Pharmacology Update 2019: Treatment of Schizophrenia

Rona J. Hu, M.D.
Clinical Professor of Psychiatry
Stanford University
Speaker Disclosure of Financial Relationship

Previous consultant/speaker for: Abbott, Astra Zeneca, Azur, Bristol Myers Squibb, Janssen, Lilly, Pfizer, Sepracor/Sunovion (none current)

Previous grant/research support from: Astra Zeneca, Bristol Myers Squibb, Forest, Janssen (none current)

Advisory Board for Bristol Myers Squibb, Lilly, Otsuka and Sunovion in the past. Most recent: Alkermes advisory board Feb 2017

Discussion of off-label or investigational use

Yes x No
Outline

• What do we know now? Risk/benefit ratio, DSM-5 update, guidelines
• Summary of studies, inc 2 antipsychotics
• Summary: medication by medication
• Formulations overview and updates
• Side effects overview and updates
• Miscellaneous practical considerations
Risk vs benefit changed

• Risks: atypicals have less TD but more wt gain, diabetes, etc.
• Previous studies suggested 75-85% of single-episode pts would relapse within 5 yrs of med withdrawal
• Gitlin et al 2001 found 96% of pts showed indications of recurrence within 2 yrs
Diagnosis

“Some clinicians are hesitant to make a diagnosis of schizophrenia, even when there is sufficient evidence to do so, because of its ominous prognosis and social stigma. This potentially denies the child or adolescent and the family access to appropriate treatment, knowledge about the disorder, and support services.” AACAP 2001
Diagnostic Update: DSM-5

- Elimination of special treatment for bizarre delusions and “special” hallucinations
- Cannot have schizophrenia without psychotic sx
- Deletion of specific subtypes
- Schizoaffective less ambiguous
- Catatonia now a specifier for a range of d/o
Neurotoxicity hypothesis

• Wyatt proposed psychosis harms the brain, similar to “kindling” in seizures and bipolar, supported by Loebel et al 1992 and Rabiner et al 1986

• Ho et al 2000 did not support hypothesis: duration of untreated initial psychosis was not prognostic of poor outcome
Neurotoxicity (cont.)

• Even if psychosis does not cause neurotoxicity, it has other effects:
  – Frightening for pt and family
  – Impairment during maturation (education, work, romance, independence, etc)
  – Harm to self or others

» Lieberman and Fenton, AJP 2000
Supporting the neurotoxicity hypothesis

Gray Matter Loss in Patients With Schizophrenia vs Controls Over 5 Years

Progression in Frontal Gray Matter Loss Is Related to the Number of Psychotic Relapses

<table>
<thead>
<tr>
<th></th>
<th>APA</th>
<th>TMAP</th>
<th>PORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode</td>
<td>SGA</td>
<td>SGA</td>
<td>SGA, FGA</td>
</tr>
<tr>
<td>Second choice</td>
<td>SGA, FGA, C</td>
<td>SGA, FGA</td>
<td>SGA, FGA</td>
</tr>
<tr>
<td>Third choice</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Fourth choice</td>
<td>(C+)</td>
<td>C+</td>
<td>–</td>
</tr>
<tr>
<td>Fifth choice</td>
<td>–</td>
<td>A,T</td>
<td>–</td>
</tr>
<tr>
<td>Combinations</td>
<td>–</td>
<td>CF</td>
<td>–</td>
</tr>
</tbody>
</table>

FGA: first-generation antipsychotic  
SGA: second-generation (atypical) antipsychotic  
C: Clozapine  
C+: Clozapine augmentation  
CF: Clozapine failure  

Clinical Antipsychotic Trials of Intervention Effectiveness

- CATIE: a landmark, NIMH funded, multi-center, double-blind, randomized study with 1493 pts at 57 sites
- First objective comparison of multiple antipsychotic drugs in “real world” setting
- Results published in phases: Phase I in NEJM (Lieberman 2005), phase II in AJP (McEvoy 2006 and Stroup 2006)
- Other papers on study design, cognitive deficits, etc.
CATIE I: results

• Atypicals (olanzapine, quetiapine, risperidone, ziprasidone) and perphenazine “differ from one another somewhat in terms of efficacy and markedly in terms of side effects”
• 64% O, 82% Q, 74% R, and 79% Z d/c in 18 mo vs 75% perphenazine
• Olanzapine more associated with wt gain or metabolic effects (30% gained >7% of body wt, 9% d/ced), perphenazine more EPS (17% reported, 8% d/ced)
### All-cause discontinuation rates in the CATIE trial

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Percent discontinued</th>
<th>Duration on antipsychotic (months)*</th>
<th>Dosage (mg/d)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>64%</td>
<td>9.2</td>
<td>20.1</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>75%</td>
<td>4.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>82%</td>
<td>4.8</td>
<td>543.4</td>
</tr>
<tr>
<td>Risperidone</td>
<td>74%</td>
<td>5.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>79%</td>
<td>3.5</td>
<td>112.8</td>
</tr>
<tr>
<td>Overall</td>
<td>74%</td>
<td>Median 6.0; mean 8.3</td>
<td></td>
</tr>
</tbody>
</table>

