
    - Locaserin (prescription weight loss agent)
    - Dexamethasone (steroid)

Fraudulent – and dangerous- supplements

- 15 of 15 male “sexual enhancers” reported by the FDA in 2015 contained sildenafil (hint: it works…it’s Viagra).
- Of 7 “natural” weight loss supplements,
  - 2 contained sibutramine
  - 1 contained d-Chi sibutramine
  - 2 contained fluoxetine (Prozac)
  - 3 contained phentermine
  - 1 contained sibutramine (Viagra)
  - 1 contained locaserin (Belviq)
  - And the grand prize goes to: “Lean Body Extreme” which contained sibutramine, desmethylsibutramine, phentermine, and, just for good measure, a dose of sildenafil.
- Sept 2015: FDA forces recall of all “Iowa Select Herbs” products, for contaminants, mislabeling, etc. etc. etc.
- Just don’t.

Ayurvedic medication warning

- Past decade has seen numerous warnings and several fatalities
- Heavy metal (lead, arsenic, cadmium) concentrations in fraudulent ayurvedic medications exceed toxic limits
- Keep in mind that “natural” medications are far more widely used than pharmaceuticals
- Renal and hepatic failure, possibly leading to death.
- Lead poisoning in pregnant women who used Ayurvedic medications from India–New York City, 2011-2012 (photos reproduced from MMWR report)
**Antipsychotics**
- Weight gain
- Hyperglycemia
- Dyslipidemia
- All essential elements of informed consent
- Caution: sudden cardiac death increased with antipsychotics (2.3 fold), evidently of all classes, in study of primary care patients
- Risk greater with higher dose, shorter duration of tx.

**FDA approved first generation antipsychotics**
- Compazine  (prochlorperazine)
- Haldol  (haloperidol)
- Loxitane  (loxapine)
- Mellaril  (thioridazine)
- Moban  (molindone)
- Navane  (thiothixene)
- Orap  (Pimozide)
- Prolixin  (fluphenazine)
- Stelazine  (trifluoperazine)
- Thorazine  (chlorpromazine)
- Trilafon  (perphenazine)

**FDA approved Second Generation Agents**
- Aripiprazole  (Abilify)
- Asenapine  (Saphris)
- Brexpiprazole  (Rexulti)
- Cariprazine  (Vraylar)
- Clozapine  (Clozaril)
- Iloperidone  (Fanapt)
- Lurasidone  (Latuda)
- Olanzapine  (Zyprexa)
- Olanzapine/Fluoxetine  (Symbyax)
- Paliperidone  (Invega; Sustenna)
- Pimavanserin  (Nuplazid*)
- Quetiapine  (Seroquel)
- Risperidone  (Risperdal)
- Ziprasidone  (Geodon)

*Only for psychosis in Parkinson’s

**Antipsychotics: Is one better than another?**
- No.
- Well, maybe Clozapine.
- World Psychiatric Assn reviewed 1,600 studies of FGAs and SGAs:
  - SGAs "inconsistently more effective than FGAs in alleviating negative, cognitive, & depressive sx...had lower liability to cause TD...these modest benefits driven by the ability of the SGAs to produce equivalent improvement in positive sx along with a lower risk of causing EPS."
  - "No consistent differences in efficacy among...SGAs"
  - "Dosing was... key variable in optimizing effectiveness of both FGA and SGA antipsychotic agents."
The more we think about the current generation, the more……

- Rx of SGAs skyrocketing, largely for off-label conditions, usually PTSD, anxiety disorders, and insomnia.
- In 2010, SGAs accounted for 18B in US sales. 75% Medicaid funded (12B/50 = 240M average per state annually)
- In a VA population Rx’ed SGAs, 32% of providers surveyed said they Rx’ed it for sleep, in 12%, sleep was only reason Rx’ed.
- Rx’s not associated with psychotic dx.
- New SGA Rx’s almost always for sleep.
- Seroquel most commonly used.
- Costs up to $10/day per patient, compared to <$1/d for FGAs.
- Academic detailing experiment did NOT decrease use of SGAs.


SGAs v. FGAs

- Atypicality not an unalloyed benefit.
- Atypicals much more costly, have numerous side effects.
- Carpenter: At low doses, typicals become atypicals.
- Numerous problematic side effects: weight gain, hepatic dysfunction, sedation.
- FDA warning for all atypicals - Zyprexa, Risperdal, Clozaril, Abilify, Seroquel, and Geodon - elevated blood sugar and diabetes: fasting glucose on initiation and periodically.
- Atypicality does not result in improved social functioning.

Cautions

- Off label use common enough to be normative
- Highly aggressive marketing efforts by PHRMA leads to marked deviations in practice, por ejemplo:
  - FDA recently accused Pfizer of significant violations in its attempt to get Geodon approved for bipolar disorder in 10-17 year old children.
  - “Widespread overdosing”
  - Large numbers of children did not complete trials
  - Significant side effects – sedation, sleepiness, EPS
- 2009 Pfizer agreed to 2.3B settlement for illegal marketing of drugs including Geodon.

Antipsychotic use in pregnancy

- 1021 database matched women
- Statistically low but present risk found of
  - Gestational diabetes
  - Hypertension in pregnancy
  - Venous thrombosis
  - Very low or very high birthweight
- Though “minimal evident impact” – monitoring recommended
Increasing use of SGAs in pregnancy


- 0.72% pregnant women exposed to SGA, 0.09% exposed to FGA.
- 2.5 fold increase in rate of Rx of SGAs, no increase in rate of Rx of FGAs.
- Most prescribed SGAs did not have psychotic spectrum diagnoses:
  - Depression (63%)
  - Bipolar Disorder (43%)
  - Schizophrenia (13%)
- Speculation: SGAs being used instead of BDZs for sedation in pregnancy? Is this wise?

Antipsychotic prescribing in children

- Extremely rapid rise in 1990’s – early 2000s
- Since 2006, Rx’s in children <12 declined slightly, up slightly in adolescents, up in young adults (18-24)
- Increased safety concerns in peds resulted in decline in that age group?
- Most common dx: ADHD, then “other”, then disruptive behavior DO.
- Almost all Rx’s (~96%) for SGAs.
- Most do not receive psychotherapy.

Antipsychotics and diabetes in youth

- Galling, et al. (2016) meta-analysis of 13 controlled studies of antipsychotics in youth.
- Youth taking antipsychotics had higher risk of Type II DM as compared to either healthy or non-drug taking controls with mental illness.
- Higher ratio seen in healthy controls than those with mental illness.
- Mostly males
- Weight gain not reported.
- Longer duration of medication, olanzapine prescription and male sex were risk factors.
- Au conclusion: Consider antipsychotics only when other interventions have failed.
- Galling, B. et al (2016). Type II DM in youth exposed to antipsychotics...JAMA Psychiatry, doi.10.1001.jamapsychiatry.2015.2923

Risperidone for disruptive behavior disorder: Cochrane review (2012)

- Meta-analysis of 8 studies from 2000-2008 on children with disruptive behavior disorders; 7 RIS and one Quetiapine.
- Limited evidence supporting RIS in irritability and conduct problems.
- But sample was heterogeneous, and included lower IQ subjects.
- Significant weight gain of X= 2.37kg over length of trials while on RIS.
- No study also addressed psychosocial intervention.
- No evidence for Quetiapine efficacy.

