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Psychiatry and Addictions Case Conference

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MIND THE GAP: SWITCHING ANTIPSYCHOTICS SAFELY

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SPEAKER DISCLOSURES

✓ No conflicts of interest

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Identify reasons that patients or prescribers switch antipsychotics
2. Explore considerations in different switching scenarios, including adverse effects and rebound symptoms.
3. Understand reasons and rationale for different switch strategies
4. Develop a framework to discussing switches in antipsychotics with patients

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WHY SWITCH ANTIPSYCHOTICS?

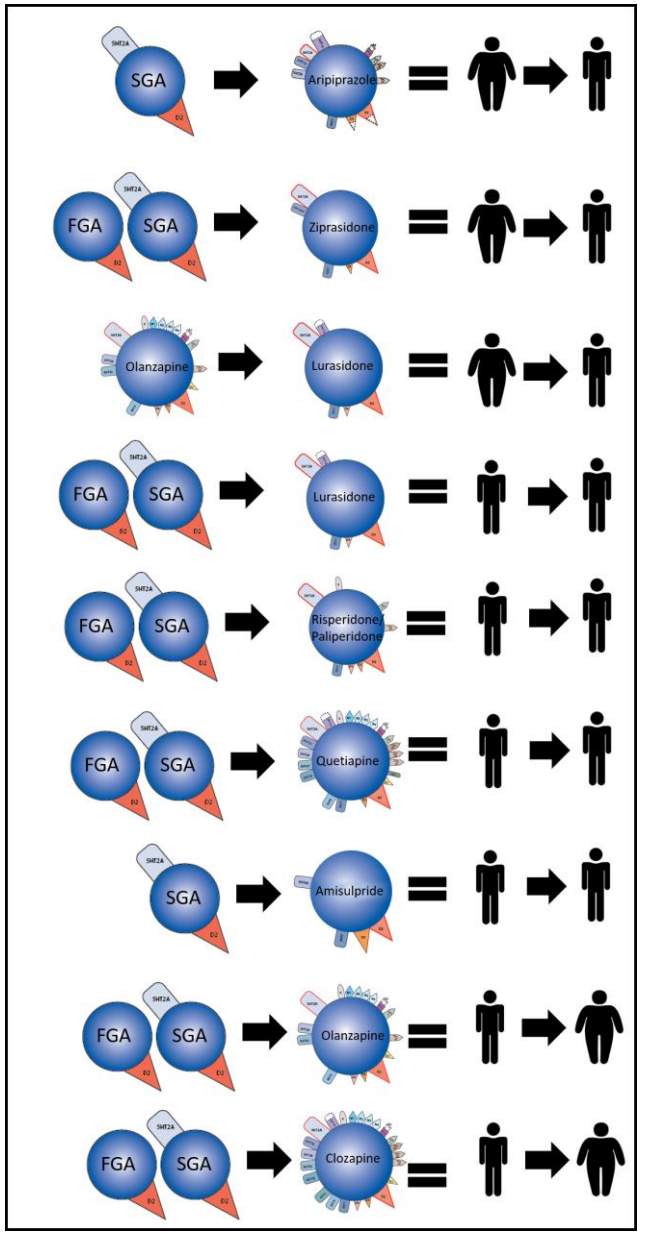
Side effects

Inefficacy

Drug interactions

Insurance

Patient Request



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SHARED DECISION MAKING

Always a risk/benefit assessment

- Psychiatric condition/diagnosis, target symptoms
- History: response, adherence, adverse reactions
- Comorbidities, metabolic risks

Shared Decision Making

- Patient-centered approach to making treatment decisions
- Options with consequences explored with decision aids during clinical encounters
- Informed decisions reflecting patient values and goals made with clinicians

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HOW TO ASSESS THE DECISION

1. Identify the patient's level of insight and motivations for switching medication

2. Elicit concerns presented by patients and caregivers

- Prior negative experiences with medication switches (efficacy and tolerability) as reported by all parties
- Ensure that caregiver input is valued, and that resources are devoted to them (e.g., disease state and family education)

3. Elicit patient treatment goals and values in the context of antipsychotic options

- Is avoidance of side effects more important than efficacy at this stage? (e.g., weight gain, sedation, sexual dysfunction)
- Is convenience important? (How can a patient with early psychosis opt for a long-acting injectable (LAI) if they are never informed?)