**Notes**
- *Mean modal
- Olanzapine’s discontinuation rate was significantly lower than those of perphenazine, quetiapine, and risperidone but not of ziprasidone.
- Olanzapine’s maximum dosage was 30 mg/d (50% higher than FDA-approved 20 mg/d); other agents were dosed within approved ranges.
- Patients reached maximum daily antipsychotic dosages at these rates: 40% with olanzapine, 40% with perphenazine, 44% with quetiapine, 40% with risperidone, and 48% with ziprasidone.
<table>
<thead>
<tr>
<th></th>
<th>Highest</th>
<th>Effectiveness</th>
<th>Lowest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall discontinuation rate*</td>
<td>O 64%</td>
<td>&lt; R 74% &lt; P 75% &lt; Z 79% &lt; Q 82%</td>
<td></td>
</tr>
<tr>
<td>Median duration on the antipsychotic (months)*</td>
<td>O 9.2</td>
<td>&gt; P 5.6 &gt; R 4.8 &gt; Q 4.6 &gt; Z 3.5</td>
<td></td>
</tr>
<tr>
<td>Discontinuation for efficacy reasons*</td>
<td>O 15%</td>
<td>&lt; Z 24% &lt; P 25% &lt; R 27% &lt; Q 28%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation for tolerability reasons</td>
<td>R 10%</td>
<td>&lt; Q 15% = P 15% &lt; O 18% &lt; Z 28%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to weight gain*</td>
<td>P 1%</td>
<td>&lt; R 2% &lt; Z 3% &lt; Q 4% &lt; O 9%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to EPS*</td>
<td>O 2%</td>
<td>&lt; Q 3% = R 3% &lt; Z 4% &lt; P 8%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to patient decision*</td>
<td>O 24%</td>
<td>&lt; R 30% = P 30% &lt; Q 33% &lt; Z 34%</td>
<td></td>
</tr>
<tr>
<td>Duration of successful treatment (months)</td>
<td>3</td>
<td>&gt; Q 1 = R 1 = P 1 = Z 1</td>
<td></td>
</tr>
<tr>
<td>Hospitalization*</td>
<td>O 11%</td>
<td>&lt; R 15% &lt; P 16% &lt; Z 18% &lt; Q 20%</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant difference

O: olanzapine; R: risperidone; P: perphenazine; Z: ziprasidone; Q: quetiapine
EPS: extrapyramidal symptoms
CATIE 2E: efficacy pathway

- 44% of clozapine pts (N=49) stayed 12 mo, vs 16%-21% on other meds (R, Q or O)
- Tx d/c due to lack of efficacy was lower with clozapine (11%) vs other meds (35-43%)
- Clozapine showed greatest improvement in PANSS and CGI
## CATIE 2E: adverse events

<table>
<thead>
<tr>
<th>Measure</th>
<th>Clozapine (N=49)</th>
<th>Olanzapine (N=19)</th>
<th>Quetiapine (N=15)</th>
<th>Risperidone (N=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod/Sv AE</td>
<td>76%</td>
<td>74%</td>
<td>67%</td>
<td>56%</td>
<td>0.51</td>
</tr>
<tr>
<td>sedation</td>
<td>45%</td>
<td>32%</td>
<td>33%</td>
<td>25%</td>
<td>1.00</td>
</tr>
<tr>
<td>Anti-chol</td>
<td>20%</td>
<td>0%</td>
<td>47%</td>
<td>6%</td>
<td>0.002</td>
</tr>
<tr>
<td>sexual</td>
<td>33%</td>
<td>11%</td>
<td>13%</td>
<td>25%</td>
<td>0.21</td>
</tr>
<tr>
<td>sialorrhea</td>
<td>33%</td>
<td>11%</td>
<td>0%</td>
<td>13%</td>
<td>0.02</td>
</tr>
<tr>
<td>orthostasis</td>
<td>12%</td>
<td>5%</td>
<td>27%</td>
<td>6%</td>
<td>0.30</td>
</tr>
<tr>
<td>insomnia</td>
<td>4%</td>
<td>16%</td>
<td>13%</td>
<td>31%</td>
<td>0.02</td>
</tr>
<tr>
<td>D/c for lack of tolerability</td>
<td>10%</td>
<td>5%</td>
<td>20%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
# APA Treatment Selection Guide

<table>
<thead>
<tr>
<th>Patient Profile</th>
<th>Group 1: 1st generation</th>
<th>Group 2: 2nd generation</th>
<th>Group 3: Clozapine</th>
<th>Group 4: Long Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode</td>
<td></td>
<td>YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide risk</td>
<td></td>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Hostility/aggression</td>
<td></td>
<td></td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td></td>
<td>YES</td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>EPS sensitivity</td>
<td></td>
<td>YES, except risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin sensitivity</td>
<td></td>
<td>YES, except risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight or metabolic</td>
<td></td>
<td>ARI&amp;ZIP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent nonadherence</td>
<td></td>
<td></td>
<td></td>
<td>YES</td>
</tr>
</tbody>
</table>

Where are we now?