**FDA Approved second generation agents:**

**Children and Adolescents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications</th>
<th>FDA Approval</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Schizophrenia, mania,</td>
<td>2002</td>
<td>13-17 yrs</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Schizophrenia, mania,</td>
<td>2002</td>
<td>13-17 yrs</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Schizophrenia, manic</td>
<td>2002</td>
<td>13-17 yrs</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Schizophrenia, mania,</td>
<td>2002</td>
<td>13-17 yrs</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Schizophrenia, mania,</td>
<td>2002</td>
<td>13-17 yrs</td>
</tr>
</tbody>
</table>

**Common side effects common to all antipsychotics (in varying degrees)**

- Stroke/CVA
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Metabolic changes
  - Hyperglycemia
  - Dyslipidemia
- Weight gain
- Orthostatic hypotension
- Leukopenia
- Neutropenia
- Agranulocytosis
- Seizures
- Cognitive/motor impairment
- Body temperature dysregulation
- Dysphagia

**Dopamine reconsidered**

Role of dopaminergic receptors questioned in recent meta-analysis

Howe et al found that most DA dysregulation occurred **PRESYNAPTICALLY**

Most current drugs target **POSTSYNAPTIC** receptors, where there is little evidence of dysfunction in drug-naïve patients.

Is this further evidence that the SGAs are not optimum treatments for psychotic spectrum disorders?


**Childhood antipsychotic prescribing: When Medicaid may not be good for your child’s health**

- Survey of Commonwealth of PA Medicaid findings (also published NEJM 1 Sept 2015).
- 1x higher use psychotropics among foster care youth (ages 6-18) than Medicaid use overall (43% v 16%).
- Antipsychotic use at 22%, 4x that of non-foster care youth.
- > 50% of youth with antipsychotic Rx had ADHD diagnosis, not psychotic spectrum diagnosis.
- Polypharmacy 4x higher in foster care youth vs. Medicaid (12% v 3%)
- Other risk factors for inappropriate Rx:
  - Male
  - European-American
  - Adolescent status (11-18 yrs)

Figure and Data: Olfson, King, Schoenbaum (2015. Young people with antipsychotic meds, *JAMA Psychiatry*, 72, 867-874)
### First generation FDA approved antipsychotics in children and adolescents

<table>
<thead>
<tr>
<th>Drug (generic)</th>
<th>Trade</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroquel, Seroquel XR or MR (modified release)</td>
<td>Quetiapine</td>
<td>Ekers with dementia; suicidal ideation</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>Ekers with dementia, suicidal ideation in 24 and younger</td>
<td></td>
</tr>
<tr>
<td>Fanapt</td>
<td>Iloperidone</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Zyprexa, Zyprexa Zydis</td>
<td>Olanzapine</td>
<td>Same + Post Injection Delirium/Sedation syndrome</td>
<td></td>
</tr>
<tr>
<td>Invega, Invega Systena</td>
<td>Paliperidone</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Risperdal, Risperdal M-Tab; Risperdal Consta</td>
<td>Risperidone</td>
<td>Ekers with dementia</td>
<td></td>
</tr>
<tr>
<td>Geodon</td>
<td>Ziprasidone</td>
<td>DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms (rash, renal/hepatic/lymph involvement)</td>
<td></td>
</tr>
<tr>
<td>Clozaril</td>
<td>Clozapine</td>
<td>(1) Seizures (2) agranulocytosis (3) myocarditis</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole Maintena (injectable)</td>
<td>Abilify</td>
<td>Ekers with dementia, suicidal ideation</td>
<td></td>
</tr>
</tbody>
</table>

*Table adapted from Oregon Health Sciences Center (2010). Drug Class Review: Atypical Antipsychotic Drugs.*


### Second Generation Oral Antipsychotics FDA approved in Adults

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abilify</td>
<td>Aripiprazole</td>
<td>10-30 mg x1 daily; As MDD adjunct: 2-5 mg, up to 15 mg</td>
<td>Bipolar I; Schizophrenia MDD adjunct</td>
</tr>
<tr>
<td>Saphris</td>
<td>Asenapine</td>
<td>5-10 mg x2 daily, up to 20 mg</td>
<td>Bipolar I; Schizophrenia</td>
</tr>
<tr>
<td>Results</td>
<td>Brexpiprazole</td>
<td>1 mg x2 daily for 4 d, then titrate up to 4 mg/d; as MDD adjunct 0.5-3 mg/d</td>
<td>Schizophrenia; MDD adjunct</td>
</tr>
<tr>
<td>Vraylar</td>
<td>Cariprazine</td>
<td>1.5 mg/d up to 6 mg/d</td>
<td>Bipolar I; Schizophrenia</td>
</tr>
<tr>
<td>Clozaril</td>
<td>Clozapine</td>
<td>12.5 mg 1-2x daily, target 300-400 mg/d; max 900 mg/d</td>
<td>Schizophrenia (tx resistant), Schizoaffective disorder</td>
</tr>
<tr>
<td>Fanapt</td>
<td>Iloperidone</td>
<td>1 mg x2 daily, target 6-12 mg/d; max 12 mg x2/d</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Latuda</td>
<td>Lurasidone</td>
<td>20 mg/d; target 20-120 mg/d; max 120 mg/d</td>
<td>Schizophrenia: 40 mg/d, target 40-160 mg/d</td>
</tr>
</tbody>
</table>

Second Generation Oral Antipsychotics FDA approved in adults II

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyprex</td>
<td>Olanzapine</td>
<td>10-20 mg/d (bipolar mixed) 5-12.5 mg/d (bipolar depressed); 5-20 mg/d (tx resistant MDD) 5-20 mg/d (schizophrenia)</td>
<td>Bipolar I; Tx resistant MDD, Schizophrenia</td>
</tr>
<tr>
<td>Invega</td>
<td>Paliperidone</td>
<td>3-12 mg/d, max 12 mg/d</td>
<td>Schizophrenia; Schizoaffective DO</td>
</tr>
<tr>
<td>Nuplazid</td>
<td>Pimavanserin</td>
<td>17 mg/d orally, 5HT2A inverse agonist; approved 3/29/2016</td>
<td>ONLY for psychosis in Parkinson’s disease</td>
</tr>
<tr>
<td>Seroquel</td>
<td>Quetiapine</td>
<td>25 mg x2/d up to 750 mg; XR 50 mg (schizophrenia); 300-800 mg/d (bipolar mania) 50-300 mg/d (bipolar depressed)</td>
<td>Bipolar I (manic or depressed) Schizophrenia</td>
</tr>
<tr>
<td>Risperdal</td>
<td>Risperidone</td>
<td>2-3 mg/d, up to 6 mg (bipolar mania) 2 mg/d, up to 16 mg/d (schizophrenia)</td>
<td>Bipolar mania Schizophrenia</td>
</tr>
<tr>
<td>Geodon</td>
<td>Ziprasidone</td>
<td>40 mg x2/day, 80 mg max (bipolar mania) 20 mg x2/d up to 80 mg x2/d (schizophrenia)</td>
<td>Bipolar I Schizophrenia</td>
</tr>
</tbody>
</table>

New cautions IRT SGAs and off label use in older patients

- I STRONGLY object to patients >60 y.o. being labelled as “older”.
- Nonetheless, most Rx’ing in this group is off-label.
- Jen et al (2012) found that aripiprazole, quetiapine, seroquel, and olanzapine most problematic in older patients.
- Caution IRT usage of these agents: should be short term, with clear clinical indications and excellent informed consent.

