New Antipsychotic Agents

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“My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:"

<table>
<thead>
<tr>
<th>Company/Position</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forum Pharmaceuticals, Norvartis</td>
<td>Research grant</td>
</tr>
<tr>
<td>Global Psychiatry CME</td>
<td>Speaker Fee</td>
</tr>
<tr>
<td>Mclean Hospital</td>
<td>Speaker Fee</td>
</tr>
<tr>
<td>Reckitt Benckiser</td>
<td>Advisory Board</td>
</tr>
</tbody>
</table>
Challenges Over the Next Decade

- Despite the increasing number of psychotropic drugs available, the mechanisms of action are predominantly the same as the original prototypes developed in the 1950s.
- There have been few innovative new compounds developed despite an array of theoretically viable biologic targets.
- Although different modes of brain stimulation beyond ECT have been invented (VNS, R-TMS, DBS, DCS), their effectiveness has yet to be established, and their availability is limited.
- The psychosocial therapies that have been proven effective are not widely available and inconsistently reimbursed.
- The health care financing system and lack of cohesion in public and private health care systems have not met the clinical need and left many patients partially or completely untreated.
Choosing an Antipsychotic

- Striking a balance between:
  - Efficacy (varies between patients)
  - Medical morbidity (weight gain, diabetes, elevated cholesterol)
  - Compliance (tolerability, oral vs. depot)

Goal: The most effective, medically benign drug that the patient will take reliably
## Frequency of Side Effects: Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>±</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>± to +</td>
<td>±</td>
<td>± to +*</td>
<td>±</td>
<td>± to +*</td>
<td>± to +*</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>± (?)</td>
<td>±</td>
<td>± (?)</td>
<td>± (?)</td>
<td>± to +</td>
<td>± (?)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>±</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>±</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>QTC prolongation</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Decrease in orthostatic BP</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>Elevated prolactin level</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Somnolence</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

* = dose related; (?) = not clearly established; ± = no to minimal, + = occasional, ++ = frequent, +++ = substantial occurrence of side effect compared with placebo rates

Switching for Persistent Positive Symptoms

- Clozapine is clearly “best” but has many problems
- No consensus on how many first-line atypicals to try before clozapine
- All first-line atypical antipsychotics roughly equal in overall positive symptom efficacy*
- Differential efficacy between individuals
- Side effect differences between atypical antipsychotics are much more predictable

* Group mean data; comparisons of efficacy are not statistically significant.
Switching for Side Effects

• Unlike efficacy switches, the side effect differences after switching are very predictable
• Magnitude of the side effect benefit = difference in side effect burden between preswitch and postswitch medication
• Many of the short-term side effect benefits go on to provide greater side effect relief over time
Predicted Δ in Metabolic Risk Factors When Switching Newer Antipsychotics

<table>
<thead>
<tr>
<th>Pre-switch</th>
<th>ARI</th>
<th>OLZ</th>
<th>QUE</th>
<th>RIS</th>
<th>ZIP</th>
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</thead>
<tbody>
<tr>
<td>ARI</td>
<td></td>
<td>↑↑ lipids</td>
<td>↑ lipids</td>
<td>≈ lipids</td>
<td>≈ lipids</td>
</tr>
<tr>
<td>OLZ</td>
<td>↓↓ lipids</td>
<td></td>
<td>↓ lipids</td>
<td>↓ lipids</td>
<td>↓↓ lipids</td>
</tr>
<tr>
<td>QUE</td>
<td>↓ lipids</td>
<td>↑ lipids</td>
<td></td>
<td>?≈ lipids</td>
<td>↓ lipids</td>
</tr>
<tr>
<td>RIS</td>
<td>≈ lipids</td>
<td>↑ lipids</td>
<td>?↑↑ lipids</td>
<td></td>
<td>?≈ lipids</td>
</tr>
<tr>
<td>ZIP</td>
<td>≈ lipids</td>
<td>↑↑ lipids</td>
<td>↑ lipids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IMPORTANT: Much of the data on weight loss and lipid improvements comes from switch studies with presumably selected patients experiencing mixture of efficacy and tolerability difficulties with prior medication.