- Atypical antipsychotics since FDA approved clozapine 1989:
  - Clozaril (clozapine)
  - Risperdal (risperidone)
  - Zyprexa (olanzapine)
  - Seroquel (quetiapine)
  - Geodon (ziprasidone)
  - Abilify (aripiprazole)
  - Invega (paliperidone)
  - Fanapt (iloperidone)
  - Saphris (asenapine)
  - Latuda (lurasidone)
  - Rexulti (brexpiprazole)
  - Vraylar (cariprazine)
- News re formulations and side effects
### Atypical Antipsychotics for Schizophrenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation (Approval)</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine (Zyprexa®)</td>
<td>Oral (1996)</td>
<td>10-20 mg/day; higher doses are often used if treatment refractory</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa Relprev®)</td>
<td>Long-acting IM (2009)</td>
<td>150-300 mg IM every 2 weeks</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®, Seroquel XR®)</td>
<td>Oral (1997, 2007)</td>
<td>150-800 mg/day; higher doses are often used if treatment refractory</td>
</tr>
<tr>
<td>Risperidone (Risperdal®)</td>
<td>Oral (1993)</td>
<td>4-16 mg/day</td>
</tr>
<tr>
<td>Risperidone (Risperdal® Consta®)</td>
<td>Long-acting IM (2003)</td>
<td>25, 37.5 , or 50 mg IM every 2 weeks</td>
</tr>
<tr>
<td>Ziprasidone (Geodon®)</td>
<td>Oral (2001)</td>
<td>80-160 mg/day</td>
</tr>
<tr>
<td>Clozapine (Clozaril®)</td>
<td>Oral (1989)</td>
<td>300-900 mg/day</td>
</tr>
<tr>
<td>Paliperidone (Invega®)</td>
<td>Oral (2006)</td>
<td>6-12 mg/day</td>
</tr>
<tr>
<td>Paliperidone (Invega® Sustenna®)</td>
<td>Long-acting IM (2009)</td>
<td>117 to 234 mg per month</td>
</tr>
<tr>
<td>Asenapine (Saphris®)</td>
<td>Oral – sublingual (2009)</td>
<td>5-10 mg twice daily</td>
</tr>
<tr>
<td>Iloperidone (Fanapt®)</td>
<td>Oral (2009)</td>
<td>6-12 mg twice daily</td>
</tr>
<tr>
<td>Lurasidone (Latuda®)</td>
<td>Oral (2010)</td>
<td>40-160 mg once daily</td>
</tr>
</tbody>
</table>


Clozapine update

- Reduced risk of suicide (InterSePT study)
- Formulations include Clozaril, generic, Fazaclo
- FDA update 9-15: monitor ANC only! Also allows for benign ethnic neutropenia
- REMS for all formulations and manufacturers
- Weekly x 6 mo, q2 wks x 6 mo, q4 wks after 1 yr
- Neutropenia Risk ~17x ^ in HLA-DQB1 (Athanisiou 2011), somewhat in females, elderly
- Myocarditis (Ronaldson 2011: monitor troponin and CRP x 4 wks), ileus, high risk wt gain, mortality in elderly
- Tiihonen study showing better outcomes inc longer life
- Clozapine handbook 2019 by Jonathan Meyer
Risperidone update

• Formulations: Risperdal M-tab (quick-dissolve), liquid, other po generics, Risperdal Consta and PERSERIS (2 and 4 wk LAIs) with better availability

• Side effects: prolactin levels and risk of prolactinoma (Doraiswamy 2006 from FDA spontaneous AE database), mortality in elderly, moderate weight gain
Olanzapine update

- Formulations update: Zyprexa and generic olanzapine, Zydis (quick-dissolve), fast-acting IM, Symbyax, Relprevv long-acting IM (special monitoring for PIDSS)
- Side effects update: mortality in elderly, high risk wt gain (30% in CATIE gained >7% of body weight, FDA labeling change from precaution to warning)
Quetiapine update

• Formulation: Seroquel and generic formulations, Seroquel XR
• Side effects update: mortality in elderly may be relatively better (NNH = 50, vs Haldol’s NNH = 15, Maust VA study, AAGP 2014)
• Mod-severe wt gain, no apparent increased risk for cataracts
Ziprasidone update

- Formulations: Geodon po and generic ziprasidone soon, fast-acting IM (20 mg IM)
- Side effects update: mortality in elderly, low risk wt gain, less QTc prolongation than initially feared
Aripiprazole update

• Partial dopamine agonist: “3rd generation?”
• Formulations: generic aripiprazole, liquid, quick-dissolve, fast-acting IM d/ced, two long-acting IM forms: Abilify Maintena and Aristada, bridging with Aristada Initio
• Abilify MyCite: first digital monitoring device embedded in the pill itself
• Side effects: mortality in elderly, low risk wt gain, “Las Vegas in a pill”?!
Paliperidone update

