Switching and Dosing of Antipsychotics: Getting it Right

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Disclosures: Christoph U. Correll

I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarized below:

Interest	Name of organization
Grants	National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation
Shares	No share holdings in pharmaceutical companies
Paid positions, honoraria and advisory boards	Alkermes, Bristol-Myers Squibb, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, Medavante, Medscape, Otsuka, Pfizer, ProPhase, Sunovion, Supernus, Takeda, and Teva

Overview

- Applied Psychopharmacology
- Concentration / Dosing
- Relative Binding Affinity
- Real-World Switching
- Cases
- Summary and Conclusions

Applied Psychopharmacology

3 Variables Determine Activity of Any Drug

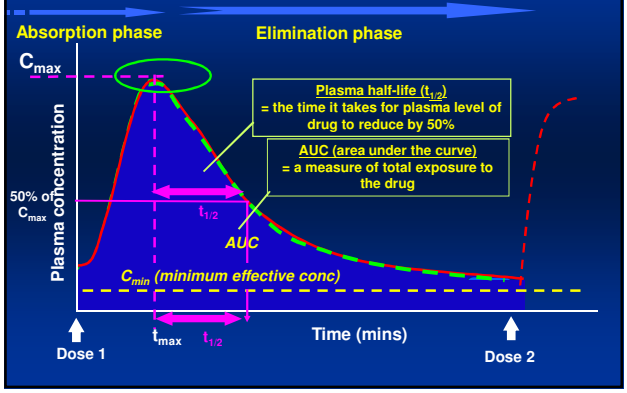
Clinical Response =

Drug Concentration at Site of Action	×	Affinity for Site of Action	×	Underlying Biology of Patient
Pharmacokinetics		**Pharmaco-**		**Individual**
Absorption		**Dynamics**		Genetics
Distribution		Drug Activity		Age
Metabolism				Disease
Elimination				Environment

Adapted from: Preskorn SH. *Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors.* Caddo, OK: Professional Communications, Inc; 1996; www.preskorn.com

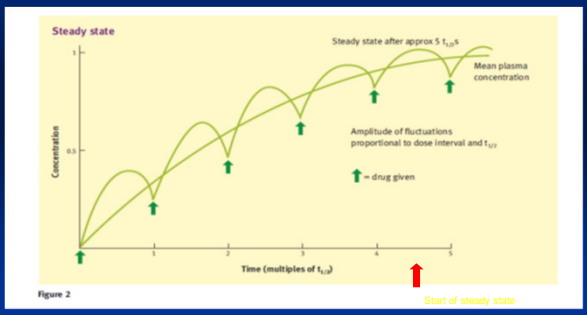
Concentration/Dosing

Basic pharmacokinetic parameters

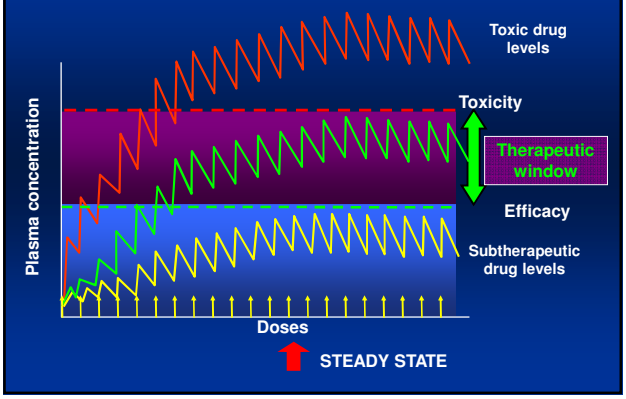


What is meant by steady state?

Steady state is achieved when a constant daily dose of a drug produces consistent blood levels of the drug



What is the therapeutic window?