Weiden PJ. *Postgrad Med.* 2006;Special Report(September):27-44.
**Consensus Statement on Antipsychotic Drugs, Obesity, and Diabetes: Monitoring Protocol for Patients on 2nd-Generation Antipsychotics**

<table>
<thead>
<tr>
<th></th>
<th>Short-Term</th>
<th></th>
<th></th>
<th></th>
<th>Long-Term</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 wk</td>
<td>8 wk</td>
<td>12 wk</td>
<td>Quarterly</td>
<td>Annually*</td>
<td>Every 5 y</td>
</tr>
<tr>
<td>Personal/family history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>[X]</td>
</tr>
</tbody>
</table>

*More frequent assessments may be warranted based on clinical status.

Adding an Adjuvant Medication

- Current medication optimized
- Known benefit from literature
- Adjuvant safe

- Current medications may be cause of problem
- Current medication not optimized
- High risk of side effects or toxicity

Add

Don’t Add
Combining Medications for Side Effects
(Think twice before adding an adjunct)

- Target side effect is **not** dose related, or, if dose-related, current medication cannot be lowered easily
- Side effect is likely to be transient
- Side effect is dose related, and dose lowering has not been tried
- Adjunct may impair efficacy of primary treatment
- Switching antipsychotics is feasible and likely to be more effective

Add

Don’t Add
Meta-Analysis: lamotrigine Added to clozapine (n=161)

Significant improvement on psychotic symptoms when added to clozapine

Tiihonen et al 2009
Nonadherence to Antipsychotic Therapy in Patients With Schizophrenia

- Average rate of nonadherence is approximately 50% during first year after discharge¹
- Postdischarge nonadherence rate estimated at 7.6% per month²
- Nonadherence is a major contributing factor to the annual cost of hospital admissions for relapsing schizophrenia²

Increase in Suicide Attempt Rate When Atypical Antipsychotic Therapy Is Interrupted

- Drug-dispensing and hospital-discharge databases in the Netherlands (N=865,000)
- Patients with schizophrenia (N=603) and interruption of ≥30 day gap in treatment (N=204; 33%)
- Adjusting for age and gender, relative risk for suicide attempts increased 4.2 x (95% CI: 1.7–10.1)

Antipsychotic Prescriptions in the US Post-CATIE

Lieberman & Stroup, AJP 2011
Schizophrenia Treatment Algorithm

Intolerance

- Sedation: aripiprazole / ziprasidone / perphenazine
- Weight gain: aripiprazole / lurasidone / ziprasidone / molindone
- EPS: Quetiapine / iloperidone
- Hyperprolactinemia: Any atypical except risperidone and paliperidone

Risperidone (generic)
- Perphenazine (cost-effective?)
- Aripiprazole (benign)

Ineffective

- Olanzapine
- Clozapine
- Combination?

Poor Compliance

Target well-being
CBT
Depot
Paliperidone Palmitate (Sustenna)

- Long-acting injectable
- Loading dose:
  - Day 1: 234 mg
  - Day 8: 156 mg
  - Every 4 weeks: 117, 156 or 234 mg

- Deltoid injection produces higher levels than gluteal (best for loading dose) but may produce more discomfort
- Single-dose syringe; does not require refrigeration
- Immediate release (unlike microspheres)
Paliperidone Palmitate

Initiation and maintenance dosing

Day 1
First initiation dose
150 mg eq. Deltoid

1 week later
Second initiation dose
100 mg eq. Deltoid

Maintenance begins
1 month after second initiation dose

1 month later
Recommended dose
75 mg eq. Deltoid/ Gluteal

± 2 days
Flexible dosing window

± 1 week
Flexible dosing window

Olanzapine Depot

- q 4 weeks
- Post-injection delirium/sedation syndrome – 0.07% of injections
- Observation for 3 hours after dose
Iloperidone (Fanapt)

- D2/5HT2a, alpha adrenergic antagonist
- Approved for the acute treatment of schizophrenia
- 18 hour half-life
- Administered twice-daily
- Dose titration daily over first week to avoid hypotension
Iloperidone Clinical Trials

