Atypical Antipsychotics from Bench to Bedside: Focus on Aripiprazole

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Objectives of the presentation

1. Psychotic symptoms across psychiatric disorders.
2. Neurochemical background of psychotic disorders
3. Binding properties of the atypical antipsychotics
4. Understanding how key pharmacological properties of antipsychotics translated into effects and side effects
5. Focus on Aripiprazole

From circuits to symptoms

Psychotic Symptoms Across Psychiatric Disorders

<table>
<thead>
<tr>
<th>Mesolimbic circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Schizoaffective</td>
</tr>
<tr>
<td>Bipolar</td>
</tr>
<tr>
<td>Depression with psychotic features</td>
</tr>
<tr>
<td>Drug induced Psychosis</td>
</tr>
<tr>
<td>Alzheimer Disease</td>
</tr>
<tr>
<td>Childhood psychotic disorders</td>
</tr>
</tbody>
</table>

Deficit Symptoms Across Psychiatric Disorders

<table>
<thead>
<tr>
<th>Mesocortical</th>
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<tbody>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Bipolar</td>
</tr>
<tr>
<td>Major Depression</td>
</tr>
<tr>
<td>Secondary to EPS</td>
</tr>
<tr>
<td>Secondary to Substance abuse</td>
</tr>
<tr>
<td>Secondary to Sensory deprivation</td>
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<tr>
<td>Drug Induced</td>
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Cognitive Symptoms Across Psychiatric Disorders

<table>
<thead>
<tr>
<th>Dorsolateral PFC</th>
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<tbody>
<tr>
<td>Alzheimer’s</td>
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<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Autism</td>
</tr>
<tr>
<td>Post Stroke</td>
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<tr>
<td>ADHD</td>
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</table>

Affective Symptoms Across Psychiatric Disorders

<table>
<thead>
<tr>
<th>Mood symptoms</th>
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</thead>
<tbody>
<tr>
<td>Major depression</td>
</tr>
<tr>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Schizoaffective</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Childhood disorders</td>
</tr>
<tr>
<td>Organic BS</td>
</tr>
</tbody>
</table>
Aggressive Symptoms Across Psychiatric Disorders

- Amygdala
- Alzheimer’s & dementia
- ADHD/ Conduct disorder
- Mood disorders
- Schizophrenia
- Childhood psychosis
- Borderline personality disorder

Developments in medical treatments for psychotic disorders

<table>
<thead>
<tr>
<th>50s</th>
<th>60s</th>
<th>70s</th>
<th>80s</th>
<th>90s</th>
<th>00</th>
<th>02</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECT</td>
<td>Clozapine</td>
<td>Risperidone</td>
<td>Haloperidol</td>
<td>Fluphenazine</td>
<td>Thioridazine</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Insulin coma</td>
<td>Leucotomy</td>
<td>Chlorpromazine</td>
<td>First-generation antipsychotics</td>
<td>Second-generation antipsychotics</td>
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<td></td>
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<tr>
<td>Leucotomy</td>
<td>Chlorpromazine</td>
<td>Loxapine</td>
<td>Perphenazine</td>
<td>Amisulpride</td>
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</tbody>
</table>

Are All Antipsychotics The Same?!!

Binding Properties of Atypical-antipsychotics

- Different receptor antagonism
- Different clinical effects

Potential Clinical Implications Of Receptor Activities

- D₂ antagonism ➔ Positive symptoms efficacy, EPS, endocrine effects
- 5-HT₂ antagonism ➔ Negative symptom efficacy, reduced EPS
- High 5-HT₂/5-HT₂ affinity ratio ➔ Antipsychotic efficacy reduced EPS (compared to D₂ antagonism alone)
- SHT1D ➔ Antidepressant activity

Are All Antipsychotics The Same?!!

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis


ECT
Insulin coma
Leucotomy
Chlorpromazine
First-generation antipsychotics
Second-generation antipsychotics

Developments in medical treatments for psychotic disorders

- ECT
- Insulin coma
- Leucotomy
- Chlorpromazine
- First-generation antipsychotics

Are All Antipsychotics The Same?!!