Pharmacokinetic Characteristics of Selected Second- and First-Generation Antipsychotics

Antipsychotic	Principal Liver Enzyme Target	Protein binding	Bio-availability	Half life (hrs)	T to peak (hrs)	CPZ Equiv. (mg)
Second-Generation Antipsychotics						
Aripiprazole	2D6>3A4	>99	87%	50-72	3-5	7.5
Asenapine	1A2>3A4 (+ glucuronid.)	98	35%	First: 6, terminal: 23	1.5	N/A
Clozapine	1A2 (30%) > 2C19 (24%) > 3A4 (22%) > 2C9 (12%) > 2D6 (6%)	97	70%	12	1-4	50
Iloperidone	2D6> 3A4>1A2	91.1	60%	14-17	2-4	N/A
Lurasidone	3A4	99	9-19%	31	2-4	N/A
Olanzapine	1A2, 2D6, 3A4	93	60%	30	6	5
Paliperidone	<10% hepatic clear.	74	28%	21-30	24	3
Quetiapine	3A4	83	<20%	6-7	2	75
Risperidone	2D6 > 3A4	90	70%	3	1-2	2
Ziprasidone	Aldehyde oxidase (2/3) > 3A4 (1/3)	>99	60%	7	5	60
First-Generation Antipsychotics						
Chlorpromazine	2D6	>90	30%	16-30	1-4	100
Haloperidol	3A4	92	60-70%	3-6 po 10-20 im	24 po 21 im	2
Perphenazine	2D6	>90	40%	8-12	1-3	10

Correll CU. Antipsychotic Medications: Typical and Atypical. In: Pediatric Psychopharmacology: Principles and Practice, Second Edition. Martin A, Scahill L and Kratochvil CJ (eds.), Oxford University Press, Inc. New York. 2010

Relative Binding Affinity - Switching

Relative Binding Affinity (RBA)

The affinity of a drug for a secondary site(s) target in relationship to most potent binding site

$$\text{RBA} = \frac{\text{Ki for secondary receptors}}{\text{Ki for primary receptor}}$$

Preskorn SH. *J Psychiatr Pract.* 2004

Approximate Receptor Binding Affinity Expressed as Equilibrium Constant (Ki)[a] of Selected SGAs and FGAs

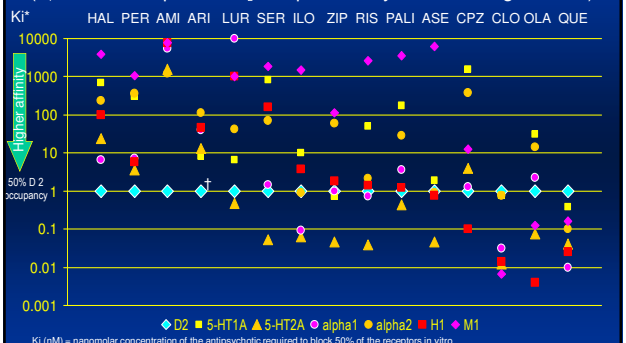
Recep-tor	AMI	ARI	ASE	CLO	ILO	LUR	OLA	PALI	RIS	QUE	ZIP	CPZ	HAL	MOL	PER
D_2	1.3	0.66 [b,c]	1.3 [c]	210	3.3	0.99	20	2.8	3.8	770	2.6	2.0 [c]	2.6	120	1.4 [c]
5-HT_{1A}	>10,000	5.5 [b,c]	2.5	160 [b]	33	6.4	610	480	190	300	1.9 [b,c]	3,115 [c]	1,800	3,797 [c]	421
5-HT_{2A}	2,000	8.7 [c]	0.06 [c]	2.6	0.2	0.47	1.5	1.2	0.15	31	0.12	8.0 [c]	61	5,000	5 [c]
5-HT_{2c}	>10,000	22 [c]	0.03 [c]	4.8	14	NR	4.1	48	32	3,500	0.9	25.0 [c]	4,700	>10,000 [c]	132 [c]
5-HT_6 [c]	4,154	574	0.25	17	63	NR	6	-	2,240	1,864	61	12	3,666	1,008	17
5-HT_7 [c]	11.5	10	0.13	18	112	0.49	112	-	6.6	308	6	21	378	3,053	23
α_1	7,100	26 [c]	1.2 [c]	6.8	0.31	NR	44	10	2.7	8.1	2.6	2.6	17	2,500	10
α_2	1,600	74 [b]	1.2 [c]	158	3	41	280	80	8	80	154	750	600	625	500
H_1	>10,000	30 [c]	1.0 [c]	3.1	12.3	>1000	0.08	3.4	5.2	19	4.6	0.2 [c]	260	>10,000 [c]	8
M_1	>10000	6,780 [c]	8128 [c]	1.4 [c]	4,898 [c]	>1000	2.5 [c]	> 10,000	>10,000	120 [c]	300 [c]	25.0 [c]	>10,000 [c]	>10,000	1,500