• Active metabolite of risperidone in extended release delivery system
• Receptor binding similar to risperidone
• FDA approved for schizophrenia and schizoaffective
• Not metabolized thru P450: few interactions
• Well-tolerated side effect profile
• 3, 6, or 9 mg tablets cannot be split
• Invega Sustenna: long-acting IM q 4 wks BETTER AVAILABILITY
• NEW 2015: Invega Trinza: loooong-acting IM q 3 mo
## Recently Approved Schizophrenia Treatments

<table>
<thead>
<tr>
<th>Structure</th>
<th>Asenapine</th>
<th>Iloperidone</th>
<th>Lurasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Asenapine Structure" /></td>
<td><img src="image2" alt="Iloperidone Structure" /></td>
<td><img src="image3" alt="Lurasidone Structure" /></td>
<td></td>
</tr>
</tbody>
</table>

### Receptor Binding Profile

<table>
<thead>
<tr>
<th>Asenapine</th>
<th>Iloperidone</th>
<th>Lurasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₂, 5HT₂A, 5HT₁A, 5HT₁B, 5HT₂B, 5HT₂c, 5HT₆, 5HT₇, alpha₁, alpha₂, H₁ antagonist; Little/no affinity for M₁ receptors</td>
<td>D₂, D₃, 5HT₂A, 5HT₁A, alpha₁, alpha₂, H₁, antagonist; Little/no affinity for M₁ receptors</td>
<td>D₂, 5HT₂A, 5HT₇, alpha₂A, alpha₂c antagonist; 5HT₁A partial agonist; Little/no affinity for H₁ or M₁ receptors</td>
</tr>
</tbody>
</table>

### Approved Dosage

<table>
<thead>
<tr>
<th>Asenapine</th>
<th>Iloperidone</th>
<th>Lurasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 mg sublingually, administered twice daily</td>
<td>12-24 mg/day administered twice daily; initiated with slow dose titration</td>
<td>40-160 mg once daily</td>
</tr>
</tbody>
</table>

### Commonly Observed Adverse Reactions*

<table>
<thead>
<tr>
<th>Asenapine</th>
<th>Iloperidone</th>
<th>Lurasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia, oral hypoesthesia, somnolence</td>
<td>Dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, weight increase</td>
<td>Somnolence, akathisia, nausea, parkinsonism, agitation</td>
</tr>
</tbody>
</table>

*Incidence ≥ 5% and 2-fold greater than placebo

Iloperidone update

- FDA-approved for acute schizophrenia in adults only
- Dose range 12-24 mg
- Same warnings for elderly and metabolic syndrome; hypotension and dizziness relatively common, but wt gain and EPS are not
- Long-acting IM is being developed
## Iloperidone Dosing & Administration

<table>
<thead>
<tr>
<th>Dose strengths available</th>
<th>1, 2, 4, 6, 8, 10 and 12 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target dose range</strong></td>
<td>6-12 mg twice daily (12-24 mg/d)</td>
</tr>
<tr>
<td><strong>Maximum recommended dose</strong></td>
<td>12 mg twice daily (24 mg/d)</td>
</tr>
</tbody>
</table>
| **Administration**       | Titration needed to reach target dose due to potential orthostatic hypotension  
- Will take 3-7 days to get to therapeutic dose for treatment of an acute psychotic episode |
Iloperidone vs Ziprasidone vs Placebo in Acute Treatment of Schizophrenia

Iloperidone in Patients with Acute Exacerbation of Schizophrenia


**Mean Change from Baseline for PANSS-T Score**

- **Iloperidone 24 mg/day (n = 283)**
- **Ziprasidone 160 mg/day (n = 144)**
- **Placebo (n = 140)**

0 7 14 21 28

Day

*P < 0.05 vs placebo
†P < 0.01 vs placebo

PANSS-T: Positive and Negative Syndrome Scale Total
Asenapine update

- FDA approved for acute schizophrenia and bipolar I in adults
- **Sublingual!**, 5-10 mg tabs since poorly absorbed in GI system (~2%)
- **Transdermal Patch**
- Same warnings for the elderly and metabolic syndrome; akathisia relatively common, weight gain is relatively favorable
Asenapine Acute Schizophrenia Trials

![Graph showing the mean change from baseline in PANSS total score for different treatments in Study 1 and Study 2.](image)
Lurasidone

- Approved in acute tx of schizophrenia, bipolar depression, seeking schizophrenia maintenance indication
- 40 or 80 mg/day UP TO 160 mg/day, titration not needed
- Should be taken with food (350 cal)
- Side effect profile esp good re wt gain
- Category B in pregnancy (most others C)
- Promising in cognition (Harvey et al, 2013)
Lurasidone in Patients with Acute Exacerbation of Schizophrenia, Pearl 2


PANSS: Positive and Negative Syndrome Scale

P-values based on Mixed Model for Repeated Measures model of change from baseline