Important study from NIMH indicates older antipsychotics as effective as newer ones, fewer side effects

NIMH study (Sikich, et al, 2008) suggests that older antipsychotics as efficacious as SGAs in kids, fewer side effects
  ➢ 119 young people 8-19 taking Zyprex, Risperdal or molindone, an older generic.
  ➢ 8 Week trial, 34% Zyprex, 46% Risperdal and 50% molindone showed improvement.
  ➢ Very large dropout rate obscures significance of results.
  ➢ Weight gain and metabolic issues prominent
    • Zyprex average 13 lb weight gain,
    • Risperdal 9 lb average
    • Molindone <1 lb

Molecular drug development: Pimavanserin

- SGAs have greater affinity for 5HT2A receptors than D2 receptors, therefore they have fewer neuromuscular side effects.
- But SGAs are nonspecific for many 5HT receptors, and cause metabolic syndrome (partially via 5HT2C inverse agonism).
- Attempt to develop drug that had antipsychotic efficacy (probably via 5HT2A agonism or inverse agonism) WITHOUT metabolic effects (probably via 5HT2C inverse agonism).
- Finding that pimavanserin had high affinity for 5HT2A and little affinity for either 5HT2C or D2; and potentiated effect of other SGAs, led to development as drug for Parkinson’s Disease Psychosis.

Market share of antipsychotics, 2011
Seroquel leads the pack (Leonhauser, 2012)

New findings IRT monitoring of clozapine

- New guidance for monitoring (presuming neutrophil count > 1,500).
- X1 weekly for 6 months, biweekly for 6 months, then monthly after 1 year.
- REMS program – Risk Evaluation and Mitigation System:
  - Registers pharmacists, prescribers and patients in combined clozapine database. Must be registered to prescribe.
  - Neutropenia now measured by ANC (Absolute Neutrophil Count) only.
  - Diabetic ketoacidosis, gastric hypomotility are equally significant concerns with higher morbidity and mortality.

- clozapine-induced agranulocytosis:
  - Incidence = 3.8‰–8.0‰
  - Mortality rate = 0.1‰–0.3‰
  - Case-fatality rate is 2.2‰–4.2‰.
- diabetic ketoacidosis:
  - Incidence = 1.2‰–3.1‰,
  - Case-fatality rate = 20%–31%.
- gastrointestinal hypomotility:
  - Incidence 4‰–8‰,
  - Case-fatality rate was 15%–27.5%.

The CATIE trials

- Clinical Antipsychotic Trials for Intervention Effectiveness – ecologically valid drug trials
- Phase I – Olanzapine somewhat more effective, but higher dose, side effects limited use. Many patients did not respond to any antipsychotic.
- Clozapine most effective antipsychotic, better symptom remission.
- 11% (n=5) of CLOZ, 35% (n=6) and 43% (n=6) discontinued treatment due to lack of efficacy, but only 27% (85/318) of pts failing phase 1 trial entered this trial.
- Olanzapine marginally more effective than risperidone or quetiapine, but side effects limited use.
- Conclusion: CLOZ superior, but severe side effects limit use (1 case each of agranulocytosis, eosinophilia in approx 50 pts taking CLOZ), other atypicals did not differ between drugs.

Phase 3 of the CATIE trials

- Followup to the first two phases involved 270 pts who had completed phases I & II.
- Inadequate symptom response to earlier phases.
- Allowed choice of antipsychotic or combination.
- Mostly evenly divided among range of SGAs,
- SGAs: Aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, clozapine.
- FGAs: Smaller numbers chose FGAs: Fluphenazine, perphenazine.
- Completion and discontinuation rates in Phase III similar across drug:
  - 50-67% completion (aripiprazole, fluphenazine, combination highest at 67%)
  - 33-50% discontinuation rate.
- In sum, no real difference from earlier phases in terms of efficacy, tolerability.
Multifamily Group Therapy

- Adherence to antipsychotics a major problem, unchanged for many years.
- Attempts to improve adherence better when individual factors considered.
- Kopelowicz (2015) used Theory of Planned Behavior & Multifamily Group Treatment in Hispanics with Schizophrenia or schizoaffective disorder.
  - 3 “joining” sessions (individual families)
  - 1 day multifamily workshop
  - 24 biweekly group sessions for 1 year.
- MFG patients had significantly greater adherence on 24 mo followup, reduced hospitalizations, increased time to hospitalization.
- Changes in “subjective norms” component of planned behavior seemed most salient.

Does combined treatment improve outcomes?

- Consistent with previous study, some (limited evidence) for:
  - Family interventions
  - CBT for psychotic symptoms
  - Mehl (2015) meta-analysis of 19 studies found CBT for psychosis better than TAU, but not better than other forms of CBT (e.g., problem-solving, family tx), in changing delusions.
  - Less evidence for:
    - CBT for thought disorders
    - Cognitive remediation training
  - Naeem et al. (2016) found a self-help guide for CBTp used by front-line professionals to be of modest assistance.

In sum, probably yes

- CBT improves outcomes when combined with pharmacotherapy.
  - Effect sizes small to modest.
  - Specific forms of CBT (e.g., for psychosis) do not appear to be more effective than non-specific CBT.
  - Sufficient evidence to suggest it be included in treatment plan.
- Those NICE Brits again (2014):
  - For prodromal sx: CBT +/- family tx, other targeted psychotherapies; no Rx to “prevent” onset.
  - For first episode: Range of CBT, other therapies, emphasis on trauma of psychotic episode, tailored Rx, no combined Rx unless resistant.

Pharmacotherapy for Borderline Personality Disorder

- No single agent – a symptom based approach.
  - Avoid temptation to sedate.
  - Antipsychotics, mood stabilizers, antidepressants all used
    - Few systematic trials, mixed evidence for all.
    - Note recent uptick in use of inhaled loxapine (ADASUVE) for agitation with BPD.
    - Neurohormone oxytocin has had a vogue (enhanced attachment) but no empirical evidence supports, the few studies are mixed and paradoxical agitation may result.
  - Disinhibiting agents (e.g., benzodiazepines) should be avoided.

McDonagh, et al. (2010) Conclusions

- Few differences among atypical antipsychotics in short-term efficacy, effectiveness outcomes in schizophrenia, bipolar disorder, dementia.
- **Schizophrenia**, clozapine reduced suicides and suicidal behavior, but high rates discontinuation due to side effects.
- But: lower rates of discontinuation of drug for any reason over periods of up to 2 years (maybe more effective?)
- **Bipolar disorder (adults)**
- Asenapine has higher risk of stopping due to adverse events than olanzapine.
- **MDD (adults)** No good data
- **Pervasive developmental disorders, disruptive behavior disorders (children and adolescents)**
  - Olanzapine - greater weight gain than other drugs (6 - 13 pounds)
  - 16% increased risk of new-onset diabetes.
  - Risperidone - increased risk of new-onset tardive dyskinesia.
  - clozapine - increased risk of seizures and agranulocytosis
- “Evidence on long-term harms for the newest drugs is lacking”.

