Antipsychotics (also known as *neuroleptics* or major *tranquilizers*)
WHAT IS YOUR DIFFERENTIAL DIAGNOSIS?

Depression
Delirium
Dementia
ETIOLOGY MNEMONIC

- Infectious
- Withdrawal
- Acute metabolic
- Trauma
- Central nervous system pathology
- Hypoxia
- Deficiencies (nutritional)
- Endocrinopathies
- Acute vascular
- Toxins/drugs
- Heavy metals

See CCSMH Delirium Guidelines p 31 (Table 3.1)
You now attempt to see Mrs. O to obtain her history and observe her current mental status. She is dressed in a hospital gown lying in bed, looking older than her stated age. Her eyes are closed, and you have a difficult time rousing her.

Her words are slurred and difficult to understand. She is unable to respond appropriately to your questions. She appears to be picking at things in the air. You are unable to assess her mood, but her affect is restricted. She is confused, and when asked where she is mumbles something about “being in Newfoundland”.
As you are unable to obtain much information from Mrs. O’Leary, what should you do now?

OBTAIN COLLATERAL
Collateral

Medications

1. Metoprolol 25 mg BID
2. Atorvastatin 20 mg OD
3. ECASA 81 mg OD
4. Multivitamin Í tab OD
5. Amitriptyline 10 mg HS
6. Ramipril 5 mg OD*
7. Ranitidine 150 mg OD*
8. Hydromorphone 2-4 mg q2h prn*
   – Receiving approx. 6 mg/day

*New medications
PHARMACOLOGICAL MANAGEMENT

WHAT TYPES OF MEDICATIONS ARE FREQUENTLY USED IN MANAGING THE SYMPTOMS OF DELIRIUM?

ANTIPSYCHOTICS
(TYPICAL, ATYPICAL)

BENZODIAZEPINES
HALOPERIDOL

WHAT SIDE EFFECTS WOULD YOU MONITOR FOR?

• QT prolongation
  – Risk of ventricular arrhythmias
  – Consider getting a baseline ECG

• Extrapyramidal side effects
  – Acute dystonia
  – Parkinsonism
  – Akathisia

• Neuroleptic malignant syndrome

• Orthostatic hypotension (falls)

• Oversedation
ATYPICAL ANTIPSYCHOTICS

• Some evidence for risperidone, olanzapine, and quetiapine
• Clozapine is NOT recommended
• Lower rates of extrapyramidal side effects compared to haloperidol
• Considerations:
  – Olanzapine has anticholinergic properties
  – Metabolic syndromes
    • Glucose dysregulation
    • Hypercholesterolemia
    • Less relevant if used for short duration
  – Increased risk of stroke/mortality in dementia patients
    • Possibly less relevant if used for short duration
ATYPICAL ANTIPSYCHOTICS

• Dosing:
  – Risperidone
    • 0.25 mg od-bid
  – Olanzapine
    • 1.25-2.5 mg/day
  – Quetiapine
    • 12.5-50 mg/day

• Preferred if patient has:
  – Parkinson’s Disease
  – Lewy Body Dementia
# Traditional Mood Stabilizers

**FDA Indications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mania</th>
<th>Mixed</th>
<th>Depression</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carbamazepine ER</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Lithium Uses

• Gold standard for BPD
  – Mania, bipolar depression, maintenance therapy

• However... a substantial number of patients do not respond to lithium

<table>
<thead>
<tr>
<th>Response Rates</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Phase</td>
<td>60-80%</td>
</tr>
<tr>
<td>Mixed Phase</td>
<td>40%</td>
</tr>
<tr>
<td>Rapid Cyclers</td>
<td>30%</td>
</tr>
</tbody>
</table>
Lithium Mechanism of Action

- Reduces norepinephrin and dopamine sensitivity in the CNS
- Inhibits dopamine synthesis
- Enhances GABA activity and normalizes its levels in CNS
  - GABA: Inhibitory neurotransmitter
- Inhibits inositol phosphatase secondary messenger system
Lithium Treatment Considerations

• Pt may not tolerate
  – Dyspepsia, GI upset, Wt gain (~20%), decreased cognition

• Dose related side effects
  – Action tremor (1-2 hours after dose), sedation, lethargy, polyuria, polydipsia,
  – Increased cognitive dulling & GI upset

• Toxicity >1.5 mEq/L
  – Course tremor/twitching, dizziness/syncope, confusion, slurred speech, ataxia, convulsions, stupor, coma, death
Lithium Side Effects

