Outline

• Considerations/Strategies for Switching between Oral Antipsychotics

• Starting an LAI
  • Antipsychotic Classes & Delivery Technology
  • Establishing Tolerability
  • Dosing considerations & Characteristics by Agent
Considerations & Strategies for Switching Oral Antipsychotics
Possible Methods for Switching APs

A. Abrupt Switch
B. Cross-Titration
C. Plateau Cross-Titration

RED closed line: Initial antipsychotic dose
GREEN closed line: New antipsychotic dose
Dotted Line: Antipsychotic plasma concentration
*Stepwise start with partial D2 agonist with lower starting dose recommended

Adapted from: Correll CU. J Clin Psychiatry 2006;67(1):160-1
Recommended Switching Strategy For Finding An Optimal Stable Dose

Plateau Cross-Titration involves the gradual initiation of the new AP with gradual discontinuation of the first AP only after steady state of the new AP has been reached.

- Expert recommendations and clinical experience indicate that the preferred switching method for a looser binding AP, a partial D2 agonist and low antihistaminergic/anticholinergic APs is the Plateau Cross-Titration strategy to reduce potential withdrawal side effects.

- This strategy involves a stepwise or low therapeutic dose initiation of the new antipsychotic with a delayed gradual discontinuation of the first medication.

**Plateau Cross-Titration**

- RED closed line: Initial antipsychotic dose
- GREEN closed line: New antipsychotic dose
- Dotted Line: Antipsychotic plasma concentration


LAI's reduce chance of rebound symptoms

• One advantage of LAIs is that if the patient stops taking the medication, there is less of a chance of a rebound withdrawal symptoms.

• This is because there is a natural gradual discontinuation of the medication over weeks if the patient does not receive the next scheduled injection.

• Lets look at some of the possibilities for rebound symptoms that occur when abruptly stopping or abruptly switching between oral antipsychotics...
Pharmacodynamic rebound effects are likely...

• ...when stopping abruptly or...

• ...when switching from an agent with more potent histaminergic blockade relative to dopamine

• ...when switching from an agent with more potent cholinergic blockade relative to dopamine

• ...when switching from a strongly antidopaminergic drug to a less tightly dopamine receptor binding antipsychotic
Agents with more potent histaminergic blockade relative to dopamine

• Stopping abruptly:
  • Chlorpromazine, clozapine, olanzapine, quetiapine

• Or switching from these agents to:
  • Aripiprazole, aiprazidone, haloperidol, iloperidone, molindone, risperidone, paliperidone

• Histaminergic rebound effects:
  • Reversal of the antihistaminergic anxiolytic, calming, sleep inducing, and anti-EPS effects, potentially resulting in rebound agitation, confusion, and EPS.
Agents with more potent cholinergic blockade relative to dopamine

• Stopping abruptly:
  • Asenapine, chlorpromazine, clozapine, olanzapine, quetiapine

• Or switching from these agents to:
  • Aripiprazole, aiprazidone, haloperidol, iloperidone, molindone, risperidone, paliperidone

• Cholinergic rebound is characterised by a reversal of the anticholinergic calming and anti-EPS effects, potentially resulting in rebound agitation, confusion, and EPS.
Strongly antidopaminergic agents to less tightly binding dopamine receptor antipsychotics

• Stopping abruptly, a high or medium potency FGA such as:
  • iloperidone, paliperidone, or risperidone

• Or switching from these agents to a less tightly binding dopamine receptor antipsychotic such as:
  • clozapine or quetiapine.

• Or to an agent with very strong 5HT2A blockade (ziprasidone)

• Or to a partial D2 agonist (aripiprazole)
• Unless the new agent is dosed at a sufficiently high/equivalent level, dopaminergic rebound can occur.

• Dopaminergic rebound can manifest as worsening or newly emerging psychosis, mania, agitation, aggression, akathisia, or withdrawal dyskinesia.

• If the patient stops taking an LAI, there is less of a chance of a rebound withdrawal symptoms, let's take a look at LAI kinetics...
LAI Kinetics

• For all LAIs, apparent plasma half life is determined by rate of drug release rather than drug metabolism.

• The rate of release determines the persistence of drug in the system, not elimination rate.

• All drugs available as LAIs have plasma half lives of 1-2 days in oral form.

• For most LAIs, the apparent half-life after repeated use is between 14 and 27 days (2-4 weeks).
LAI Kinetics

• Time to steady state is (4-5 half lives), therefore, also prolonged with LAI use.

• At that point, rate of drug elimination equals rate of release, plasma profile does not change between dose intervals.