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Sedation
- Clozapine
- Quetiapine
- Olanzapine
- Asenapine
- Iloperidone
- Paliperidone
- Ziprasidone

Orthostatic Hypotension and Dizziness
- Clozapine
- Quetiapine
- Iloperidone
- Paliperidone
- Asenapine
- Olanzapine
- Ziprasidone
- Lurasidone

Anticholinergic Effects (M1)
- Clozapine
- Olanzapine
- Iloperidone
- Paliperidone
- Asenapine
- Lurasidone
- Ziprasidone

Metabolic Changes (H1-5HT2c)
- Clozapine
- Olanzapine
- Iloperidone
- Quetiapine
- Asenapine
- Paliperidone
- Ziprasidone

Weight gain
- (H1 & α1) antagonism
- 5HT2c affinity
- Dysregulation of leptin
**Extrapyramidal Side Effects**

**EPS**
- D$_2$ Antagonism

**Management**
- Anticholinergic drugs
- Switch to another AP

---

**Extra Pyramidal Symptoms (EPS)**

- Dystonia
- Parkinsonism
- Tardive Dyskinesia
- Akathisia

**DA**

**ACh/5HT**

**NE/5HT**

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**Parkinsonism**
- Risperidone
- Paliperidone
- Olanzapine
- Ziprasidone
- Lurasidone
- Asenapine
- Quetiapine
- Clozapine

**Akathisia**
- Risperidone
- Paliperidone
- Lurasidone
- Asenapine
- Quetiapine

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**Hyperprolactinemia (D2)**

**Prolactin increase**

- Sexual side effects
  - α1 Antagonism

**Management**
- Dose
- Bromocryptin
- Switch to another AP

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**Cardiac Side effects**

- Cardiac and postural hypotension
- Reflex tachycardia

**Management**
- Slowly movement
- Beta blockers
What makes Aripiprazole a unique molecule for different medication?

- Partial agonist at dopamine D2, D3 and serotonin 5-HT2A receptors.
- Antagonist at 5-HT2A receptors.
- No action on muscarinic, histaminergic, Alpha Adrenergic receptors.

Aripiprazole as Partial Agonist

Acts as functional antagonist in hyper-dopaminergic state as functional agonist in hypo-dopaminergic state.

ARIPIPRAZOLE

- The most common side effects of aripiprazole are:
  - Headache, nausea,
  - Vomiting, insomnia,
  - Tremor, constipation.
  - Akathisia

- The drug has:
  - Lower risk of extrapyramidal symptoms,
  - Lower risk of increases in lipid,
  - Lower risk of increase of prolactin levels,
  - Lower risk of sedation

Drug-drug interactions have not commonly been reported with aripiprazole.

Aripiprazole in Schizophrenia effective for all symptoms clusters

Positive symptoms: delusions, hallucinations, disorganized speech, catatonia

Cognitive symptoms: attention, memory, executive functions (e.g., abstraction)

Mood symptoms: depressive flattening, anergia, anhedonia

Negative symptoms: affective flattening, anergia, avolition, anhedonia

Social, Occupational, Interpersonal, Work, Self-care

Aripiprazole FDA Approvals

- 2002: Schizophrenia
- 2004: Acute manic and mixed episodes
- 2005: Bipolar Maintenance-Continuation Treatment
- 2006: Acute Agitation (IM)
- 2007: Adolescent Schizophrenia (age 12 above)
- 2007: Major Depressive Disorder (Adjunctive Treatment)
- 2008: Treatment of Mania in Adolescents (6-17 years)
- 2009: Treatment of irritability associated with Autistic Disorder in pediatric patients
- Tourette's disorder (6-18 years)
Off Label Use Of Aripiprazole

- Schizoaffective disorder
- Borderline personality disorder
- Drug induced psychosis
- Generalized anxiety disorders
- OCD
- Dementia
- Eating disorders
- Schizoaffective disorder
- Borderline personality disorder
- Drug induced psychosis
- Generalized anxiety disorders
- OCD
- Dementia
- Eating disorders

Aripiprazole Dose

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initial dose</th>
<th>Recommended Dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHIZOPHRENIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>10-15 mg</td>
<td>10-15 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Adolescents</td>
<td>5 mg</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>MONOTHERAPY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>15 mg</td>
<td>15 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Adjunct to mood stabilizer</td>
<td>10 mg</td>
<td>15 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Bipolar mania pediatric</td>
<td>5 mg</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Bipolar maintenance</td>
<td>15-30 mg</td>
<td>15-30 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>SPECIFIC POPULATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunct to AD</td>
<td>5 mg</td>
<td>5-10 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>AUTISM SPECTRUM DISORDER</td>
<td>5 mg</td>
<td>5-10 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>AGITATION WITH SCHIZOPHRENIA OR</td>
<td>10 mg</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>BIPOLAR MANIA</td>
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</tbody>
</table>