• Excreted primarily through the kidney
  – Use cautiously in pts with Renal failure, dehydration, Na depletion
  – Renal damage may occur in long term usage (10 years+)
• May cause benign and reversible heart arrhythmias & bradycardia
  – Use cautiously in pts with cardiovascular disease
• Concentrates in the thyroid
  – 5-35% of pts may develop hypothyroidism within 6-18 months of treatment
• Rarer side effects
  – Dermatology: psoriasis, alopecia, folliculitis
  – Diabetes insipidus (blocks ADH)
  – Leukocytosis
Lithium Drug Interactions

• Increased [Li]:
  – ACEI or ARBS 200-300%
    • Case reports up to 3 months
  – NSAIDs/Cox2 inhibitors (except sulindac) 50%
  – Diuretics (esp. thiazides) 20-50%

• Decreased [Li]
  – Increase renal blood flow thus decrease Li levels: Caffeine and theophylline

• Increased risk of neurotoxicity
  – With antipsychotics, SSRI, TCA, calcium channel blockers, carbamezepine
    • Increases in slurred speech, ataxia, confusion
Lithium Dosing

• Initial titration phase
  – 300 mg BID or TID
  – Lithium levels 5-7 days after dosage change trough at 8-12 hours after last dose
  – Titration: every 300mg increase will led to a 0.3 change in serum levels

• Doses as high as 1200 to 1800

• Dose increase until level is in therapeutic range or until side effects are present (lower for elderly)
Lithium Dosage Forms

- Immediate release capsule
  - 150, 300, 600mg
- Eskalith CR
  - 450mg tablet
- Lithobid SR
  - 300mg tablet
- Lithium citrate syrup
  - 300mg/5ml
Lithium Levels

• Narrow therapeutic index
  – Acute mania: 1.0 and 1.2 mEg/L
  – Maintenance: 0.6 to 1.0 mEg/L
• May take 5-10 days to see therapeutic effects
  – Maximal effects 2-3 weeks
• Abrupt withdraw is associated with high relapse rates
Lithium Monitoring

• TSH, Chem7 (for Cr, BUN, electrolytes), pregnancy testing, base line ECG, Wt, CBC (leukocytosis)
Valproic Acid Uses & Mechanism of Action

• Wide therapeutic window
  – Preferred in mixed episodes, rapid cyclers
• Na channel blocker, decreases glutamine release
• Affects potassium channels to have a stabilizing effect on membranes
• Enhances GABA activity within the brain
Valproic Acid Characteristics

• Valproate to Valproic acid
  – stomach

• Divalproex to Valproic acid
  – Small intestine
Valproic Acid Side Effects

• GI upset (anorexia, nausea, dyspepsia)
  – Reduce dose, add H2 antagonist, take with food, enteric coated

• Dose related side effects
  – Elevated liver enzymes, resting tremor, sedation, weight gain, somnolence, weakness, HA, thrombocytopenia

• Rare Side Effects:
  – Hepatic dysfunction: easy bruising, jaundice
  – Pancreatitis, Hyperammonemnia, Alopecia

• Toxicity
  – Tremor, ataxia, nystagmus, visual hallucinations, coma
Valproic Acid Dosing

• Initial dose 500 qd to bid
  – Loading/target dose 20mg/kg
• Increase every few days to serum concentration
  – Draw levels every 3-5 days
  – 50-125mcg/ml seizure control
• Divalproex EC/ Divalproex ER
  – 2X daily/ 1X daily
  – Increase dose by 20%
Valproic Acid Monitoring

• Base line, monthly for 2 months then 3-6 months thereafter
  – CBC, LFTs
• Also weight, ammonia (if mental status changes), serum levels
• Pregnancy test in women of child bearing years
  – Check level 5-7 days after dosage change
Carbamazepine

- Second line agent
- May be better than lithium with **rapid cycling**, mixed episodes, or atypical presentation
- Carbamazepine ER (Equetro\textsuperscript{TM})
  - New indication for acute mania and mixed episodes
- Mechanism of action
  - Augmentation of GABA
Carbamazepine Side Effects

• Dose related side effects occur 1\textsuperscript{st} month of treatment
  - Dizziness, drowsiness, HA, diplopia, nystagmus, ataxia, blurred vision, nausea, weight gain
  - Transient effects and may resolve with dose reduction