Has adherence been an issue and a Long-Acting Injectable (LAI) should be offered?

Has this patient been offered clozapine (if treatment resistant)?

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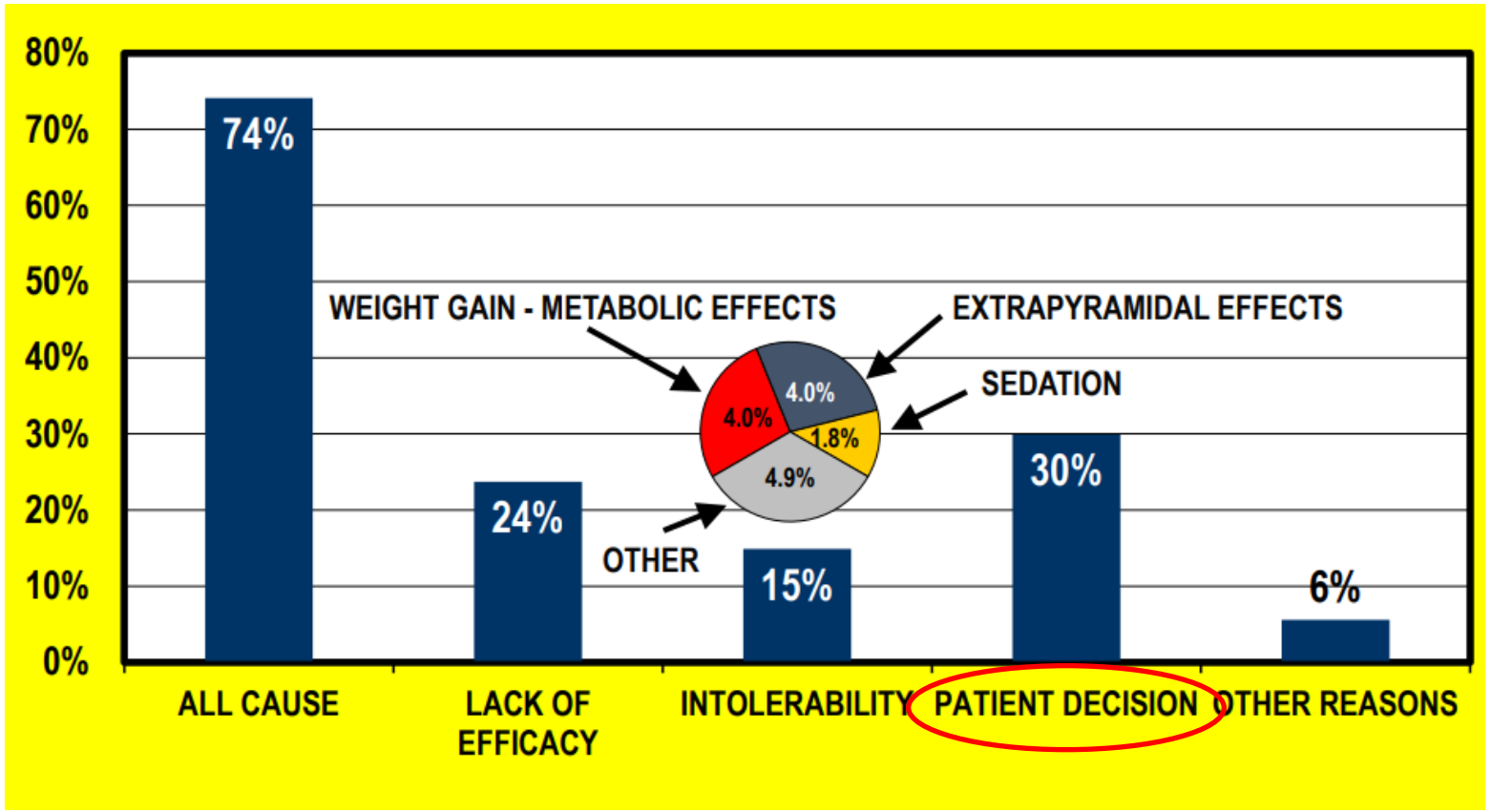
A LOOK AT THE CATIE TRIAL – REASON FOR DISCONTINUATION