Placebo (n = 114)
Lurasidone 120 mg (n = 118)
Lurasidone 40 mg (n = 118)
Olanzapine 15 mg (n = 121)
Brexpiprazole (Rexulti)

- Partial dopamine agonist like aripiprazole
- Approved Sept 2015 for schizophrenia and adjunct in depression
- 2-4 mg with or without food
- Similar warnings as others, but little wt gain, maybe less akathisia than aripiprazole
- Efforts to be accessible (patient assistance program)
Cariprazine (Vraylar)

- D2/D3 partial agonist
- Approved Sept 2015 for schizophrenia and bipolar
- Dose 1.5-6 mg/day
- Most common side effects are EPS and akathisia
Current Formulations

- **TRANSDERMAL PATCH**: Secuado (asenapine)
- **INHALED LOXAPINE**: ADASUVE available!
- Fast-acting IM: Geodon (20 mg), Zyprexa (10 mg), but Abilify (9.75 mg) no longer made
- Dissolving (Abilify, Risperdal, Zyprexa, FazaClo, Saphris) or liquid po: (Abilify, Risperdal, Geodon)
- Extended release po: Invega and Seroquel XR
- Long-Acting Injectables work! Risperdal Consta (2wks) and PERSERIS, Invega Sustenna (4 wks), Zyprexa Relprevv (4 wks), Abilify Maintena (4wks), Aristada (4, 6 or 8 wks) Invega Trinza (3 mo)
Secuado (asenapine)

- First and only transdermal patch for schizophrenia: FDA approved October 2019
- Safety similar to sublingual asenapine except for possible skin irritation (redness, itching): rotate sites qd.
Now Approved: Inhaled Loxapine

- Indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults, as established in randomized controlled trials
  - Schizophrenia (2; one of which was a Phase III pivotal study)
  - Bipolar mania (1)
- Rapid onset of efficacy
- Dosage 10 mg; only a single dose within a 24-hour period is recommended; administered only by a healthcare professional, in an enrolled healthcare facility
- Favorable EPS profile
- Cautions: bronchospasm

Inhaled Loxapine

Figure 1  Schematic of the Staccato device. A single inhalation on the mouth-end starts an flow of air into the device and activates the breath sensor (A), which is connected electronically to the heat package (B), which vaporises the thin coating of medication surrounding it (C), leading to the creation of aerosol particles (D), which is then taken into the lungs. See also figures 1–3 in Noymer et al. (10)
Inhaled Loxapine: REMS Program

• Bolded boxed warning re: bronchospasm
• Prior to administering inhaled loxapine, patients must be screened for a history of pulmonary disease, and examined by chest auscultation for respiratory abnormalities such as wheezing
• After administration, patients are required to be monitored for signs and symptoms of bronchospasm at least every 15 minutes for at least one hour.
• Inhaled loxapine is to be made available in the US only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation)
Abilify Maintena

• ------------------------DOSAGE AND ADMINISTRATION----------------------
• Only to be administered by intramuscular injection in the gluteal muscle by a healthcare professional (2.1)
• For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating ABILIFY MAINTENA (2.1)
• Recommended starting and maintenance dose is 400 mg administered monthly as a single injection (2.1)
• In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic (2.1)
• Some patients may benefit from a reduction to a 300 mg dose (2.1)
• Dosage adjustments are required for missed doses (2.2)
• See instructions for use for reconstitution procedures (2.4, 2.5, 2.6, 2.7, 2.8)
• Dosage adjustments for patients who are CYP2D6 poor metabolizers and
• for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers for greater than 14 days (2.3):

• ----------------------DOSAGE FORMS AND STRENGTHS---------------------
• For extended-release injectable suspension: 400 mg/vial and 300 mg/vial of lyophilized powder for reconstitution (3)

• -----------------------------CONTRAINDICATIONS-----------------------------
• Known hypersensitivity to aripiprazole (4)
Aristada (aripiprazole lauroxil)

- Approved Oct 2015 for tx of schizophrenia
- Aripiprazole linked to fatty acid
- 441 mg deltoid q 4wks, 662 mg gluteal q 4 wks, 882 mg gluteal q 4-6 wks, NOW 1064 mg up to q 8 weeks!
- Bridge: either po x 3wks, or INITIO 675 mg
- Safety warning for elderly
Perseris
(Risperidone monthly depot)

- 90 or 120 mg monthly depot: risperidone in PLGH (poly D,L lactide co-glycolide), total volume 0.6 or 0.8 mL
- NO ORAL BRIDGING required
- Requires mixing of liquid and powder in syringes 5 + 55x
- Subcutaneous abdominal injections, not at belt or waistline, don’t rub the depot site
## Depot SGAs for Schizophrenia: What’s Different?