• Rare, serious side effects
  - Stevens-Johnson syndrome
  - Aplastic anemia, agranulocytosis, thrombocytopenia, leukopenia
Carbamazepine Interactions

- Potent CYP 450 inducer and 3A4 substrate
  - Carbamezapine auto-induction
  - Levels quarterly or sooner if indicated
- Increased [CBZ]
  - Azole antifungals, macrolides, fluoxetine, fluvoxamine, cimetidine, protease inhibitors
- CBZ decrease
  - Antidepressants, antipsychotics, benzos, oral contraceptives, thyroid hormone, warfarin, phenytoin, felodipine
Carbamazepine Dosing & Monitoring

• Start therapy
  – 200mg BID titrate to response
  – 400-800 mg daily
• Therapeutic level
  – Seizure disorders 6-12mg/ml
• Laboratory monitoring
  – CBC with differential bi-weekly to monthly for 2 months then every 3-6 months
  – LFTs every 6 months
    • Pt education of signs and symptoms of toxicity and adverse effects
    • Fever, sore throat, mouth ulcers, rash, easy bruising
Lamotrigine

• Approved for **maintenance** therapy only
• Effective for bipolar depression and rapid cycling
• Mechanism of action
  – Inhibits Na channels
  – Inhibits release of glutamate
Lamotrigine Side Effects

• Common side effects
  – Dizziness, tremor, somnolence, HA, nausea, ataxia, diplopia
• Seizure withdraw in epileptic patients
  – Discontinue over a 2 week period
• Rare serious adverse effect RASH
  – May resolve spontaneously but medication should be DC if occurs
  – Stevens-Johnson syndrome and epidermal necrolysis
Lamotrigine Dosing

• RASH associated with fast titration:
  – Start 12.5 to 25mg QD.
  • Increase 25-50mg daily every q 2 weeks
  • Slow titration to 200-500mg per day usually BID
  • Even slower if on Valproic Acid interaction with CYP 3A4
Oxcarbazepine

- Prodrug of Carbamazepine’s metabolite
- Second line agent for mania
  - Few controlled trials
- Initial dosing 300mg BID
  - Increase 600mg/day weekly to 1200mg total daily dose
- No auto-induction
  - Fewer drug-drug interactions than Carbamazepine
- Increases metabolism of oral contraceptives
Antipsychotics

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Nephrology & Hypertension
Oregon State University and Oregon Health & Science University
Timeline of Major Antipsychotic Therapies

ECT, etc.

- Chlorpromazine
- Fluphenazine
- Thioridazine
- Haloperidol
- Clozapine
- Olanzapine
- Quetiapine
- Aripiprazole
- Risperidone
- Ziprasidone
- Paliperidone
- Consta = Long-acting injectable risperidone
History of Antipsychotics

- 1954-1975 development of typical Aps
  Thioridazine – Mellaril
  Haloperidol- Haldol
  Trifluoperazine- Stelazine
  Perphenazine- Trilafon
  Fluphenazine- Prolixin
  Molindone-Moban
  Pimozide
Atypical Antipsychotics

Aripiprazole- Abilify
Asenaphine- Saphris
Clozapine- Clozaril
Iloperidone- Fanapt
Lurasidone- Latuda
Olanzapine- Zyprexa
Risperidone- Risperdal

Quetiapine- Seroquel
Ziprasidone- Geodon
Mechanism of Action of Antipsychotics

• Dopamine antagonist- D1-4 R
• Typical APs / Neuroleptics- D2R (tightly bound)
• Atypical Aps- D1 & 2R (loosely bound or rapid dissociation), 5HT 2A and 5HT2C
Side Effects

• EPS-Parkinsonian, Dystonia, Akathisia, Tardive Dyskinesia
• Elderly patients are at higher risk for EPS and TDs – develops more readily and are more persistent
• Mostly seen in use of Conventional APs or neuroleptics and Risperidone
Side Effects

• Metabolic: weight gain, hyperglycemia, hyperlipidemia

Most likely to cause Metabolic side effects: Olanzapine, Quetiapine, Risperidone

Less Likely: Ziprasidone, Asenapine, Lurasidone
Side Effects

• Prolonged QTc Interval and Sudden Death:
  • Most APs will carry this risk (Haloperidol, Droperidol, Pimozide)
  • Highest risk:
    Thioridazine
    Ziprasidone (no evidence yet to suggest that this leads to sudden death)
The CATIE Schizophrenia Trial
**CATIE Schizophrenia Trial Design**