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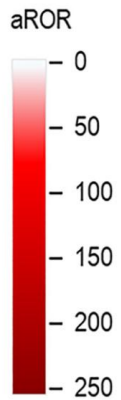
ADVERSE EFFECT FREQUENCY IN SCHIZOPHRENIA

	SGA					FGA
SMQ	Clozapine	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Haloperidol
Accidents / injuries						
Agranulocytosis	2.0					
TdP / QT prolongation	2.7		5.7	6.3	3.2	6.8
Anticholinergic syndrome	4.1	2.4	16.2	14.9	13.0	15.2
Weight gain		5.9	10.1	5.5	12.1	9.8
Dyslipidaemia		2.0	9.3	6.8		
Hyperglycaemia			7.9	8.7		
Akathisia		45.2	18.3	7.9	14.4	28.7
Dyskinesia	2.6	23.5	8.5	10.0	12.9	20.7
Dystonia	3.6	19.0	11.9	7.1	17.8	45.7
Parkinson-like events	2.8	12.3	10.1	6.7	10.9	27.5
NMS	3.6	8.5	16.1	11.4	11.6	32.5
Suicide		2.7	4.0	6.5	3.7	6.2
Sedation	2.3	3.8	7.2	6.1	4.6	5.3
Cognitive impairment		5.9	3.6	2.7	2.0	3.3
SIADH / Hyponatriaemia			4.7		3.1	3.1
Hyperprolactinaemia		7.5	8.2	3.9	211.9	6.0
Sexual dysfunction		3.2	2.6	2.3	2.2	



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THE SMARTS CHECKLIST

Systematic **M**onitoring of **A**dverse events Related to **T**reatment**S**

Table 1. Potential side effects of antipsychotics addressed by questions in the SMARTS checklist.

SMARTS checklist questions (Are you troubled by...)	Potential side effect addressed
1. Difficulties in your movement such as shaking, stiffness or muscle aches?	Parkinsonism, tremor
2. Changes in your weight or appetite?	Weight and appetite change
3. Problems with your sex life?	Sexual dysfunction (may reflect raised prolactin and/or other pharmacological mechanisms)
4. Changes in your periods or changes in your breasts?	Hyperprolactinaemia
5. Dizziness or light-headedness?	Postural hypotension
6. Tiredness or sleepiness?	Sedation
7. Restlessness or feeling fidgety?	Akathisia
8. Constipation, diarrhoea, nausea, stomach problems or dry mouth?	Gastrointestinal side effects (e.g. antimuscarinic side effects)
9. Difficulty passing water or passing water very frequently?	Urinary symptoms (e.g. antimuscarinic action may cause urinary retention; type 2 diabetes may cause polyuria)
10. Problems with your concentration or memory?	Sedation
11. Feeling anxious or depressed?	Affective side effects
12. Any other problems that you think may be related to your medication? Please state	Miscellaneous side effects

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SHOULD I STAY OR SHOULD I SWITCH?

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SWITCHES OFFER BOTH OPPORTUNITY AND RISK

A medication does not have to be perfect...

- Does it relieve symptoms well enough?
- Is it tolerated well enough?
- Does the patient/family have unrealistic expectations about new medication (i.e., it will 'cure' their symptoms)?