<table>
<thead>
<tr>
<th></th>
<th>RLAI</th>
<th>OLAI</th>
<th>PLAI</th>
<th>ALAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year approved</td>
<td>2003</td>
<td>2009</td>
<td>2009</td>
<td>2013</td>
</tr>
<tr>
<td>Other indications?</td>
<td>Bipolar Disorder</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Injection sites</td>
<td>Deltoid or gluteal</td>
<td>Gluteal</td>
<td>Deltoid or gluteal</td>
<td>Gluteal</td>
</tr>
<tr>
<td>Needle gauge</td>
<td>20G or 21G</td>
<td>19G</td>
<td>22G or 23G</td>
<td>21G</td>
</tr>
<tr>
<td>Injection volume</td>
<td>~2 ml</td>
<td>1.0-2.7 ml</td>
<td>0.25-1.5 ml</td>
<td>2 ml (400 mg)</td>
</tr>
<tr>
<td>Injection frequency</td>
<td>q2 weeks</td>
<td>q2 or q4 weeks</td>
<td>q4 weeks</td>
<td>q4 weeks</td>
</tr>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>Varies from 210 mg q2wk or 405 mg q4wk to 300 mg q2wk</td>
<td>234 mg Day 1 + 156 mg Day 8 in deltoid</td>
<td>400 mg</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>25 mg (max 50 mg)</td>
<td>Varies from 150 mg q2wk or 300 mg q4wk to 300 mg q2wk</td>
<td>117 mg (range 39-234 mg)</td>
<td>300 or 400 mg (adjust for CYP2D6 or CYP3A4 issues)</td>
</tr>
<tr>
<td>Oral supplementation?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reconstitution needed?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Refrigeration needed?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Requires observation?</td>
<td>No</td>
<td>3 hours</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Citrome L. Expert Review of Neurotherapeutics. [in press]*
Curious About Cost?

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Cost to Hutchings Psychiatric Center, NY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine Dec.</td>
<td>$68 per 5-mL vial (25 mg/mL)</td>
</tr>
<tr>
<td>Haloperidol Dec.</td>
<td>$18 for 1 mL 50 mg/mL; $34 for 1 mL 100 mg/mL</td>
</tr>
<tr>
<td>Risperdal Consta</td>
<td>$128 for 12.5 mg, $257 for 25 mg, $385 for 37.5 mg, $514 for 50 mg</td>
</tr>
<tr>
<td>Invega Sustenna</td>
<td>$256 for 39 mg, $513 for 78 mg, $771 for 117 mg, $1028 for 156 mg, $1542 for 234 mg</td>
</tr>
<tr>
<td>Zyprexa Relprevv</td>
<td>$540 for 210 mg, $772 for 300 mg, $1042 for 405 mg (not including post-IM monitoring)</td>
</tr>
<tr>
<td>Abilify Maintena</td>
<td>$1050 for 300 mg, $1408 for 400 mg</td>
</tr>
<tr>
<td>Avoidance of Relapse</td>
<td>Priceless</td>
</tr>
</tbody>
</table>

Adapted from Citrome L. Expert Review of Neurotherapeutics. [2013]
Relative Ranking of Side Effect Interventions

**Strategies for managing side effects in stable patients.** We asked the experts what initial strategies they would recommend to manage side effects in patient who has achieved a satisfactory response, is stable and achieving functional improvements, but is experiencing side effects they believe to be medication related.

<table>
<thead>
<tr>
<th>Side effect:</th>
<th>Preferred management strategies</th>
<th>Also consider</th>
</tr>
</thead>
</table>
| Parkinsonian symptoms or akathisia | Dose adjustment | Add adjunctive medication  
Switch to a different antipsychotic |
| Tardive dyskinesia | Switch to a different antipsychotic | (Dose adjustment) |
| Persistent sedation | Dose adjustment | Switch to a different antipsychotic |
| Persistent insomnia | Dose adjustment | Add adjunctive medication  
Dose adjustment  
Switch to a different antipsychotic |
| Prolactin-related side effects (e.g., amenorrhea, galactorrhea) | Switch to a different antipsychotic  
Dose adjustment | |
| Sexual difficulties judged to be due to the antipsychotic | | Switch to a different antipsychotic  
Dose adjustment |
| Anticholinergic side effects of antipsychotic | Dose adjustment  
Switch to a different antipsychotic | |
| Anticholinergic side effects related to adjunctive anticholinergic agent | Dose adjustment of anticholinergic  
Switch to antipsychotic with lower EPS liability with plan to then discontinue anticholinergic agent | Dose adjustment of antipsychotic |

Weiden; P; J Preskorn; S; H; Fahnestock; P; A; Carpenter; D; Ross; R; Docherty; J: Translating the psychopharmacology of antipsychotics to individualized treatment for severe mental illness: a Roadmap. *J Clin Psychiatry*, 68 Suppl 7:1-48, 2007.
Side effects update

• All have black-box warning re risk of death in elderly, none approved for dementia
• All have FDA warning re weight gain and metabolic syndrome, but risks are not equal
• Effective treatments for tardive dyskinesia are available, but very expensive (Ingrezza and Austedo)
Ingrezza (valbenazine)

- VMAT2 inhibitor
- 40 or 80 mg qd
- Decreased TD starting 2 wks up to 48 wks
- SE: somnolence most common
- QT prolongation not clinically significant
- Interactions: MAOI’s, 3A4, 2D6
Austedo (deutetrabenazine)