Data based exclusively on human brain receptors; [a]Data represented as Ki(nM), i.e., nanomolar amount of the antipsychotic needed to block 50% of the receptors in vitro. Thus, lower number denotes stronger receptor affinity and binding. [b] Partial agonism; [c] Data from cloned human brain receptors; - = not available; ARI = aripiprazole (Abilify®); ASE= asenapine (Saphrys®); CLO = clozapine (Clozaril®); ILO= iloperidone (Fanapt®); LUR= lurasidone (Latuda®); OLA = olanzapine (Zyprexa®); PAL = paliperidone (Invega®); QUE = quetiapine (Seroquel®); ZIP = ziprasidone (Geodon®); CPZ= Chlorpromazine (Thorazine®); HAL = haloperidol (Haldol®); MOL = molindone (Moban®); PER = perphenazine (Trilafon®)

Based on: PI for Asenapine and Lurasidone and Brian Roth NIH Psychoactive Drug Screening Program (http://pdsp.med.unc.edu) and **Correll CU. European Psychiatry 2010;25 (Suppl 2):S12-21**

Approximate *Relative* K_i Values for Receptor Binding Profiles of Atypical and Selected Typical Antipsychotics

(K_i value for Dopamine D_2 receptor affinity for each drug set as 1)



Ki (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (ie, lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. † Partial D2

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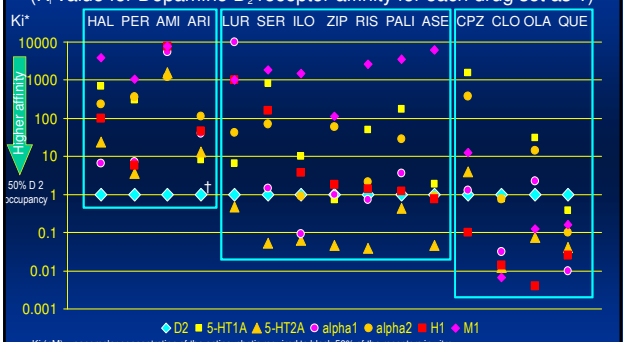

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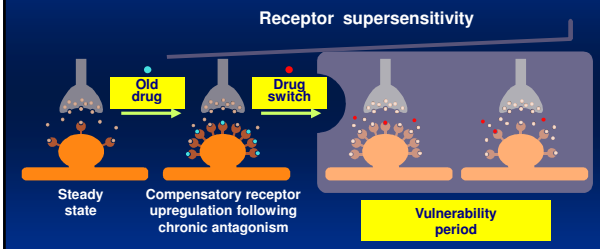
Real-World Switching

Upregulation: what happens when receptor antagonists are withdrawn?



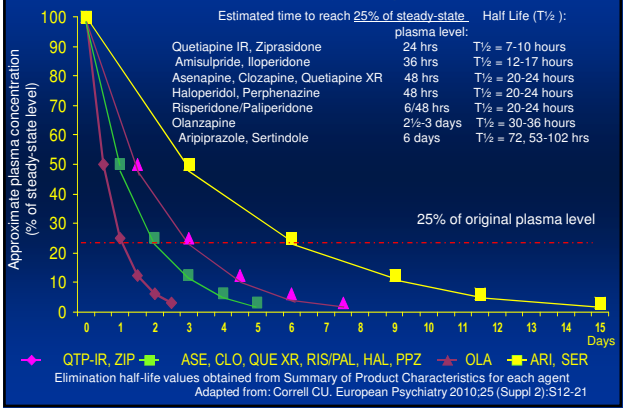
Ossowska K. Pol J Pharmacol. 2002;54:299–312
Kirkpatrick B et al. J Nerv Ment Dis.1992;180:265–270.

Pharmacodynamic Side Effects During Switching: Acute Rebound from Complementary Blockade of Previous Antipsychotic

Receptor	Blockade	Rebound/Withdrawal
D_2	Antipsychotic, antimanic, antiaggressive, EPS/akathisia, tardive dyskinesia, increased prolactin	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
H_1	Anxiolytic, sedation, weight gain, anti-EPS/akathisia	Anxiety, agitation, insomnia, EPS/akathisia
M_1 (central)	Memory, cognition, dry mouth, anti-EPS/akathisia	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS/akathisia
M_{2-4} (peripheral)	Blurry vision, constipation, urinary retention, tachycardia, hypertension,	Diarrhea, diaphoresis, nausea, vomiting, bradycardia, hypotension, syncope
5-HT2A	Anti-EPS/akathisia, ?antipsychotic	EPS/akathisia, ?psychosis

Correll CU. J Clin Psychiatry;69 (suppl 4):26-36.