Getting the patient on the same page is key in switching to a new agent

- Individuals have their own preferences and values regarding which symptoms or adverse effects are important to target
- Individuals have their own preferences and values in how to switch (i.e., longer or faster overlap and cross-titration)
- Realistic expectations must be set for the goals of the switch

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DETAILS TO GUIDE CHOICE OF NEW AGENTS

- History of efficacy of drug response
- Nature of psychiatric condition, acuity
- Target signs and symptoms
- Patient preference
- History of adherence
- Need for special monitoring
- Amenability to other interventions to address tolerability in lieu of switching
- Insurance

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IS IT TRULY A BIG DEAL TO SWITCH?

1. Meyer (2009): 55 stable schizophrenia patients on risperidone or olanzapine (baseline PANSS 64) randomized to stay on current meds or open-label switch to ziprasidone with 6-month follow-up. Efficacy failure (hospitalization rates):

- Stay: 16.0%
- Switch: 16.7%

Number Needed to Harm = 143

2. Stroup (2011): 187 stable schizophrenia patients (baseline PANSS 66) on risperidone, olanzapine, or quetiapine randomized to stay on current meds or open-label switch to aripiprazole with 24-week follow-up. Efficacy failure:

- Stay: 17.0%
- Switch: 20.6%

Number Needed to Harm = 28

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ADVERSE EFFECTS CAN BE MITIGATED BY DOSING SCHEDULE

Here's an example: **Lurasidone**

	40 mg	80 mg	120 mg	160 mg
Akathisia — AM	7.1%	9.1%	20.3%	--
Akathisia — PM	2.3%	8.7%	--	6.5%
Somnolence — AM	3.6%	4.9%	9.3%	--
Somnolence — PM	2.8%	0.2%	--	5.8%

Switching to PM schedule decreases akathisia rates despite higher dose

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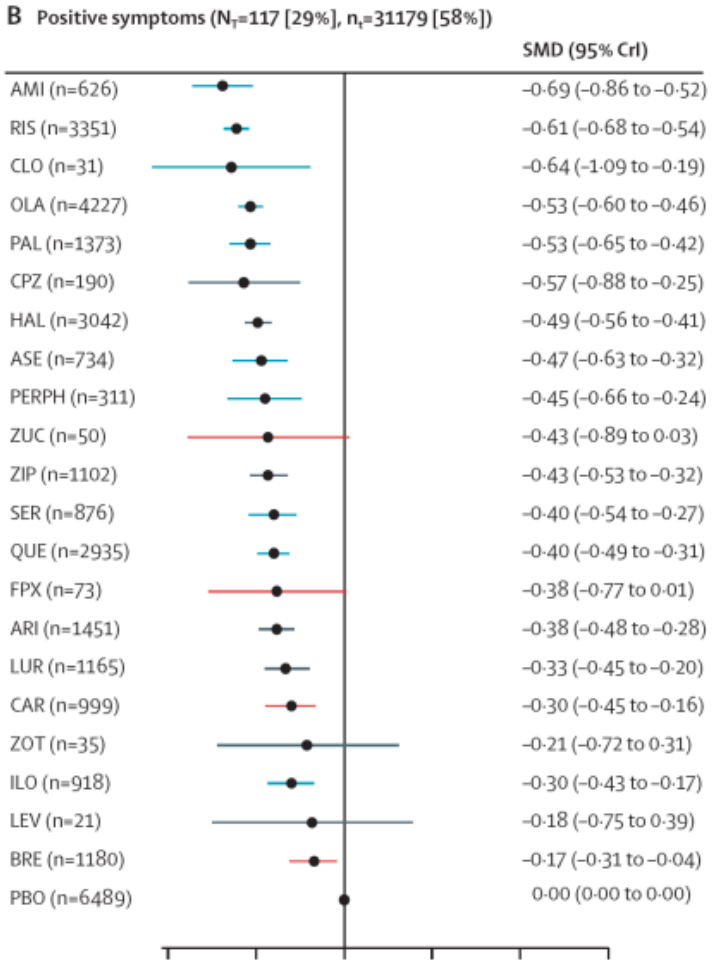
EFFICACY IS GENERALLY EQUIVALENT IF EQUIVALENT DOSES ARE USED

Method: Network meta-analysis of short-term (≤ 6 wk) clinical trials in adults with multi-episode schizophrenia experiencing an exacerbation.