**Phase 1**
- Double-blind, random treatment assignment.
  - OLANZAPINE
  - QUETIAPINE
  - RISPERIDONE
  - ZIPRASIDONE
  - PERPHENAZINE

1460 patients with SCZ Comorbidity Other meds

**Phase 2**
- Participants who discontinue Phase 1 choose either the clozapine or the ziprasidone randomization pathways
  - CLOZAPINE (open-label)
    - OLANZAPINE, QUETIAPINE or RISPERIDONE
  - ZIPRASIDONE
    - OLANZAPINE, QUETIAPINE or RISPERIDONE

No one assigned to same drug as in Phase 1

**Phase 3**
- Participants who discontinue Phase 2 choose one of the following open-label treatments
  - ARIPIPRAZOLE
  - CLOZAPINE
  - FLUPHENAZINE DECANOATE
  - OLANZAPINE
  - PERPHENAZINE
  - QUETIAPINE
  - RISPERIDONE
  - ZIPRASIDONE
  - 2 of the antipsychotics above

*Phase 1A: participants with TD (N=231) do not get randomized to perphenazine; phase 1B: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.*


**CATIE Study Phase 2T:**
Time to Discontinuation for Any Cause
Average Monthly Symptom Scores

Mean Total Score on Positive and Negative Syndrome Scale (least square mean from mixed model; adjusted for site, baseline, exacerbation)

Initial medication
- Olanzapine
- Quetiapine
- Ziprasidone
- Perphenazine
- Risperidone

Time (months)
- Baseline
- 1
- 3
- 6
- 9
- 12
- 15
- 18

Medical and Safety Issues During Antipsychotic Treatment
<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence in Schizophrenia</th>
<th>Prevalence in Bipolar</th>
<th>Prevalence in General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>75%</td>
<td>43-75%</td>
<td>25%</td>
</tr>
<tr>
<td>Obesity</td>
<td>50%</td>
<td>58%</td>
<td>33%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>13-14%</td>
<td>9.9-26%</td>
<td>7%</td>
</tr>
<tr>
<td>HIV</td>
<td>3%</td>
<td>?</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>20%</td>
<td>?</td>
<td>1.8%</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- inactivity, poor nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- substance use</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Side Effects of Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Effect</th>
<th>INVEGA/CLOZARIL</th>
<th>RISPERDAL</th>
<th>ZYPREXA</th>
<th>SEROQUEL</th>
<th>GEODON</th>
<th>ABILIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Blood Pressure</td>
<td>+++</td>
<td>+</td>
<td>+/-0</td>
<td>++</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>Dry mouth, constipation</td>
<td>+++</td>
<td>0</td>
<td>+++/++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tremors, stiffness, endocrine problems</td>
<td>0</td>
<td>+++/++</td>
<td>0/+0</td>
<td>0</td>
<td>+/+0</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>+++</td>
<td>+/-/-</td>
<td>+++++</td>
<td>++++++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Lipids</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CLOZ = clozapine; RIS = risperidone; OLZ = olanzapine; QUET = quetiapine; ZIP = ziprasidone; ARIP = aripiprazole; Adapted from: Nasrallah HA, Mulvihill T. Ann Clin Psychiatry. 2001(Dec);13(4):215-227
Shift in Risk Perception of Antipsychotics

Past Areas of Concern
- Tardive Dyskinesia
- Sedation
- Weight Gain
- Insulin Resistance
- Hyperlipidemia
- CHD

Current Medical Realities
- Diabetes
- Weight Gain
- Prolactin
- Hyperlipidemia
- Insulin Resistance
- Sedation
- Coronary Heart Disease
- TD
## ADA/APA Consensus Conference on Antipsychotic Drugs and Obesity and Diabetes Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (Clozaril)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole* (Abilify)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone* (Geodon)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = increase effect; - = no effect; D = discrepant results. *Newer drugs with limited long-term data.
## What We Should Be Doing

<table>
<thead>
<tr>
<th>Inquiry</th>
<th>Measure</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal or family history:</td>
<td>• Height</td>
<td>• Fasting Glucose</td>
</tr>
<tr>
<td>– Diabetes</td>
<td>• Weight</td>
<td>• Fasting Lipids</td>
</tr>
<tr>
<td>– Hypertension</td>
<td>• Waist circumference</td>
<td></td>
</tr>
<tr>
<td>– CHD (MI or Stroke)</td>
<td>• Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>– Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Physical Activity</td>
<td></td>
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</tr>
</tbody>
</table>