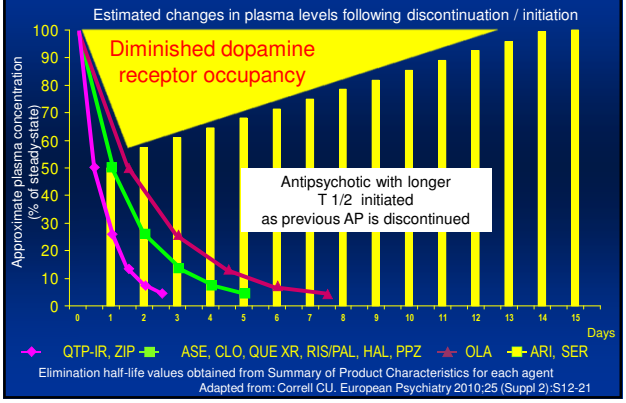
Second-Generation Antipsychotics: Estimated Reduction in Plasma Levels Following Abrupt Discontinuation



Elimination half-life values obtained from Summary of Product Characteristics for each agent

Adapted from: Correll CU. European Psychiatry 2010;25 (Suppl 2):S12-21

Pharmacokinetic Rebound: Differences in Half Life or Absorption Can Result in Dopamine Rebound



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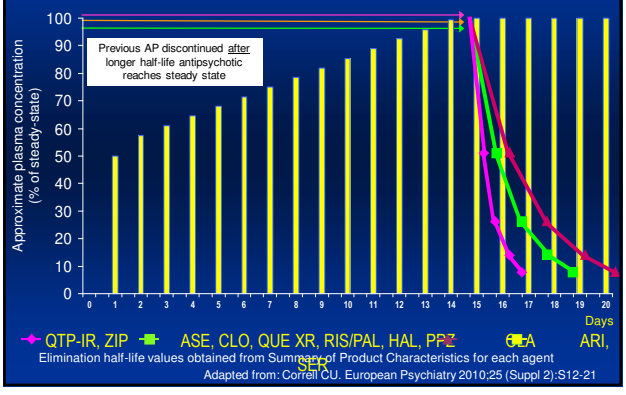
Avoiding Pharmacokinetic Rebound: Implementing an Overlapping Plateau Cross Titration



Elimination half-life values obtained from Summary of Product Characteristics for each agent

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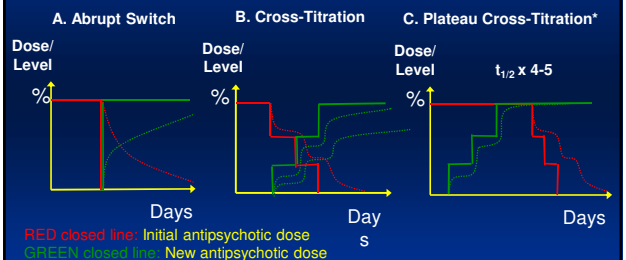
Managing Undesirable/Rebound Effects at Treatment Initiation

Side effect	Corrective approach or (transient) adjuvant* medications
Akathisia	Lower dose, slow down switch Add benzodiazepine, antihistamine, beta-blocker, mirtazapine, gabapentin
Mania, psychosis	Slow/reverse down titration of prior antipsychotic, increase aripiprazole Add benzodiazepine, valproate
Agitation	Less likely with lower starting dose, slow switch, increase aripiprazole, Add benzodiazepines, valproate
Anxiety	Use lower starting dose, slow switch, restrict excessive caffeine use, Add benzodiazepine, antihistamine, antidepressant, gabapentin
Insomnia	Less likely with lower starting dose, slow switch, restrict excessive caffeine use, add benzodiazepine, hypnotic, antihistamine, trazodone
Nausea/ vomiting	Less likely with lower starting dose, slow switch, Consider dosing twice daily, give with fatty food (to slow absorption) Add antihistamines or anti-emetics if needed

Adapted from: Correll CU. European Psychiatry 2010;25 (Suppl 2):S12-21

Plateau Switch Strategy Minimizes Rebound When Switching to an Agent with Little Histaminic or Cholinergic Blockade and/or a Long Half Life