• If the patient stops taking an LAI, there is less of a chance of a rebound withdrawal symptoms because there is a natural gradual discontinuation of the medication.
Starting a LAI
First, choose an agent based on patient history

- Is there history of poor tolerance to certain oral agents or preferences based on side effect profile?

- Is there history of medical co-morbidities (obesity, diabetes, metabolic syndrome) that suggest use of one antipsychotic class over another?

- Is the patient in their first episode and antipsychotic naïve?

- Is there a history of good response to an agent available as a LAI?

- Are they currently prescribed an oral antipsychotic available as a LAI?
LAI antipsychotics in the United States
Based on Antipsychotic class/Depot Delivery Technology

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DELIVERY</th>
<th>AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation Antipsychotic</td>
<td>Oil</td>
<td>Fluphenazine decanoate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haloperidol decanoate</td>
</tr>
<tr>
<td>Second Generation Antipsychotic</td>
<td>Microspheres</td>
<td>Risperidone LAI</td>
</tr>
<tr>
<td></td>
<td>Crystal</td>
<td>Olanzapine pamoate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paliperidone palmitate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aripiprazole monohydrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aripiprazole lauroxil</td>
</tr>
</tbody>
</table>
Depot Delivery Technology: Oil-based

• Long period before they achieve clinically effective results

• Takes many months to achieve steady state

• Can increase time to steady state with more frequent loading initially

• Takes many months to eliminate

• Pharmacokinetics vary widely within and between patients
FGAs: Decanoates

• The First Generation Antipsychotic LAIs are combinations of the specific antipsychotic agent and a long chain fatty acid.

• The process of combining the antipsychotic agent with a long chain fatty acid is called esterification.

• Esterification makes the antipsychotic fat soluble so that it can be dissolved in oil.

• For agents available in the United States, the long chain fatty acid decanoic acid.

Ereshefsky et al. 1984; Barnes & Curson 1994; Den key & Axelsson 1996
FGAs: Decanoates

• Once injected intramuscularly, the medication slowly leaves the oil reservoir.

• Once in the bloodstream, the antipsychotic is separated from the fatty acid.

Ereshefsky et al. 1984
Barnes & Curson 1994
Den key & Axelsson 1996
FGAs: Decanoates

• Advantages of decanoates include they are the most inexpensive LAIs.

• For Medicaid coverage in New York State, they do not require prior authorization.

• They come in reusable bottles that do not require refrigeration.

• A disadvantage is that their pharmacokinetics can vary widely within and between patients.

Ereshefsky et al. 1984; Barnes & Curson 1994; Den key & Axelsson 1996
FGAs: Decanoates

• Advantages over SGA LAIs include lower metabolic side effect profile.

• Disadvantages compared to SGA LAIs include higher risk of EPS.

• Formulations available in the United States include:
  • Fluphenazine decanoate
  • Haloperidol decanoate

Ereshefsky et al. 1984; Barnes & Curson 1994; Den key & Axelsson 1996
Depot Delivery Technology: Microspheres

• Pharmacokinetics more predictable than with oil-based technology

• Three week period of no release of medication following initial injection

• Requires oral medication for at least the first 3 weeks and for as long as 6 weeks until the LAI reaches steady state.
Depot Delivery Technology: Crystals

• Sustained delivery of clinically effective doses from first day of injection (initial oral supplementation required for aripiprazole).

• Well-defined, predictable pharmacokinetic profiles.

• Take months to achieve steady state.

• Can increase time to steady state with more frequent loading initially.
After an considering which agent to use, next establish tolerability
Next, Establish Tolerability

• Tolerability is your clinical assessment that the subject tolerates the antipsychotic medication in the LAI.

• It consists of an oral trial of the antipsychotic

• We don’t need to find the optimal oral dose—tolerability is different from dose optimization.
After tolerability is established, how to initiate the LAI
haloperidol decanoate: dosing

• Haloperidol decanoate comes in 50mg and 100mg doses. The preferred approach to determining the minimum effective dose is to begin with lower initial doses and to adjust the dose upward as needed.

• For patients previously maintained on low doses of antipsychotics (e.g. up to the equivalent of 10 mg/day of oral haloperidol), it is recommended that the initial dose of haloperidol decanoate be 10-15 times the previous daily dose in oral haldol equivalents.
haloperidol decanoate: dosing

• In patients previously maintained on higher doses of antipsychotics for whom a low dose approach risks recurrence of psychiatric decompensation and in patients whose long-term use of haloperidol has resulted in a tolerance to the drug, 20 times the previous daily dose in oral haloperidol equivalents should be considered for initial conversion, with downward titration on succeeding injections.