• Four acute and two maintenance trials reported
• Efficacy similar to ziprasidone 80 mg bid
• Increasing efficacy with increasing dose from 2-12 mg bid
Combined Results From Phase III iloperidone Studies for Patients That Remained in Study for At Least 2 Weeks

Potkin et al, J Clinical Psychopharm 2008
Iloperidone

- How supplied: 1, 2, 4, 6, 8, 10, 12 mg tablets
- Start at 1 mg bid
- Can increase tablet strength daily
- Typical dose 8-12 mg bid
Iloperidone Adverse Effects

- Dizziness
- Dry mouth
- Somnolence
- Fatigue
- Nasal congestion
- Minimal EPS and Prolactin Elevation
- Weight gain, hypotension and QTc effects are dose-related:
  - QTc similar to ziprasidone at 12 mg bid
  - Weight gain greater than risperidone at higher doses
  - Sustained hypotension in 5% at higher doses
Asenapine (Saphris)

- D2, 5HT2a antagonist
- Approved for acute treatment of schizophrenia and mania
- Half life: 24 hours
- Metabolized by CYP450 1A2
- 30% increase in AUC with fluvoxamine
Asenapine

- How supplied:
  - 5 & 10 mg sublingual tablets
- Typical dose in schizophrenia: 5-10 mg bid
- Typical dose in mania: 5-10 mg bid
Asenapine

- Extensive first-pass hepatic metabolism: <2% bioavailability when swallowed
- Sublingual rapidly-dissolving tablets: 35% bioavailability
- Absorption reduced if liquids swallowed within 2 minutes (20% decrease) or 5 minutes (10% decrease)
Asenapine Clinical Trials

• Schizophrenia
  – Asenapine 5 mg bid more effective than placebo in 2/3 trials
  – Comparable to risperidone in 2/2 trials
  – In one trial, olanzapine 15 mg/d more effective than placebo; asenapine 10 mg bid did not separate from placebo
Asenapine Adverse Effects

• Schizophrenia Trials
  – Akathisia
  – Oral hypoesthesias
  – Somnolence

• Bipolar Mania Trials
  – Dizziness
  – EPS (other than akathisia)

• Minimal effects on prolactin and QTc
• Weight gain less than risperidone & olanzapine
Lurasidone (Latuda)

• D2/5HT2 antagonist
• 5HT7, alpha 2c adrenergic antagonist
• Absorption (AUC) increases 3x with food
• Steady state half-life= 36 hrs
• Metabolized by CYP3A4

Nakamura et al, J Clin Psychiatry 2009
Lurasidone

• How supplied: 20, 40, 60, 80 & 120 mg tablets
• Starting dose 20-40 mg/d with food
• Maximum approved dose 160 mg/d
Placebo-controlled Trial of lurasidone & olanzapine (PANSS total score)

Meltzer et al, Am J Psychiatry 2011
## Side effects:

<table>
<thead>
<tr>
<th></th>
<th>Lurasidone 40 mg/d</th>
<th>Lurasidone 80 mg/d</th>
<th>Olanzapine 15 mg/d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>12%</td>
<td>23%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Sedation</td>
<td>9%</td>
<td>14%</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>8%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Dystonia</td>
<td>3%</td>
<td>8%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Meltzer et al, Am J Psychiatry 2011
## Side effects (con’t)

<table>
<thead>
<tr>
<th></th>
<th>Lurasidone 40 mg/d</th>
<th>Lurasidone 120 mg/d</th>
<th>Olanzapine 15 mg/d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>1.0</td>
<td>1.0</td>
<td>4.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-8.3</td>
<td>-5.0</td>
<td>+50.0</td>
<td>+0.1</td>
</tr>
<tr>
<td>HOMA</td>
<td>-1.3</td>
<td>-0.28</td>
<td>+2.6</td>
<td>-1.3</td>
</tr>
<tr>
<td>Prolactin</td>
<td>+2.1</td>
<td>+10.9</td>
<td>+5.0</td>
<td>-2.5</td>
</tr>
</tbody>
</table>

Meltzer et al, Am J Psychiatry 2011
Aripiprazole Maintena

- **Aripiprazole Maintena:**
  - First dopamine D2 partial agonist given regulatory clearance as a once-monthly injection
  - Microsphere long-acting injectable (similar to RLAI)
Aripiprazole LAI

– The most frequently reported adverse events were akathisia, insomnia and injection-site pain.