Reviews to have confidence in: Cochrane review of SGAs and Major Depression I

- Cochrane review of SGAs alone or as augments versus antidepressants or placebo in MDD or dysthymia.
- 28 trials with 8487 participants on five SGAs: amisulpride, aripiprazole, olanzapine, quetiapine and risperidone, included drug-placebo RCTs
- ARI (3 trials, >1,000 participants): Some benefit of ARI v placebo noted, but SEs of weight gain, EPS.
- Olanzapine 7 trials (1754 participants). No differences in efficacy between olanzapine and ADPs, but weight gain and prolactin increases; less tx discontinuation due to inefficacy vs placebo.

High quality review of SGA efficacy:
Data from McDonagh, Peterson, Carson, & Thakurta (2010)

- **Schizophrenia and Related Psychoses**: clozapine and olanzapine: lower discontinuation rates up to 2 years.
  - Clozapine: possible reduction in suicide in high risk patients
  - More adverse events than other SGAs.
  - Risperidone and extended-release paliperidone: higher rates of extrapyramidal symptoms in some studies, the majority of studies find no differences.
  - Risperidone: more frequent severe sexual dysfunction symptoms vs quetiapine, but similar to extended-release paliperidone or ziprasidone.
- **Adolescents with schizophrenia, quetiapine: not superior to placebo based on response rate, but superior based on improvements measured by the Positive and Negative Syndrome Scale.
- **Bipolar Disorder** in adults with bipolar disorder, no significant differences between risperidone and olanzapine or asenapine and olanzapine in quality of life, remission, and response outcomes.
Reviews to have confidence in: Cochrane review of SGAs and Major Depression II

- Quetiapine (7 trials, 3414 participants). Quetiapine monotherapy and augmentation yielded more symptom relief than placebo but with SE of sedation.
- 4 risperidone augmentation trials, RIS better than placebo but with prolactin increase and weight gain.
- Amisulpride (5 studies, 1313 subjects) for dysthymia. Some benefits compared to placebo or ADPs but with worse tolerability than either.
- Author conclusions:
  - Quetiapine more effective than placebo. Aripiprazole, quetiapine and partly olanzapine and risperidone augmentation showed beneficial effects over placebo.
  - Some evidence indicated beneficial effects of low-dose amisulpride for dysterphonic people. Most SGAs showed worse tolerability.


Off label use of Second Generation Antipsychotics

- Practice of off-label use is extremely common, but few systematic studies.
- For elders with dementia, some evidence of efficacy, but health risks are prominent (aripiprazole (Abilify), olanzapine (Zyprexa), risperidone (Risperdal)).
- Quetiapine (Seroquel) shown to have some efficacy in GAD.
- Risperidone had some efficacy in OCD.
- Side effects common.


Antipsychotics and chronic pain

- 11 studies, small overall N (<800 pts); 5 RCTs
- EPS (parkinsonism, akathisia), sedation most common side effects
- "Antipsychotics possible as adjunct therapy, but
  - Side effects of EPS and sedation must be considered
  - Study results are mixed, relatively low confidence due to small samples, nonstandard outcomes.


Olanzapine + Fluoxetine v. Fluoxetine in Treatment Resistant MDD: Time to relapse following successful combination treatment

Cariprazine (Vraylar)

- FDA approved 17 Sept 2015 after long delay.
- Adult schizophrenia and bipolar disorder.
- Potentially novel mechanism of action: post synaptic dopamine partial agonist (D2, D3).
- Rec. dose: 1.5-6 mg/d*
  - But.
  - But, But, But.
- Many SE’s are those of typical dopamine blockers (tremor, extrapyramidal sx)
- Weight gain in short (3 wk trial) of >1 lb.
- Zo….wait and see, my pretties…”
  - (But the snark in me says a partial agonist is a partial antagonist)

Brexpiprazole (Rexulti)

- Novel, “rationally designed” adjunct for treatment of MDD, schizophrenia.
- Dose 1-3 mg d (adjunctive MDD); 2-4 mg/d (schizophrenia)
- Similar to aripiprazole, but more 5HT1a activity and less D2 activity
- Several short term, controlled trials suggest efficacy
- Weight gain (modest) and akathisia seen in short term trials
- Difference between this and aripiprazole unclear.


Rexulti (brexpiprazole)

- Second generation antipsychotic; July 2015 FDA approval for adult schizophrenia, adjunct for MDD.
- Activity at dose 2-4 mg/d in schiz, 0.5 1 mg/d for MDD.
- Like other SGAs: Partial D2 and 5HT1a agonist, partial 5HT2a antagonist.
- Weight gain, akathisia, sedation common side effects.
- Weight gain and lipids changes less than with other SGAs?*
  - Strong 2D6 and 3A4 metabolism, lower doses with slow metabolizers.
  - Boxed warning: elders with dementia.
  - *NB, trials were only 6 weeks

Olanzapine long acting – RELPREVV

- Olanzapine pamoate – long acting injection.
- For RELapse PREVention?
- Small number of deaths due to Post Injection Delirium Sedation Syndrome.
- Likely due to injection error – drug entered bloodstream directly.
- Patients must wait in clinic 3 hours post injection for monitoring.
- Duration of action up to 1 month.
- Dose conversion: 10 mg oral = 150 mg injectable every 2 wks or 300 mg every month.
### Symbyax

- Combination of olanzapine and fluoxetine (6/26 or 12/50), released late 2003, indicated for depression in bipolar DO.
- Published data only on 86 patients in 8 week trial.
- No evidence of antidepressant induced mania in this small # of patients.
- Symbyax more effective in reducing depressive sx than olanzapine alone or placebo
- Cx: MAOIs, thioridazine, elders with dementia
- Precautions: Endocrine dysfunction, weight gain, higher risk of TD in patients with affective psychosis. Warn re: hyperglycemia/diabetes, weight gain.

### PSYCHOSTIMULANTS

### ADHD diagnosis and treatment 2000-2010

**Stimulants - general considerations**

- Largest effect size for ADHD of any medication or treatment.
- Issues of dependence make all DEA schedule II drugs (no phone Rx, no refills)
- Are sympathomimetics - may lower seizure threshold, cx in hypertension
- Weight loss, insomnia, headache, irritability common side effects; may worsen anxiety, tics (but not associated with irreversible tic)
- Cannot be used with MAOIs

**General considerations - ADHD**

- 13.3% boys and 5.6% girls aged 4-17 have dx ADHD
- In general, 10% of children have dx ADHD
- Boys 2x more likely than girls
- Largest increase in dx in the 6-12 age range in past 7 years.
- Highest rate of dx in Caucasian children (11.5%)
  - African American (8.9%)
  - Hispanic (6.3)
- More commonly diagnosed in children with public or private insurance.
- More commonly diagnosed in relatively low income children

**Stimulants in children - controversies**

- Long term neuronal development
  - evidence unclear, some animal models suggest deficits may occur
- Propensity for later drug abuse
  - evidence unclear, answer is likely no
- Growth retardation
  - short term appetite, growth suppression seen, no long term effects noted

**Stimulants strength of evidence**

- Well conducted meta-analysis suggests that methylphenidate use results in
  - VERY MODEST improvements in
    - Teacher reported symptoms
    - Teacher reported general behavior
    - Parent reported quality of life
    - Some mild adverse effects (physiological, appetite)
    - No serious adverse effects.