• The initial dose of haloperidol decanoate should not exceed 100mg regardless of previous antipsychotic dose requirements. If conversion requires more than 100mg of haloperidol as an initial dose, that dose should be administered in two injections, i.e. a maximum of 100mg initially followed by the balance in 3 – 7 days.
fluphenazine decanoate: Dosing

• A dose of 12.5 – 25mg (0.5 – 1mL) may be given to initiate therapy.
• Subsequent injections and the dosage interval are determined in accordance with the patient’s response.
• Fluphenazine hydrochloride 20mg daily is equivalent to 25mg (1mL) of fluphenazine decanoate injection every 3 weeks.
• This represents an approximate conversion ratio of 12.5mg (0.5mL) of decanoate every 3 weeks for every 10mg of fluphenazine hydrochloride daily.
• A single dose has been found to be effective for patients for 4-6 weeks in maintenance therapy.
SGAs: risperidone microspheres

• Risperidone LAI was the first non-oil based LAI.

• Risperidone is encapsulated in microspheres that require cold storage.

• Microspheres are composed of biodegradable polymers that are slowly broken down to release risperidone.

• Risperidone LAI is administered every 2 weeks.
risperidone microspheres: Dosing

• Dosing options include 12.5mg, 25mg, 37.5mg, and 50mg.
• The recommended dose is 25mg every 2 weeks.
• Although dose response for effectiveness has not been established, some patients not responding to 25mg may benefit from a higher dose of 37.5mg or 50mg.
• The maximum dose should not exceed 50mg every 2 weeks.
risperidone LAI Kinetics

• After administration, release is delayed or 2-3 weeks during which time erosion of the microspheres takes place.

• Peak release is about 28 days.

• Peak plasma levels continue to be seen around 4 weeks after the injection.

• The plasma half life is 4-6 days.
risperidone LAI Kinetics

• The apparent half life is more complicated due to the initial absence of release followed by progressive release as microspheres break down.

• Steady state levels are obtained after 8 weeks.

• When stopped, there is a maintenance of adequate plasma levels for 4-5 weeks before there is a rapid reduction.

• By 8 weeks following the last injection risperidone has been eliminated from the system.
olanzapine

- Olanzapine pamoate is the first of the crystal-based LAIs.

- It is a salt of pamoic acid and olanzapine suspended in water.

- After the micron-sized crystals are injected into muscle tissue, the pamoate salt slowly dissolves, releasing free olanzapine and pamoic acid.

- The long acting properties result from the slow rate at which the crystalline salt dissolves.

Taylor 2009
olanzapine

- Olanzapine pamoate can be administered at 2 – 4 week intervals
- Patients can switch abruptly from oral to LAI
- It does not need to be refrigerated
- It comes in a powder requiring reconstitution

Taylor 2009
olanzapine pamoate: dosing

• Olanzapine pamoate is available in doses of 210mg/2wk, 300mg/2wk, and 405mg/4wk.

• An oral olanzapine dose of 10mg/day corresponds to 210mg/2 weeks or 405mg/4 weeks (changed to 150mg/2 weeks or 300mg/4 weeks after 8 weeks).

• An oral dose of 15mg/day corresponds to 300mg/2 weeks (changed to 210mg/2 weeks or 405mg/4 weeks after 8 weeks).

• An oral dose of 20mg/day corresponds to 300mg/2 weeks (same dose in maintenance).
olanzapine pamoate Kinetics

• Following injection, peak plasma levels occur 2-4 days later.
• Apparent plasma half life is about 26 days (range 2-3 weeks).
• With regular injections, the time to steady state is approximately 2-3 months.
• In 2 week dosing, trough levels are approx 50% of peak level
• In monthly dosing, trough levels are 75% of peak level.
olanzapine

• A post-injection syndrome which is rarely seen but unique to this agent.

• Olanzapine pamoate crystals are relatively insoluble in muscle, but rapidly dissolve in blood.

• Theorized mechanism is damaged blood vessels during injection with leakage of blood into the injection site.

Taylor 2009
Post-injection Delirium/Sedation Syndrome

• Symptoms are similar to an oral olanzapine overdose.

• **Delirium-like symptoms** (occurring in 97% of cases) include disorientation, confusion, ataxia, dysarthria, irritability, anxiety, and aggression.

• **Sedation-related symptoms** (occurring in 87% of cases) include changes in level of consciousness such as somnolence.