Aripiprazole in Special Population

- Dosage adjustments are not routinely indicated on the basis of age, renal or hepatic impairment.
- As Aripiprazole is metabolized via CYP 450 2D6 & 3A4, so dose should be adjusted as follows:
  - With Enzyme Inducers e.g.: Carbamazepine, dose should be increased.
  - With Enzyme Inhibitors (3A4) e.g.: Ketoconazole, dose should be decreased.
  - With Enzyme Inhibitors (2D6) e.g.: Fluoxetine or Paroxetine, dose should be decreased.

Choosing an Antipsychotic Drug

Safety
Tolerability
Efficacy
Price (Adwiprazole)
Simplicity

Use of Aripiprazole for treatment of patient with schizophrenia
- Who are newly diagnosed or have not received any treatment;
- Who are unable to tolerate the current antipsychotic;
- Who developed metabolic side effects;
- Whose symptoms did not remit;
- Who experienced acute exacerbation while on the current antipsychotic or
- Who discontinued current antipsychotic due to poor efficacy or tolerance,
  are likely to benefit from aripiprazole treatment.
How to Switch?

Switching patients to aripiprazole should be done slowly because of aripiprazole's exceptionally high affinity for dopamine D2 receptors in the face of its partial agonism at this receptor.

• Metabolic Side Effects (weight gain/dyslipidemia/altered glucose tolerance)
• Hyperprolactinemia
• EPS
• Tardive Dyskinesia
• Insufficient Efficacy/Dissatisfaction
• Postural Hypotension
• Prolonged QTc
• Sedation
• Sexual Side Effects
• Negative/Depressive Symptoms
• Cognitive Function

Patients with First Episode Psychosis

Outpatients with Stable Schizophrenia

Switching to aripiprazole in case of outpatients with stable schizophrenia.

Inpatients

Outpatients with Recurrent Psychotic Exacerbation

Switching to aripiprazole in the inpatient setting.

Switching to aripiprazole for treatment of outpatients with recurrent psychotic exacerbation.
Optimizing Aripiprazole Medication
Managing Adverse Effects during Switching

Possible adverse effects during switch from other antipsychotics to aripiprazole and their management

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Approach/additional drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>Decrease aripiprazole dose, slow down dose reduction of the previous antipsychotic; add benzodiazepine &amp; possibly a beta-blocker &amp; possibly anticholinergics.</td>
</tr>
<tr>
<td>Mania, psychosis</td>
<td>Slow down dose reduction of the previous antipsychotic or reverse switch; increase aripiprazole dose. Add benzodiazepine &amp; possibly valproate (for bipolar disorder)</td>
</tr>
<tr>
<td>Agitation</td>
<td>Slow down dose reduction of the previous antipsychotic or reverse switch; increase aripiprazole dose. Add benzodiazepine &amp; possibly valproate (for bipolar disorder)</td>
</tr>
</tbody>
</table>

Long-Term Antipsychotic Treatment

• For long term maintenance treatment of schizophrenia, you need an antipsychotic that is:
  – Effective in psychotic symptoms as well as having neurocognitive functions.
  – Does not induce dopamine receptor supersensitivity.
    • Chronic treatment with antipsychotics induces dopamine supersensitivity leading to loss of effectiveness through the development of supersensitivity of the dopamine D2 receptor.
  – Has high tolerability and efficacy profile.
    • Does not cause metabolic issues, EPS, hyperprolactinemia, & prolonged QTc interval.

Overall

• Aripiprazole treatment is associated with a low incidence of EPS (other than akathisia) & EPS-related symptoms & with minimal or no effects on weight gain, QTc interval, or circulating levels of cholesterol, glucose, & prolactin.
• Treatment with Aripiprazole may reduce the burden of antipsychotic-associated side effects, thereby leading to improved patient adherence & decreased risks of acute relapse.