Basic Science and the psychostimulants: 2 easy pieces

- Basically, there remains a simmering controversy about whether exposure to stimulants in childhood leads to changes in (a) brain morphology or (b) drug seeking behavior.
- In general, the answer is a qualified “no”. But many studies are in non-humans, e.g.:

From the abstract: “… methylphenidate and amphetamine at therapeutic blood/plasma levels during peri-adolescence in non-human primates have little effect on physiological or behavioral/cognitive development.”

2016: A stimulating year

- Two new preparations of MPH, AMPH
  - QuilliChew ER:
    - Long acting MPH chewable tablet
    - Once daily dosing (30% IR and 70% ER)
    - Age 6 and above; starting dose 20 mg up to 60 mg.
  - Methyl CT is also a chewable tablet, but IR MPH
  - Dynavel XR
    - Amphetamine in d and l forms: 2.5 mg/ml = 4 mg tablet
    - Both IR and XR amphetamine in liquid
    - Age 6 and above
    - 2.5 to 5 mg in morning, up to 20 mg/d

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<table>
<thead>
<tr>
<th>Drug (Trade)</th>
<th>Drug (generic)</th>
<th>Age range</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderal and others</td>
<td>Adderal and others; Amphetamine + dextroamphetamine</td>
<td>3-5</td>
<td>2.5 mg – 40 mg 5-40 mg/d (up to 60 in narcolepsy)</td>
<td>ADHD Pediatric narcolepsy (6 and older)</td>
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<tr>
<td>Adderal ER</td>
<td>Methyl salt amphetamines ER</td>
<td>6-12</td>
<td>10-30 mg/d</td>
<td>ADHD</td>
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<tr>
<td>Dexedrine, Dexedrine Spanules (LA)</td>
<td>Dexedrine</td>
<td>6 and up</td>
<td>5-40 mg (5-60 mg/d for narcolepsy)</td>
<td>ADHD Pediatric narcolepsy</td>
</tr>
<tr>
<td>Zentedri</td>
<td>methamphetamine</td>
<td>6 and older 12 and older</td>
<td>5-25 mg/d 5 mg before meals</td>
<td>ADHD Exogenous obesity</td>
</tr>
<tr>
<td>Dynavel XR</td>
<td>Amphetamine CR oral</td>
<td>6 and older 12 and older</td>
<td>2.5-20 mg</td>
<td>ADHD</td>
</tr>
<tr>
<td>Regimex</td>
<td>Benzphetamine</td>
<td>12 and older</td>
<td>25-150 mg/d</td>
<td>Exogenous obesity</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Lisdexamphetamine</td>
<td>6 and older</td>
<td>30-70 mg/d</td>
<td>ADHD</td>
</tr>
</tbody>
</table>

Methylenidate preparations (partial)

<table>
<thead>
<tr>
<th>Drug (trade)</th>
<th>Drug (generic)</th>
<th>Ages</th>
<th>Doses</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta</td>
<td>Lisdexamphetamine</td>
<td>13-17</td>
<td>10-72 mg/d</td>
<td>ADHD</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>MPH ER</td>
<td>6-15</td>
<td>10-60 mg/d</td>
<td>ADHD</td>
</tr>
<tr>
<td>Aparistine XR</td>
<td>MPH ER</td>
<td>6 and up</td>
<td>2.5 mg x2 daily, to 10 mg x2 daily</td>
<td>ADHD</td>
</tr>
<tr>
<td>Quillichew</td>
<td>dexMPH ER</td>
<td>6 and up</td>
<td>20-60 mg/d</td>
<td>ADHD</td>
</tr>
<tr>
<td>Focalin</td>
<td>dexmethylphenidate</td>
<td>6-17</td>
<td>2.5 mg x2 daily, to 10 mg x2 daily</td>
<td>ADHD</td>
</tr>
<tr>
<td>Methylin CT</td>
<td>MPH IR (chewable)</td>
<td>6 and up</td>
<td>10 mg patch daily</td>
<td>ADHD; FDA (2015) adds warning re: permanent skin color changes under patch.</td>
</tr>
<tr>
<td>Daytrana</td>
<td>MPH transdermal patch</td>
<td>6 and up</td>
<td>10 mg patch daily</td>
<td>ADHD</td>
</tr>
</tbody>
</table>

*also indicated for pediatric narcolepsy
Other agents

<table>
<thead>
<tr>
<th>Drug (trade)</th>
<th>Drug (generic)</th>
<th>Ages</th>
<th>Doses</th>
<th>Indications</th>
<th>Concerns, cautions, pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strattera</td>
<td>Atomoxetine</td>
<td>6-17; up to 70 kg</td>
<td>0.5 mg/kg/d up to 1.2 mg/kg/d; max 100 mg/d</td>
<td>ADHD</td>
<td>Black box (suicide); 2D6 poor metabolizers; BP concerns</td>
</tr>
<tr>
<td>Kapvay</td>
<td>Clonidine ER</td>
<td>6-17</td>
<td>0.1 mg at bed up to 0.4 mg in divided dose</td>
<td>ADHD</td>
<td>Very sedating; BP change, orthostasis</td>
</tr>
<tr>
<td>Intuniv</td>
<td>Guanfacine ER</td>
<td>6-17</td>
<td>1-7 mg/d</td>
<td>ADHD</td>
<td>Very sedating; BP change, orthostasis</td>
</tr>
</tbody>
</table>

Modafinil (Provigil), Armodafinil (Nuvigil)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Indications</th>
<th>Dose</th>
<th>Notes</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>Provigil</td>
<td>Excess sleepiness associated with: Narcolepsy, Shift work sleep disorder, Obstructive sleep apnea</td>
<td>100-200 mg/d</td>
<td>2D6 inducer: May induce steroid birth control 3A4 inhibitor: diazepam, phenytoin</td>
<td>Controlled: Cat IV; Rare Stevens-Johnson, heart rate abnormalities; No data in pregnancy/lactation</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>Nuvigil (R-antipode of modafinil)</td>
<td>Excess sleepiness associated with: Narcolepsy, Shift work sleep disorder, Obstructive sleep apnea</td>
<td>150-250 mg/d</td>
<td>2D6 inducer: BCPs 3A4 inhibitor: Diazepam, phenytoin</td>
<td>Controlled: Cat IV; Rare Stevens-Johnson, heart rate abnormalities; No data in pregnancy/lactation</td>
</tr>
</tbody>
</table>


Vyvanse (lisdexamfetamine)

- Prodrug - metabolized on RBCs to dexamphetamine
- Evidently lower potential for abuse due to time to metabolize
- Longer half life = longer duration of action
- Dosage (pediatrics, adolescents (6-17 yrs), adults, 30 mg in the morning, up to maximum of 70 mg.
- DEA Schedule II drug.