Data: 402 studies (n=53,463) covering 32 oral antipsychotics.

Results: In general, antipsychotics confer similar efficacy in short-term studies for the positive symptoms of schizophrenia



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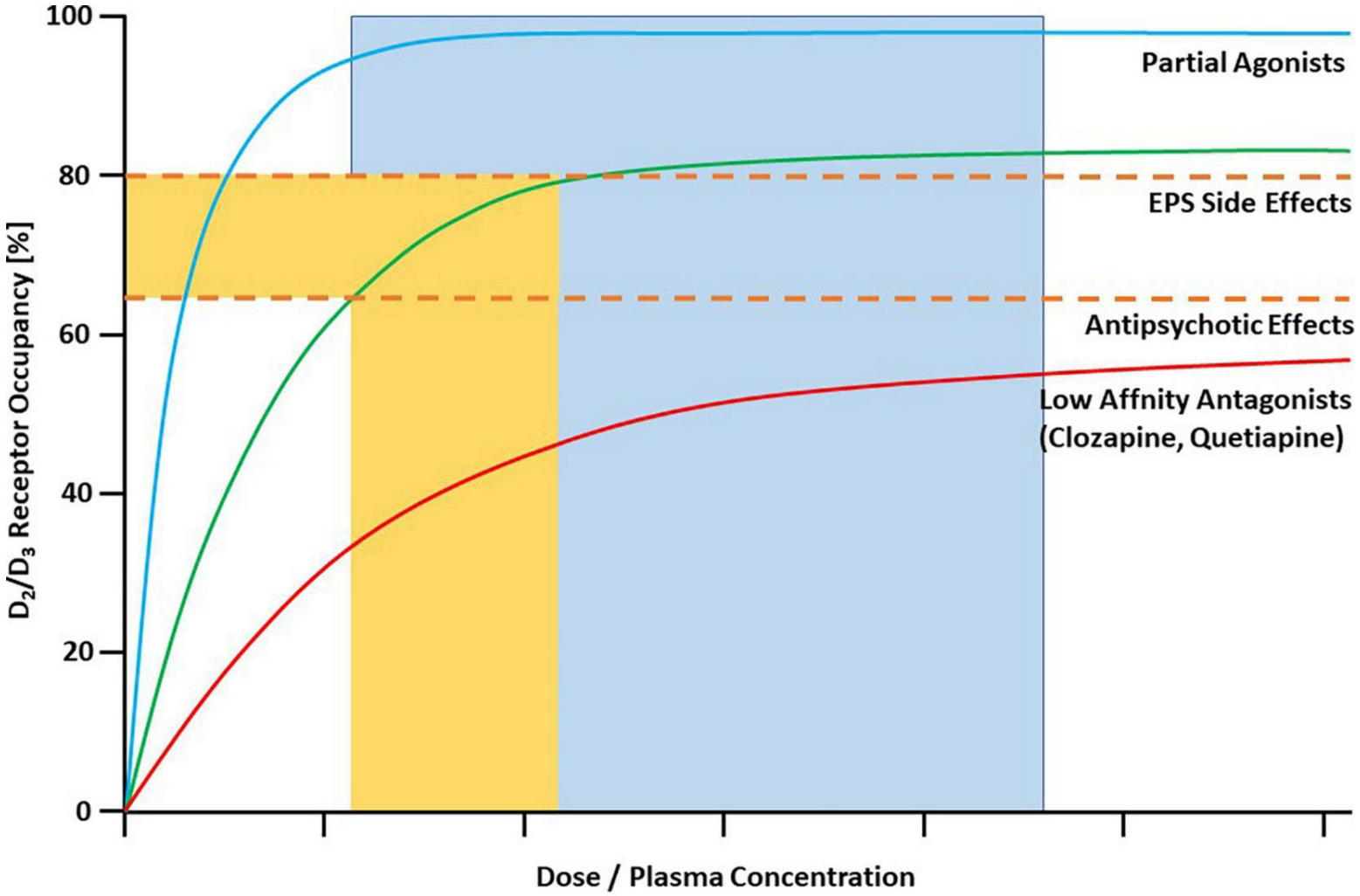
SWITCHING FROM A D2 ANTAGONIST TO A D2 PARTIAL AGONIST: HIGH BINDING AFFINITY



D2 partial agonists also characteristically have a longer half-life!