• **General malaise** including nonspecific symptoms of weakness, dizziness, or not feeling well were reported in 67% of cases.

Taylor 2009
Post-injection Delirium/Sedation Syndrome

• The majority of cases occur in the first hour following the injection.

• Patients should remain in clinic for observation for 2 hours after each injection.

• Patients should be advised to not drive or operate heavy machinery the same day after injection.

Taylor 2009
Post-injection Delirium/Sedation Syndrome

• Reduce risk by using proper injection technique to prevent contact with the bloodstream.

• To assure deep intramuscular application:
  • 1.5 inch (35mm) 19 gauge needle is recommended.
  • For obese patients, a 2 inch (50mm) needle is recommended.

• Aspiration prior to injection (check for visible blood).

• If blood is visible in the aspirate:
  • withdrawal of the syringe
  • inject into the alternate buttock
paliperidone palmitate

• Paliperidone palmitate is the second crystal-based LAI developed.

• It is a salt supplied in an aqueous suspension in pre-filled syringes.

• Originally it was only available in once monthly formulation.

• It is now also available in dosing frequency of every 3 months.

Citrome et al 2010
paliperidone palmitate

- It is a metabolite of risperidone with several advantages over microspheres:
  - Immediate loading
  - Oral supplementation not required (after initial loading doses)
  - Four week dosing interval (after initial loading doses)
  - Greater dosing range
  - Refrigeration and reconstitution are not required
paliperidone palmitate – monthly: dosing

- To initiate, inject 234mg day 1, followed by 156mg day 8, followed by first maintenance dose five weeks after first injection.
- Maintenance doses are 39-234mg/month with recommended maintenance dose of 117mg monthly.
- Dosing options are 39mg, 78mg, 117mg, 156mg, or 234mg.
- Oral dose of 3mg daily corresponds to 39-78mg monthly.
- Oral dose of 6mg daily corresponds to 117mg monthly.
- Oral dose of 12mg daily corresponds to 234mg monthly.
paliperidone palmitate – Q 3 months: dosing

- Dosing options include 273mg, 410mg, 546mg, or 819mg.
- Transition to every 3 months—paliperidone palmitate should follow treatment with monthly paliperidone palmitate.
- 78mg monthly corresponds to 273mg every 3 months.
- 117mg monthly corresponds to 410mg every 3 months.
- 156mg monthly corresponds to 546mg every 3 months.
- 234mg monthly corresponds to 819mg every 3 months.
paliperidone palmitate Kinetics

• Peak plasma concentration occurs about 13 days after injection.

• Apparent half life is between 25 and 49 days (doses 25 – 150mg equivalents)
Aripiprazole differs from other SGAs as it is a partial dopamine agonist.

Differences from other agents includes decreased metabolic side effect profile and lower risk of hyperprolactinemia.
aripiprazole monohydrate

- Crystalline aripiprazole monohydrate is a dry powder requiring resuspension with sterile water at room temperature immediately before administration.

- It is available in prefilled dual chamber syringes and single dose vials.

- Once injected into muscle, it is slowly absorbed into systemic circulation due to its low solubility, there is no release vehicle or release controlling membrane.

- Oral supplementation is required for 14 days after first dose.
aripiprazole monohydrate: Dosing

- The recommended starting and maintenance dose is 400mg monthly (no sooner than 26 days after the previous injection).

- If there are adverse reactions to the 400mg dose, consider reducing the dosage to 300mg monthly.
aripiprazole monohydrate Kinetics

• Peak plasma levels are seen 6-7 days after injection.

• Apparent plasma half life is 29.9 – 46.5 days.
aripiprazole lauroxil

• Aripiprazole lauroxil, a prodrug ester of aripiprazole, is available supplied as an aqueous suspension in prefilled syringes.

• Once injected into muscle, it is slowly absorbed into systemic circulation and converted to its active form.

• It offers a 6 week dosing option.

• Oral supplementation is required for 21 days after first dose.
Dosing depends on the daily oral dose of aripiprazole.
• The 441mg dose per month is equivalent to 10mg oral dose daily.
• The 662mg dose per month is equivalent to 15mg oral dose daily.
• The 882mg dose per month is equivalent to ≥ 20mg oral dose daily.
aripiprazole lauroxil Kinetics

• After a single IM dose, appearance in systemic circulation starts day 5 or 6 and continues to be released for an additional 36 days.

• With oral supplementation for 21 days, concentrations reach therapeutic levels in 4 days.

• Steady state is reached after the 4th monthly injection.

• Apparent half life ranges from 29.2 to 34.9 days after every 4 week injection.
References