Non-stimulant for ADHD – guanfacine (Intuniv; Intuniv ER; Shire)

- An older antihypertensive agent (Tenex; approved 1986) now approved for adjunctive therapy – ie, in addition to stimulant management – in ADHD
- Nonselective alpha-2 agonist
- Intuniv IR released 2009; Intuniv ER – once daily dosing: 1-4 mg daily
- Somnolence, fatigue, hypotension, syncope possible adverse effects
- Pregnancy category “B”
- Metabolized via CYP 3A4 – serum concentrations increased with coadministration of CYP3A4 inhibitors, decreased with coadministration of CYP3A4 inducers.
- Clonidine – potent alpha agonist – also indicated.
Atomoxetine (Strattera)

- Released January 2003 Eli Lilly
- Presynaptic norepinephrine reuptake inhibitor
- Investigated as non-stimulant pharmacotherapy in ADHD
- Controlled trials suggest some global benefit in ADHD over placebo, few adverse events - rash? Insomnia? BP/HR?
- Genotyping for poor metabolizers?
- Doses in children 0.5-1.5 mg/kg; adults 40-80 mg, Start low, titrate up, caution with 2D6 inhibitors, cx with MAOI
- Theoretically a potential antidepressant - long history of investigation
- Dec 2004 Lilly adds warning to patients with jaundice or liver injury to stop - 2 reported cases of hepatic failure
- FDA public health advisory 2005: Increased risk of suicidal thinking/behavior in children using atomoxetine

Clonidine’s effect on sleep architecture

- Poorly studied phenomenon.
- Recall that clonidine is a alpha 2 noradrenergic agonist, used in HTN, others.
- Miyazaki (2004) found differences in low v. high dose clonidine:
  - Low-dose increased REM, decreased non-REM. Medium dose decreased REM, increased non-REM.
  - Hypothesis: Low dose affects presynaptic neurons in locus coeruleus, medium dose acts post-synaptically.
  - Clonidine does apparently affect sleep architecture, but behavioral effects uncertain.

Black Box Warnings re: Stimulants (3)

1. Amphetamines and amphetamine derivatives: Potential for Abuse
2. Methylphenidate: Drug Dependence
3. Atomoxetine: Suicidal ideation in Children and Adolescents
   - Bolded warning for atomoxetine: risk of hepatic injury/jaundice

Anxiolytics and GABA Receptor Agonists
Methaqualone

- Non-barbiturate sedative (quinazolobenzodiazepine) introduced in the 1950s
- Once was among most widely used drugs in the US.
- Mechanism of action is GABA-ergic at BDZ receptor sites.
- No longer used in the US, but widely available elsewhere, often under the name Mandrax (methaqualone + diazepam).
- One of the most commonly smuggled drugs into certain countries.

Ah, the 50’s….

- New Yorker cartoon, late 1950s
- When meprobamate (Equanil, Miltown) was King –
  - First “lifestyle” drug –
  - Minor “tranquillizer”
  - Carbamate derivative:
  - Acts at barbiturate subunit of GABA receptor complex
- The first Prozac

Syndromes of the 60’s: Marketing the first lifestyle drug

FDA approved sedative hypnotics

- **Alcohols:**
  - Placidyl (ethchlorvynol)
- **Barbiturates:**
  - Butisol sodium (butabarbital sodium)
  - Parasol (pentobarbital and carbromal)
  - Seconal (secobarbital sodium)
- **Benzodiazepines:**
  - Dalmane (flurazepam hydrochloride)
  - Boral (quazepam)
  - Edluar (zolpidem tartrate)
  - Halcion (triazolam)
  - Prosom (estazolam)
  - Restoril (temazepam)

- **GABA receptor agonists:**
  - Ambien, Ambien CR (zolpidem tartrate)
  - Edluar (zolpidem tartrate)
  - Intermezzo (zolpidem)
  - Lunesta (eszopiclone)
  - Sonata (zaleplon)
  - Zolpimist (zolpidem tartrate)

- **Melatonin receptor agonists:**
  - Rozerem (ramelteon)

- **Orexin receptor agonists:**
  - Belsomra

- **Tricyclics:**
  - Silenor (doxepin hydrochloride)
Anxiety disorders in primary care: CALM down

- Craske et al (2011) compared computer assisted, modularized treatment of common anxiety disorders vs TAU in 1004 primary care patients with GAD, SAD, PTSD, PD.
- Coordinated Anxiety Learning Management (CALM) + Rx (SNRI or SSRI, +/- BDZ, or TAU).
- CALM is 6 based cognitive restructuring plus 2 exposure modules.
- CALM+ Rx > TAU for GAD, PD, SAD, usually at up to 18 months followup.


CBT plus GRA: Modest improvement with combined tx

- Morin, et al (2009): 6 wks of CBT or 6 wks combined CBT and 10 mg hs zolpidem, 6 wk acute or 6 mo extended tx, rated at 6 mo. followup. Both were efficacious.
- Acute CBT group: 6 90 min. group sessions of CBT focusing on distorted sleep beliefs, sleep hygiene, sleep logs. Acute combined group had slightly better outcomes (longer sleep time with zolpidem).
- Extended combined group: combined group (monthly indiv CBT + pm zolpidem, up to 10/mo) slightly worse outcomes than acute combined followed by CBT alone.

Insomnia and the “Z” drugs – Zaleplon, Zolpidem, Zopiclone

- Selective BDZ 1 receptor drugs are effective for insomnia
- But tolerance, dependence have been observed.
- Should not be used for long term use
- Behavioral treatments (sleep hygiene) more efficacious in the long run
Do Benzodiazepines cause dementia?

- Almost certainly NOT. BUT:
  - BDZs affect cognitive efficiency, may differentially impair same in patients with dementia/head injury, etc.
  - BDZs have a panoply of adverse side effects in addition to cognitive effects:
    - Psychomotor slowing, impaired coordination = falls risk, disorientation in elders.
  - Many BDZs highly lipophilic, elders have higher fat:striate muscle ratios, may accumulate BDZs in peripheral fat tissue.
  - Ergo: use sparingly, only shorter acting agents, watch for physical/cognitive sequelae.
  - Good recent review found no increased risk assoc with BDZ use in elders:

Asleep at the wheel: Emerging problems with GRAs

- Many reports of anterograde amnesia
- Dyscoordination
- Impaired reflexes
- Hallucinations (visual) other unusual behavior rare but well documented in literature
- Medicolegal file growing –
  - Excellent review is:
  - Recent population study demonstrated higher risk of hip fracture in elders with use of zopiclone (Nishtala, et al., 2017, Zopiclone use and risk of fractures in older people, J. Am. Med. Dir. Assoc., 18, 368.