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PHARMACOLOGIC CONSIDERATIONS: SWITCH TO/FROM PARTIAL D2 AGONISTS

- **It may take longer to reach steady state**
  - Dose adjustments take time
  - Medications will last longer when switching off
  - Side effects may appear later than expected
- **What to do when coming off D2 antagonists?**
  - Slow the taper while titrating partial agonist (ie Abilify)
  - Warn patients about potential withdrawal effects
- **What about when coming off partial agonists?**
  - Washout of medication may take longer = potential adverse effects
  - It may be ok to taper partial agonists quickly

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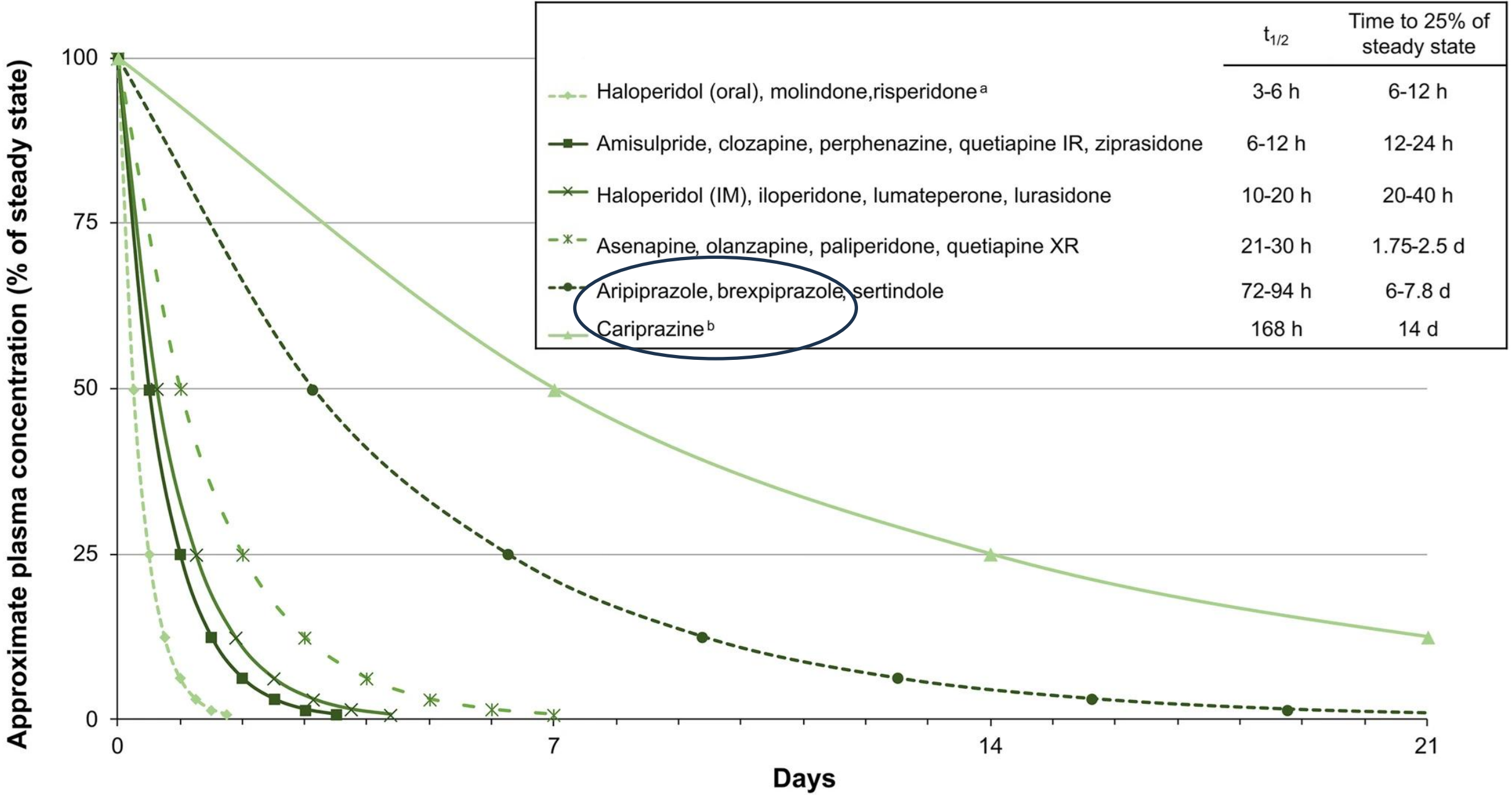