- Depletes vesicles for monoamines
- 6, 9 or 12 mg BID with food
- Approved for TD and Huntington’s chorea
- Black box: SI and depression in Huntington’s
- QT prolongation, NMS, agitation/insomnia, sedation, binds to melanin-containing tissues
- Interactions: MAOIs, reserpine, Ingrezza
Side effects, practical tips

- Neuroleptic malignant syndrome: less common for SGAs: call 1-888-NMS-TEMP
- Akathisia: try anticholinergics, propanolol, benzodiazepines, lower dose, switch (to clozapine?) (Bratti 2007)
- Prolactin elevation: Risp and FGAs, may be less in Invega
- Sedation: adjust dose and timing, switch, try stimulants or Provigil (modafenil)?
FDA “Black Box” Warning

“Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death; most appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg pneumonia) in nature. ___ is not approved for the treatment of patients with dementia-related psychosis.”
Increased mortality in elderly

• Warnings: Risperdal 2003, Zyprexa 2004, Abilify 2005, extended to entire class 2005: 1.7x risk of death (4.5% vs. 2.6% in placebo over 10 wks)

• Nothing approved for dementia-related psychosis

• Studies of dementia-related psychosis: pre-existing risk factors, deaths from different causes (even among CVAs)

• Higher with typical antipsychotics? (Wang 2005)

• Differential risk among antipsychotics (Maust AAGP 2014)
“Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications”

- Philip S. Wang et al, NEJM 2005
- Retrospective cohort analysis of 22,890 pts >65 yo (9142 conventional, 13,748 atypical)
- Conventional pts slightly younger, male, less likely to be in hospital or nursing home
- Conventional pts had 37% higher, dose-dependent risk of dying within 180 days
- FDA added black box warning for conventionals in 2008
Update:
Antipsychotics risk in dementia

• Donovan Maust, presented AAGP 2014
• Retrospective of 45,669 matched pairs at VA with dementia 1998-2009
• NNH in 180 days (longer than prior studies)
• NNH = 15 (Haldol), 22 (Risp), 28 (Olanz), 29 (VPA), 50 (Que) vs 158 (antidepressants)
• Challenges practice patterns after FDA black box warnings (atyp 2005, conv 2008)
APA New Practice Guideline on Antipsychotic Use for Dementia

• Released May 1, 2016
• Chaired by Victor Reus at UCSF
• Taper meds in 4 wks if no response
• Taper in 4 mo if response
• Use comprehensive treatment plan, not just meds
Nuplazid (pimavanserin)

- Atypical approved for Parkinson’s disease psychosis, same warning for elderly with other dementia-related psychosis
- 17 mg bid = 34/day, adjust for 3A4
- Side effects: QT prolongation, peripheral edema, confusion, constipation, gait
- Not recommended for hepatic impairment
Metabolic syndrome: criteria

3 out of 5 of the following criteria:

- Waist > 35 inches women, >40 inches men
- Fasting glucose >100
- Triglycerides >150
- Blood pressure >130/85
- HDL <50 women, <40 men
“Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes”

- Consensus of APA, ADA, AACE, NAASO
- Published 2004 in Diabetes Care and J Clin Psychiatry
- Reviewed all clinical and pre-clinical studies and concluded:
  - Aripiprazole and ziprasidone are less likely to cause diabetes
  - Quetiapine and risperidone intermediate
  - Clozapine and olanzapine are more likely
Consensus statement: monitoring

• Baseline: personal and family hx of obesity, diabetes, dyslipidemia, BP and CV disease
• Wt (BMI): recheck at 1, 2, 3 mo, then quarterly
• Waist circumference annually
• Blood pressure: baseline, 3 mo, then yearly
• Fasting plasma glucose: baseline, 3 mo, yearly
• Fasting lipid profile (cholesterol, triglycerides): baseline, 3 mo, then q 5 yrs
What to do next

• If pt gains > 5% of initial weight, considering switching (cross-titrate, especially with clozapine)

• Consultation for glu>300 or < 60 even if asymptomatic

• Be alert for DKA: polyuria, polydipsia, sudden wt loss, N/V, dehydration, rapid respirations, clouded sensorium
Consensus statement: recommendations

• Those at greatest risk should be prescribed the SGA’s least likely to cause these problems
• HOWEVER “benefits to specific patients could outweigh the potential risks”
• Nutrition and physical activity counseling
• Referral to specialists if problems occur
**Mean Change in Weight With Antipsychotics**

*Estimated Weight Change at 10 Weeks on “Standard” Dose*

†Extrapolated from 6-week data.
## Diabetes Case Reports*: Summary

<table>
<thead>
<tr>
<th></th>
<th>New Onset DM</th>
<th>DKA/Coma</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>242</td>
<td>80</td>
<td>25</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>225</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>33</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Risperidone</td>
<td>131</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- *MedWatch* findings are especially striking\(^1,2\)
  - Because of the high proportion of new-onset DM cases in younger patients that was temporally associated with initiation of antipsychotic therapy and improved with cessation of therapy
  - Because DKA is unusual among patients with type 2 diabetes and is very rare as a first manifestation of illness\(^3\)

---

*Number of cases based on a search of the literature up to July 2003, unpublished post marketing data up to September 2002, plus clozapine, risperidone, and olanzapine reports include recent analyses of FDA *MedWatch* events database.