And - trying to use medications which have fewer metabolic side effects!
## Atypical Antipsychotics

### FDA Indications

*Olanzapine-fluoxetine combo
**Adjunct in depression
**QuetiapineXR
† CONSTA
† † CONSTA

<table>
<thead>
<tr>
<th>Drug</th>
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<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Clozapine</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>+*</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>-</td>
<td>+**</td>
<td>-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+†</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Olanzapine-fluoxetine combo
-**Adjunct in depression
**QuetiapineXR
† CONSTA
Atypical Antipsychotics Treatment Considerations

• May take up to 3 weeks until effective
• Adverse effects:
  – Day time sedation
  – Hyperglycemia
  – Hyperlipidemia
  – Weight gain with Olanzapine, Clozapine,
    • Less with Risperidone, Quetiapine
  – Anticholinergic effects
  – Orthostatic hypotension
  – EPS: TD, Dystonia, Pseudo-Parkinsonism, Akathesia
  – Prolactin elevations
Atypical Antipsychotic Recommended Monitoring

- Waist circumference
  - Intervene if >40 inches man >35 woman
- Weigh at every visit
  - Unless pt under weight, gain >1BMI indicates need for intervention
- Fasting blood glucose
  - Base line, 3 months and yearly
    - Tests every 6 months for Olanzapine and Clozapine yearly for others
- Fasting lipids
  - Base line, 3 months, 6 months, then yearly
    - High risk patients – more frequent monitoring
- Encourage diet and exercise
Atypical Antipsychotic Caution

• Atypical black box warning
  – Increased risk of hyperglycemia, diabetes, dyslipidemia, and wt gain

• Evidence based
  – Double blind placebo controlled trials
  – Typicals as good as atypicals
  – No head to head studies for maintenance
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<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>+*</td>
<td>+</td>
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<td>+**</td>
<td>-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+†</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
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*Olanzapine-fluoxetine combo

**QuetiapineXR

-**Adjunct in depression

† CONSTA
Atypical Antipsychotics
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  – Hyperlipidemia
  – Weight gain with Olanzapine, Clozapine,
    • Less with Risperidone, Quetiapine
  – Anticholinergic effects
  – Orthostatic hypotension
  – EPS: TD, Dystonia, Pseudo-Parkinsonism, Akathesia
  – Prolactin elevations
Atypical Antipsychotic Caution

• Atypical black box warning
  – Increased risk of hyperglycemia, diabetes, dyslipidemia, and wt gain

• Evidence based
  – Double blind placebo controlled trials
  – Typicals as good as atypicals
  – No head to head studies for maintenance
Treatment of ADHD: Non-Amphetamine Behavioral Stimulants

• **Methylphenidate (Ritalin)**
• Used in treatment of ADHD to calm hyperactivity and improve attention (prescribed in 90% of cases)
• Half-life ≈ 2-4 hours
• Variable absorption rates, but generally a rapid onset with short duration (multiple administrations needed over the course of a day)
Treatment of ADHD:
Non-Amphetamine Behavioral Stimulants

- **Methylphenidate (continued)**
- No currently available sustained-release preparation
- Low-abuse potential
- Increases syn. conc. of DA by blocking the presyn. DA transporter (like cocaine) and increases the release of DA (like amphetamine)
Treatment of ADHD:
Non-Amphetamine Behavioral Stimulants

- **Pemoline (Cylert)**
  - Structurally dissimilar to amphetamine & methylphenidate
  - Decreases ADHD symptoms by potentiating dopaminergic transmission
  - May cause hepatitis-like liver damage
- **Modafinil**
  - Potentiates glutamate neurotransmission, and inhibits activity of GABA neurons in the nucleus accumbens and cerebral cortex
  - Used in treatment of ADHD, narcolepsy and causes cognitive improvement in Alzheimer’s patients
Treatment of ADHD: Amphetamines

- Dextroamphetamine (Dexedrine) and an amphetamine mixture (Adderall)
- A one-time dose of Adderall is similar in effect to the typical two daily doses of methylphenidate
Treatment of ADHD

• Stimulants improve behavior and learning in 60-80% of correctly diagnosed children
• 10-30% of ADHD individuals are treatment resistant (little to no response to treatment)
• Alternatives: antidepressants like fluoxetine (Prozac), buproprion (Welbutrin) and buspirone (Buspar)
• With antidepressants, rare cases of high cardiac toxicity have been found