<table>
<thead>
<tr>
<th>GABA RECEPTOR AGONIST TYPE DRUGS</th>
<th>Class</th>
<th>Drug</th>
<th>FDA Schedule</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-drugs</td>
<td>Zolpidem (Ambien; Intermezzo SL)</td>
<td>IV</td>
<td>5-10 mg or 1.75-3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eszopiclone (Lunesta)</td>
<td>IV</td>
<td>1-3 mg, maybe lower?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zaleplon (Sonata)</td>
<td>IV</td>
<td>5-20? Recommend lower, &quot;middle&quot; insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zopiclone (Imovane*)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Melatonin Agonist</td>
<td></td>
<td>Ramelteon (Reserem) MT1 agonist</td>
<td>Not scheduled</td>
<td>8 mg</td>
</tr>
<tr>
<td>Orexin Agonist</td>
<td></td>
<td>Suvorexant (Belompra)</td>
<td>IV</td>
<td>5-20 mg</td>
</tr>
<tr>
<td>GABA agonist</td>
<td></td>
<td>Zyrem (sodium oxybate)</td>
<td>III</td>
<td>4.5-9 grams nightly in 2 doses</td>
</tr>
</tbody>
</table>

Recall – low doses always better

Summary of GRAs and related compounds

- Z-drugs
- Zolpidem – Ambien, Ambien CR, Zolpimist, Intermezzo
- Zopiclone – Imovane (Canada) not avail in US
- Eszopiclone – Lunesta
- Zaleplon – Sonata
- Indiplon – not released
- Melatonin agonists
  - Ramelteon – Rozerem (MT1 agonist)
- Orexin antagonists
  - Belsomra
- GHB – gamma hydroxybutyrate (GABA agonist Zyrem – sodium oxybate)
The Sleeper Summary Slide

- Short to medium acting BDZs and GRAs have utility in short term tx of insomnia.
- Should be combined with sleep hygiene instruction and possibly CBT for insomnia.
- Use only intermittently to avoid risks of habituation/rebound insomnia.
- Both BDZs and GRAs have risks, particularly in combo with other sedatives/EtoH.
- OTCs often have daytime hangovers, mental confusion, dry-mouth, generally not well tolerated.
- Herbals: Kava, valerian and others may work, but patients rarely get what’s on the bottle – hence, avoid.

<table>
<thead>
<tr>
<th>Sleep Hygiene</th>
<th>CBT</th>
<th>Hypnotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed for sleeping, no other activities; dark room, eye patch?</td>
<td>Distorted thinking about sleep</td>
<td>GRAs</td>
</tr>
<tr>
<td>No daytime napping; no EtoH, tobacco</td>
<td>Insomnia troubling, but common</td>
<td>MT1 (melatonin) agonists (Ruzerem)</td>
</tr>
<tr>
<td>Restrict caffeine - oil or none in pm; check for hidden stimulants</td>
<td>8 hours uninterrupted sleep not norm</td>
<td>Medium acting BDZs (temazepam, lorazepam, oxazepam)</td>
</tr>
<tr>
<td>Dinner several hours before bedtime; 'power-down' routine (bath, PMR, no TV)</td>
<td>Query for anxiety producing cognitions/events</td>
<td>Avoid: OTCs (mostly diphenhydramine, other antihistamines) herbals</td>
</tr>
<tr>
<td>7 day sleep wake cycle</td>
<td>Thought substitution for anxiety reduction</td>
<td>Note: Falls risk, dependence, interaction with EtoH, other sedatives</td>
</tr>
</tbody>
</table>

Ethchlorvynol – Placidyl

- Of a class of chloral derivative alcohol based compounds.
- Rarely if ever used.
- Use is NOT recommended but there is a slight chance you may encounter this.
- FDA Schedule IV drug.
- Use: night and daytime sedation.
- Dose: Unknown, Abbott suggested 200-500 mg for sleep.
- Interactions: alcohols, any class of benzodiazepine or nonbenzodiazepine sedative/hypnotic.
- Mechanism of action: Unknown.

Belsomra (suvorexant; Merck)

- Orexin receptor antagonists.
- Orexin – neurotransmitter associated with wakefulness.
- Specific for neuropeptide orexin.
- Single or dual antagonists (SORAs or DORAs).
- New DORA (approved 2014) Belsomra.
- Many side effects similar to other sedative hypnotics, benzodiazepines, GABA receptor agonists* (daytime sedation; psychomotor dyscoordination, interactions with benzodiazepines, alcohol, other sedatives).
- Category IV controlled substance.
- Dose: Initiate with 5 mg, up to 20 mg.

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THIS JUST IN:

WEBINAR: SAHMSA HRSA Center for Integrated Care:
Managing Benzodiazepines: Best Practices and Alternatives

Wednesday, May 31, 2017, 12:00 PM ET/ 9:00 AM PT. Register for free at: https://goto.webcasts.com/starthere.jsp?ei=1146055.
Drugs for Alzheimer’s disease and other dementias

Cognitive Enhancers for Alzheimer’s Dementia

<table>
<thead>
<tr>
<th>Drug (generic)</th>
<th>Drug (trade)</th>
<th>Mild</th>
<th>Mod/Sev.</th>
<th>MOA*</th>
<th>Dose</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (tablet, oral)</td>
<td>Aricept</td>
<td>X</td>
<td>Cholinesterase inhibitor</td>
<td>T: 5 mg/d, up to 10 mg (4–6 wks); max 23 mg/d</td>
<td>O: Same</td>
<td>N/V; diarrhea, weight loss, fatigue</td>
</tr>
<tr>
<td>Galantamine (tablet, oral)</td>
<td>Razadyne</td>
<td>X</td>
<td>Cholinesterase inhibitor; nicotinic receptor agonist</td>
<td>T: 4 mg 2x/d, then 8, 12 mg 2x/d at 4 wk intervals; max 24 mg/d</td>
<td>O: Same, but 1x/d</td>
<td>N/V; diarrhea, weight loss, fatigue</td>
</tr>
<tr>
<td>Rivastigmine (capsule, patch, liquid)</td>
<td>Exelon</td>
<td>X</td>
<td>Cholinesterase inhibitor, butyrylcholine enhancer</td>
<td>C: 1.5 mg x2/d; then 6, 9, 12 mg x2/d q 2 wks; P: 4.6 mg/d, then 9.5, 13.3 mg/d q 4 wks</td>
<td>O: Same as capsule</td>
<td>N/V; diarrhea, weight loss, fatigue</td>
</tr>
<tr>
<td>Memantine (tablet, liquid, ER capsule)</td>
<td>Namenda</td>
<td>X</td>
<td>NMDA antagonist (GLU inhibitor)</td>
<td>T, O: 5 mg/d, then 10, 15, 20 mg/d (divided doses)</td>
<td>ER: 7, 14, 21, 28 mg/q 1 wk</td>
<td>Headache, N/V, diarrhea, dizziness</td>
</tr>
<tr>
<td>Memantine ER + donepezil</td>
<td>Namzaric</td>
<td>X</td>
<td>Cholinesterase inhibitor; NMDA antagonist</td>
<td>28 mg MEM ER + 10 mg DON daily; 14 + 10 mg/d for renal disease</td>
<td>Same as both drugs</td>
<td></td>
</tr>
</tbody>
</table>

*MOA = Mechanism of Action; GLU = Glutamate; ER = extended release

NICE Guidance on drugs for Alzheimer’s disease
(National Institute for Health and Care Excellence; www.nice.org.uk)

- Recommends AChE inhibitors (donepezil, galantamine, rivastigmine).
- Drugs initiated by specialist in dementias.
- Treatment continued only when demonstrable effect on cognitive, behavioral, functional or global symptoms.
- Regular re-assessment of patients taking meds; input from team and families.
- No difference among AChEs, therefore start with least costly drug as tolerated.