	$t_{1/2}$	Time to 25% of steady state
Haloperidol (oral), molindone,risperidone[a]	3-6 h	6-12 h
Amisulpride, clozapine, perphenazine, quetiapine IR, ziprasidone	6-12 h	12-24 h
Haloperidol (IM), iloperidone, lumateperone, lurasidone	10-20 h	20-40 h
Asenapine, olanzapine, paliperidone, quetiapine XR	21-30 h	1.75-2.5 d
Aripiprazole, brexpiprazole, sertindole	72-94 h	6-7.8 d
Cariprazine[b]	168 h	14 d

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OTHER SWITCH CONSIDERATIONS

- **Cholinergic effects**
  - Switching from medications with anticholinergic effects (ie clozapine, olanzapine, quetiapine) to those with low anticholinergic activity (aripiprazole, ziprasidone, risperidone, haloperidol) can precipitate withdrawal
- **Sedation**
  - Consider risk of rebound psychosis when sedating agent is discontinued
  - Note risk of insomnia, restlessness, and anxiety during switch period
  - Consider short course of adjunct agents

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REBOUND/WITHDRAWAL SYMPTOM MANAGEMENT

SIDE EFFECT	CORRECTIVE APPROACH
Agitation	• Slow down taper • Increase new antipsychotic • Adjunct medications (benzos, valproic acid)
Akathisia	• Lower dose or slow down titration • Add adjunct medications (propranolol, benzo, antihistamine, mirtazapine)
Anxiety	• Use lower starting dose • Add adjunct medication (short-course benzo, antidepressant, gabapentin)
Insomnia	• Sleep hygeine, reduce caffeine • Add adjunct medication (short course benzo, • Slow taper, switch medication administration timings
Mania, psychosis	• Increase new antipsychotic more rapidly • Slow taper • Add adjunct medications (valproic acid, lithium, benzos)
Nausea/vomiting	• Use lower starting dose • Split dosing • Take with food (to slow absorption)