– Injection-site reactions were generally mild to moderate in severity and resolved over time.

– Extrapyramidal symptoms were reported more frequently with aripiprazole 400 mg or 300 mg prolonged-release injection than oral aripiprazole...
Paloperidone 3-month injectable (Invega Trinza)

Start patients on INVEGA TRINZ (paliperidone palmitate) after initiating stabilization with INVEGA SUSTENNA.

INVEGA TRINZA is to be used only after the 1-month paliperidone palmitate extended-release injectable suspension (INVEGA SUSTENNA) has been established as adequate treatment for at least 4 months.

In order to establish a consistent maintenance dose, it is recommended that the last 2 doses of INVEGA SUSTENNA be the same dosage strength before starting INVEGA TRINZA.

For those who have not taken oral paliperidone, oral risperidone, or injectable risperidone previously, establish tolerability with oral paliperidone or oral risperidone before starting INVEGA SUSTENNA.
## Dosing

<table>
<thead>
<tr>
<th>Invega Sustnna</th>
<th>Invega trinza</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 mg</td>
<td>273 mg</td>
</tr>
<tr>
<td>117 mg</td>
<td>410 mg</td>
</tr>
<tr>
<td>156 mg</td>
<td>546 mg</td>
</tr>
<tr>
<td>234 mg</td>
<td>819 mg</td>
</tr>
</tbody>
</table>
Brexpiprazole (Rexulti)

- Otsuka Pharmaceuticals
- Indication: Monotherapy for schizophrenia and adjunctive therapy to treat major depressive disorder (MDD)
- Serotonin-Dopamine Activity Modulator (SDAM)
  - $5HT_{1A}$ partial agonist
  - $D_2$ partial agonist
  - $5HT_{2A}$ and $\alpha_{1B/2C}$ antagonist
- Dose: Available orally in 0.25, 0.5, 1, 2, 3, 4 mg tablets
- Dosing titration has been recommended to 4 mg

## Brexipiprazole vs. Aripiprazole

<table>
<thead>
<tr>
<th>Brexipiprazole</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action:</strong></td>
<td><strong>Mechanism of Action:</strong></td>
</tr>
<tr>
<td>- D₂ partial agonist</td>
<td>- D₂ partial agonist</td>
</tr>
<tr>
<td>- 5HT₁₅ partial agonist</td>
<td>- 5HT₁₅ partial agonist</td>
</tr>
<tr>
<td>- 5HT₂₅ antagonist</td>
<td>- 5HT₂₅ antagonist</td>
</tr>
<tr>
<td><strong>Approved July 2015</strong></td>
<td><strong>Approved 2002</strong></td>
</tr>
<tr>
<td><strong>Less affinity</strong> for D₂ receptor $\rightarrow$ less EPS</td>
<td><strong>More affinity</strong> for D₂ receptor $\rightarrow$ more EPS</td>
</tr>
</tbody>
</table>

Pharmacokinetics

Absorption
- Peak concentration in 4 hours; 95% bioavailable

Distribution
- Highly plasma protein bound (>99%)
  - Not affected by hepatic or renal impairment

Metabolism
- Mainly by CYP3A4 and CYP2D6
- Inactive metabolite (DM-3411)

Excretion
- <1% excreted in urine unchanged
- <14% excreted in feces unchanged
- Half-life=91 hours

Second-generation LAIs

- **ILOPERIDONE:**
  - Microencapsulated depot formulations of iloperidone and a poly-glycolide polylactide glucose star polymer.
  - Under trial
Massachusetts General Hospital
Department of Psychiatry

Presents

39th Annual
Psychopharmacology
Conference

THURSDAY-SUNDAY, OCTOBER 22-25, 2015
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