CONCLUSION

Effective control of
• Psychotic symptoms
• Mood symptoms
Favorable tolerability and safety profile
Improves quality of life
**NOT ONLY DRUGS**

You should Consider

Psychosocial Intervention and

Rehabilitation

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**Aripiprazole as Partial Agonist**

Aripiprazole binds to D2 and 5HT1A (partial agonism)

Aripiprazole - binds to 5HT2a (antagonism)

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**Reasons for Switching**

<table>
<thead>
<tr>
<th>Possible Causes</th>
<th>Alternative Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic: Side Effects (weight gain/dyslipidemia, altered glycemic tolerance)</td>
<td>Olanzapine, Quetiapine</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Amisulpride, Risperidone, Paliperidone</td>
</tr>
<tr>
<td>EPS</td>
<td>Haloperidol, Risperidone, Amisulpride</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>Haloperidol, Risperidone, Clozapine, Aripiprazole</td>
</tr>
<tr>
<td>Insufficient Efficacy/Discontinuation</td>
<td>Quetiapine, Haloperidol</td>
</tr>
<tr>
<td>Neuroplastic Hypertension</td>
<td>Chlorpromazine, Quetiapine</td>
</tr>
<tr>
<td>Prolonged QTc</td>
<td>Ziprasidone, Sulfpiride</td>
</tr>
<tr>
<td>Sedation</td>
<td>Quetiapine, Chlorpromazine, FGAs</td>
</tr>
<tr>
<td>Negative/Depressive Symptoms</td>
<td>FGAs, Haloperidol</td>
</tr>
</tbody>
</table>

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**Key Points in Switching**

1. Aripiprazole has some unique receptor binding qualities that provides advantages over other antipsychotic in certain clinical situations.
2. The management of switching from an atypical antipsychotics to Aripiprazole is critical because of the pharmacological properties.
3. The duration of the steady state is 2 weeks. Waiting for 2 weeks to decide about increasing the dose is recommended.

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**Long-Term Benefits of Aripiprazole**

- Aripiprazole exhibited efficacy similar to that of other antipsychotic drugs & a better safety profile than that of typical & atypical antipsychotic drugs.

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### Potential Aripiprazole Advantages:
1. Some cases of psychosis & bipolar disorder refractory to treatment with other antipsychotics.
2. Patients concerned about gaining weight & patients who are already obese or overweight.
3. Patients with diabetes.
4. Patients with dyslipidemia (especially elevated triglycerides).
5. Patients requiring rapid onset of antipsychotic action without dosage titration.
6. Patients who wish to avoid sedation.

### Potential Aripiprazole Disadvantages:
- Patients in whom sedation is desired.
- May be more difficult to dose for children, elderly, or "off-label" uses.

### Aripiprazole Primary Target Symptoms:
1. Positive symptoms of psychosis.
2. Negative symptoms of psychosis.
4. Unstable mood & depression.
5. Aggressive symptoms.

### Pearls
1. Aripiprazole is well accepted in clinical practice when wanting to avoid weight gain because less weight gain than most other antipsychotics.
2. Aripiprazole is well accepted in clinical practice when wanting to avoid sedation because less sedation than most other antipsychotics at all doses.

### Pearls
3. Aripiprazole can even be activating, which can be reduced by lowering the dose or starting at a lower dose.
   - If sedation is desired, a benzodiazepine can be added short-term at the initiation of treatment until symptoms of agitation & insomnia are stabilized or intermittently as needed.

### Pearls
4. Aripiprazole may not have diabetes or dyslipidemia risk, but monitoring is still indicated.
   - Aripiprazole has a very favorable tolerability profile in clinical practice.
   - Aripiprazole favorable tolerability profile lead to "off-label" uses for many indications other than schizophrenia (e.g., bipolar II disorder, including hypomanic, mixed, rapid cycling, & depressed phases; treatment-resistant depression; anxiety disorders).

### Pearls
5. Aripiprazole lacks D₄ antagonist, anticholinergic, & antihistamine properties, which may explain relative lack of sedation or cognitive side effects in most patients.
6. Aripiprazole when administration of even low dose (1-5 mg) can reverse the hyperprolactinemia/galactorrhea of other antipsychotics, also proving that Aripiprazole interferes with the D₂ actions of other antipsychotics.
<table>
<thead>
<tr>
<th>When to Switch?</th>
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### Long-Term Benefits of Aripiprazole

- Stay with Aripiprazole for long term maintenance of schizophrenia.
  - Aripiprazole treatment is associated with the lowest rate of rehospitalization (71% risk reduction) among antipsychotics in clinical use, including both FGAs & SGAs.
  - Aripiprazole more efficiently lower the risk of relapse of psychotic symptoms compared with other antipsychotics.
  - Because Aripiprazole prevents the development of dopamine supersensitivity.