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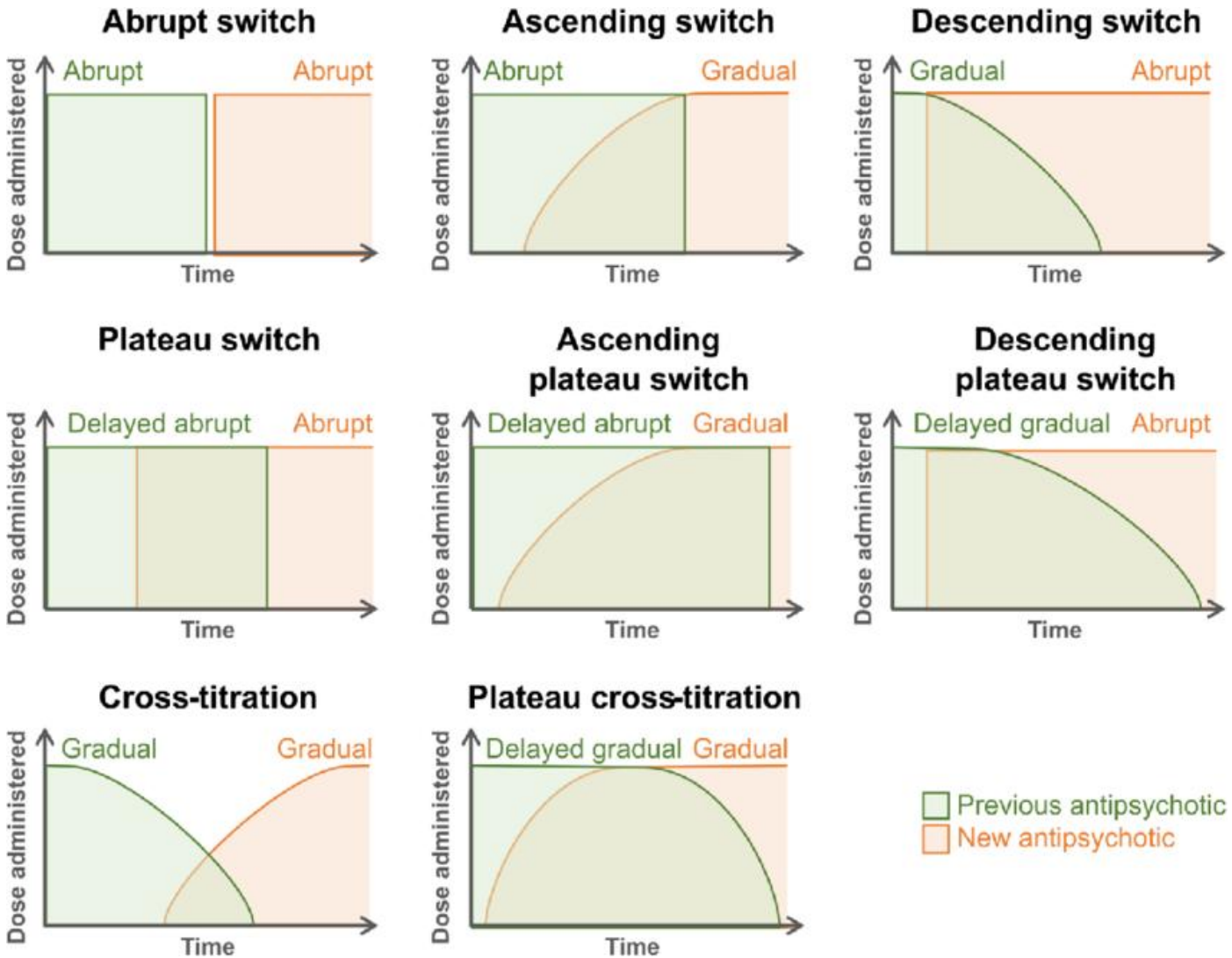
SWITCH STRATEGIES

AVOID ABRUPT SWITCH WITH GRADUAL TITRATION



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LONG-ACTING INJECTABLES

Ensure that the patient tolerates the PO equivalent of dose prior to administration

When switching between LAIs, the initial medication will naturally taper with metabolization.

Safety data in switches between LAI formulations is currently limited

There are both loading dose and PO overlap strategies to ensure coverage during time to steady state

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CASE

A 28-year-old man with schizophrenia would like to switch off quetiapine 400 mg due to intolerable sedation. Lower doses in the past have led to relapse. A shared decision is made to switch to aripiprazole.

What strategy would you select for the switch?

What adjustments would you make for a patient switching between these two medications?

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SUMMARY

1. You or your patient may want to switch antipsychotics for a variety of reasons, including adverse effect profile, efficacy, or patient preference.
2. Individual patient heterogeneity in terms of efficacy and tolerability tells us “one size does not fit all”
3. There may be options to improve tolerability of the current regimen to explore first.
4. Pharmacokinetics and secondary effects should play a role in choice of switch strategy.
5. There are multiple methods of effecting a switch in antipsychotics, but ensure that you are not leaving the patient vulnerable to relapse during the switch.

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