Hyperlipidemia

- 13,133 cases matched with 72,140 controls from Medi-Cal records
- Pts 18-64 with schiz, bipolar, or depression: prior hx of hyperlipidemia excluded
- Odds ratios compared to no antipsychotic medication: CLO 1.82, OLZ 1.56, RIS 1.53, QUE 1.52, ZIP 1.4, ARI 1.19 (Olfson 2006)
Weight Gain:
Possible Mechanisms

• $H_1$ receptor antagonism
  – Interferes with satiety signals from the gut

• $5-HT_{2C}$ receptor antagonism
  – Increases food intake

• Leptin

Receptor Binding Profile of Antipsychotics

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Aripiprazole (Zyprexa)</th>
<th>Olanzapine (Risperdal)</th>
<th>Quetiapine (Seroquel)</th>
<th>Ziprasidone (Geodon)</th>
<th>Clozapine (Clozaril)</th>
<th>Haloperidol (Haldol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associated with efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_2$</td>
<td>0.45*</td>
<td>11</td>
<td>4</td>
<td>160</td>
<td>5</td>
<td>126</td>
</tr>
<tr>
<td>$5-HT_{1A}$</td>
<td>4.4*</td>
<td>&gt;10,000</td>
<td>210</td>
<td>2800</td>
<td>3</td>
<td>875</td>
</tr>
<tr>
<td>$5-HT_{2A}$</td>
<td>3.4*</td>
<td>4</td>
<td>0.5</td>
<td>295</td>
<td>0.4</td>
<td>16</td>
</tr>
<tr>
<td><strong>Associated with safety/tolerability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>47</td>
<td>19</td>
<td>0.7</td>
<td>7</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>$H_1$</td>
<td>61*</td>
<td>7</td>
<td>20</td>
<td>11</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>$M_1$</td>
<td>&gt;10,000</td>
<td>1.9</td>
<td>&gt;10,000</td>
<td>120</td>
<td>&gt;1000</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Data with cloned human receptors; Bymaster et al, 1996; Seeger et al, 1995; Daniel et al, 1999; Arnt and Skarsfeld, 1998.
5HT2C knockout mice, Tecott
Antipsychotic Treatment on Leptin and Metabolic Effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>At 10 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mmol/L)</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Non-fasting glucose (mmol/L)</td>
<td>6.3</td>
<td>7.2†</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Fasting leptin (ng/ml)</td>
<td>7.7</td>
<td>21.6*</td>
</tr>
</tbody>
</table>

Chinese inpatients with first psychotic episode receiving antipsychotics, primarily risperidone or chlorpromazine (n=46)

* p<0.001; † p<0.01
Effect on compliance

• Obese pts 13x more likely to request d/c of current antipsychotic

• Obese pts 3x more likely to be noncompliant with tx than non-obese pts
  » (Weiden et al, APA 2000)
Switching antipsychotics

• Switching from Zyprexa or Risperdal to Geodon lost weight (Weiden 2004)
• Switching from Zyprexa or Risperdal to Abilify lost weight (Casey 2002)
• Switching partially from Clozapine to Seroquel lost weight (Reinstein 1999)
Switching from 2 to 1 antipsychotic medications

- Outpatients stable on 2 antipsychotics for 90 days: randomized to switch to 1 vs stay
- 52 switched to 1, 52 stayed on 2, followed 12 mo (vs 6 mo for Hori 2013 and Essock 2011)
- 42% of switch pts d/ced, vs 13% of stay
- No significant difference in side effect measures (Tandon 2015)
Antipsychotic combination may reduce schizophrenia hospitalizations

• Up to 25% of pts with schizophrenia don’t respond to monotherapy

• Clozapine + LAIM decreased #hosp by 62% (2.1 → 0.8), and total duration by 83% (155 → 27 days)

• Combo tx didn’t increase BMI or new onset of hyperglycemia, hypercholesterol, or LDL

• (Souaiby et al, Schizophr Res 2017)
Practical considerations

• Cost: more atypicals becoming generic
• Compliance: a major issue in schizophrenia, so alternate formulations can be helpful
• JCAHO still requires justification for >1 antipsychotic: 3 prior trials, cross-taper, or augmenting clozapine
• Acute inpatient psychiatry: Meredith in CA
• HIPAA clarification “best interest of pt”
The bottom line

- Nothing works if you don’t take it
- Risk/benefit ratio: “Never sacrifice antipsychotic efficacy in pursuit of a regimen with more benign side effects.” (Wirshing 2003)
- Recommendations still favor SGAs
- More tools being developed all the time