US approved Psychopharmacological Treatment for AD

Cholinesterase Inhibitors
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Donepezil (Aricept)
- Tacrine (Cognex) withdrawn in 2013

Neuromodulators
- Memantine (NMDA receptor antagonist)

Combination
- Memantine and Donepezil (Namzaric)

Unapproved/Alternative therapies
- Estrogen replacement, NSAIDS, Vitamin E
  - No evidence that estrogen replacement, NSAIDS or Vitamin E have a protective effect or a therapeutic effect in the treatment of dementia.
  - Cochrane review (McGuinness, et al., 2014; Statins for the treatment of Alzheimer’s disease): No evidence supporting use of statins in AD.
- Potential new drugs: huperzine, vinpocetine [vinca alkaloid]
AD Symptom Control Approaches

- For depression and insomnia,
  - minor tranquilizers or antidepressants
- For psychotic symptoms,
  - Neuroleptics may be prescribed, but may cause serious unwanted side-effects
- Instead of behavioral management, use environment restructuring to
  - Ensure safety
  - Provide appropriate stimulation and
  - Redirect inappropriate behavior

Tacrine (Cognex)

- Older cholinesterase inhibitor; withdrawn in 2013.
- More associated with gastrointestinal and hepatic problems:
  - Alanine transferase elevations noted (ALT); strong CYP450 metabolism
  - Monitor at 3x normal; discontinue at 5x normal
  - Level of investigation less certain for this agent, often due to large numbers of withdrawals from trials.
  - Less evidence of a significant difference in cognitive functioning compared to placebo with tacrine versus other cholinesterase inhibitors.

Memantine (Namenda; with donepezil, Namzaric)

- A partial antagonist of the NMDA receptor.
- Blockade of the NMDA receptor may downregulate activity of the excitatory neurotransmitter glutamate.
- Excessive glutamate activity is speculated to lead to destruction of glutaminergic neurons.
- Doses of 20 mg/day commonly studied, suggest some small clinical improvement, moderate side effects (agitation not among them), at least one study suggests memantine may be used with donepezil with no adverse interactions.
- Short-term studies (<26 weeks), clinical outcomes uncertain.
- Memantine and donepezil (Namzaric) may confer small benefit (cognitive decline) at 6-months, no compelling evidence of improvement in other symptoms.

Depression in dementia

- Depression
  - Not infrequently co-occurs with dementia
  - About 40% of AD patients have depressive symptoms, though not necessarily a major depressive episode
  - Exploration of depressive symptoms may reveal motivational and affective difficulties, perhaps reaction to lifestyle changes due to disability
Lewy body dementia

- 2nd most common form of dementia, after Alzheimer’s (approx 20% of pts with dementia have LBD). Histological findings of Lewy bodies in cells and amyloid plaques.
- Dementia with delirium, visual hallucinations, and parkinsonism, along with syncope, falls, sleep disorders, and depression.
- AchE inhibitors are possibly more effective than in Alzheimer’s
- Clinical caution: Antipsychotics, particularly FGAs, should not be used in patients with Lewy body dementia, they can cause a precipitous decline in cognitive and physical functioning.

Anticonvulsants

Significant increase in use of anticonvulsants in children over past 15 years

- For anticonvulsant visits, 1.7 fold increase for psych reasons, no change in level of visits for seizure disorders
- Average use of anticonvulsants for psych disorders increased from .33% to .68% of all visits
- Significant increase in use of anticonvulsants for bipolar disorder and disruptive behavior disorders

### Anticonvulsants with FDA indication for bipolar disorder

<table>
<thead>
<tr>
<th></th>
<th>Acute Bipolar Depression</th>
<th>Acute Bipolar Mania</th>
<th>Bipolar Maintenance</th>
<th>Not approved for BPD (partial list)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Lithobid; 1970</td>
<td>Lithobid; 1974</td>
<td>Gabapentin (Neurontin)</td>
<td>Topiramate (Topamax)</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Depakote, 1994/2005</td>
<td>Lamotrigine (Lamictal, 2004)</td>
<td>Pregabalin (Lyrica) Others...</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Equetro; 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### “Second generation” anticonvulsants and beyond

- All have been used in managing bipolar disorder
- Investigations unsystematic
  - open label trials, small n’s, no convincing meta-analyses
  - Some have significant toxicity, but often overall profile superior to lithium.
- Only Carbamazepine (Tegretol, generic, others) and Valproic acid (Depakote, Depakene, generic) and Lamotrigine (Lamictal, generic) indicated for management of bipolar depression, mania, or maintenance.

### Serum levels: Anticonvulsants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Therapeutic level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine(ER)</td>
<td>4 mg/5 mg/10 mg/15 mg per ml</td>
</tr>
<tr>
<td>Carbamazepine(DEP)</td>
<td>200 mg/300 mg/500 mg/600 mg per ml</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>10 mg per ml to 26 mg per ml</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>50 mcg per ml to 166 mcg per ml</td>
</tr>
</tbody>
</table>
### Anticonvulsants used in mania

<table>
<thead>
<tr>
<th>Name (trade)</th>
<th>Name (generic)</th>
<th>Indications</th>
<th>Dose</th>
<th>Cautions, Concerns, Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depakote, Depakene, Stavzor</td>
<td>Valproic acid, Sodium divalproex</td>
<td>Mania in bipolar disorder, Seizure disorder, Migraine headache pain</td>
<td>500-2,000 mg/d</td>
<td>Target plasma levels: 50-150 mg/ml Hepatotoxicity Contraindicated in pregnancy (D)</td>
</tr>
<tr>
<td>Eskalith, Lithobid</td>
<td>Lithium carbonate</td>
<td>Mania in bipolar disorder</td>
<td>600-1,200 mg/d</td>
<td>Target plasma levels: 0.6-1.2 meq/l Brugada syndrome (sudden death due to cardiac arrhythmia) Renal, thyroid toxicity Elevate levels with NSAIDs Contraindicated in pregnancy (D)</td>
</tr>
<tr>
<td>Lamotrigine Lamictal</td>
<td></td>
<td>Bipolar Maintenance, &gt; 18</td>
<td>200-400 mg/d, 100 mg/d if taking valproic</td>
<td>No target plasma levels Valproate decreases clearance (100 mg/d) Oral contraceptives may need higher doses Rash, Stevens-Johnson Syndrome NOT cx in pregnancy</td>
</tr>
</tbody>
</table>

### Update on lithium

- Recent review of 60 years of lithium studies. **LITHIUM DOES**
  - Impair urinary concentration and kidney function, however overall rates of renal failure low.
  - Decrease thyroid function leading to clinical hypothyroidism (OR 5.78 compared to placebo) and increases parathyroid activity (increased serum calcium and parathyroid hormone).
  - Definitely associated with increased weight gain (OR 1.89 compared to placebo).
  - Lithium’s association with teratogenicity may not be as robust as previously assumed.
  - Lithium’s dermatologic effects may be more benign than previously assumed.
- **Cautions:**
  - Authors noted that dose ranges unclear, studies of variable quality
- **Conclusions:**
  - Lithium may not be as toxic as previously assumed (note however, that sudden death, cardiac arrhythmias, suicide were not analyzed in meta-analysis).
  - Newer anticonvulsants have numerous toxicities and side effects.
  - **Clinical judgment** is key in initiating, maintaining and discontinuing lithium.

Thank you for your kind attention!!