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

Meta-Analysis of Switch Approaches

Aspect of switch studied	Alternatives compared	Outcome: Arm with more all-cause discontinuation	Relative risk (RR ± 95% CI) for comparison
Initiation of post-switch AP	Abrupt vs ascending (gradual)	Abrupt	1.65* (1.21-2.24), p=0.001
Discontinuation of pre-switch AP	Abrupt vs descending	Abrupt	1.28 (1.08-1.51), p=0.004
Overlap	Non-plateau vs plateau switch	Non-plateau switch	1.42 (1.12-1.79), p=0.003
	Non-overlapping vs partial/ complete overlap	Non-overlapping	1.40 (1.14-1.72), p=0.002
		Non-overlapping (SGA to SGA)	1.28 (1.01-1.61), p=0.04 [FGA to SGA: p=0.72]
		Non-overlapping (SGA/FGA to ARI or ZIP)	1.36 (1.10-1.68), p=0.005 [SGA/FGA to OLA or RIS: p=0.71]

* For discontinuation due to inefficacy: 2.49 (CI: 1.43-4.35). AP: antipsychotic; SGA: 2nd generation AP; FGA: 1st generation AP; ARI, aripiprazole; ZIP, ziprasidone

Correll CU, *et al.* Poster presented at the ACNP congress, Hawaii, December 2011.

Cases

Case 1: First Episode Schizophrenia

- 20 y/o White male, accompanied by parents
- Presenting to ER acutely agitated, paranoid, afraid to be poisoned, hallucinating
- Day 1: Aripiprazole 5 mg po plus lorazepam IM 2 mg
- Day 2: Aripiprazole 10 mg p.o. with lorazepam 1 mg p.o. bid for 7 days
- Day 8: Aripiprazole 15 mg p.o.
- Patient improving over the next 3 weeks
- Lorazepam tapered off after 2 weeks and discontinued at week 3
- Discharged to outpatient care after 3.5 weeks

Case 2: Acute Exacerbation

- 35 y/o male, paranoid schizophrenia since age 17
- Alcohol abuse since age 19
- Living in a group home
- Multiple psychiatric hospitalizations, some due to non-adherence, some apparently breakthrough psychosis
- Stopped his antipsychotic due to weight gain, and sexual side effects and started drinking daily
- Found wandering in the streets, poor hygiene, disorganized speech, talking to himself, belligerent when police brings him to the hospital

Case 2: Acute Exacerbation –Scenario 1

- Day 1: Aripiprazole 20 mg p.o. started for agitation and psychosis
- Patient restless, confused, agitated, unable to sleep, no improvement in psychosis
- PRN 5 mg haloperidol i.m.
- Day 3: increase of aripiprazole to 30 mg
- Day 4: still marked agitation and psychosis
- Day 5: Aripirazole changed to olanzapine 20 mg p.o
- Over the next 5 days, patient improvimg slowly with adjunctive haloperidol i.m. (stopped day 14)
- Further improvement and d/c to day hospital at 5 wks

What can we learn from this case?

- Starting dose?
- Target dose?
- Titration?
- Cotreatment?
- Management of illness-related agitation, insomnia, anxiety?
- Management of "activation" possibly related to early sensitivity?
- When to give up?

Case 2: Acute Exacerbation – Scenario 2

- Day 1: Aripiprazole 10 mg p.o. started together with lorazepam 1 mg p.o. tid
- Day 3: aripiprazole increased to 20 mg p.o.
- At 2 weeks, lorazepam tapered over 10 days and d/c'd
- Insomnia emerged, treated with zolpidem 10 mg qHS
- At 3 weeks, patient improved, but still residual hallucinations and delusion of persecution
- Aripiprazole increased to 30 mg p.o.
- Further improvement and d/c to day hospital at 5 wks

Case 3: Schizophrenia Switch

- 37 yr old female with schizophrenia since age 23
- Treated during last admission with olanzapine 20 mg
- Lithium 900 mg added for mood symptoms
- Outpatient x 9 mo, mild residual positive and relevant negative sxs
- Complaining of 7 kg weight gain, daytime sedation, fasting triglycerides: 265 mg/dL, glucose: 95 mg/dL
- Decision made to switch to aripiprazole

Case 3: Switch – Scenario 1

- Initiated aripiprazole 10 mg, with taper of olanzapine over 1 week
- On day 10, presenting with agitation, restlessness, insomnia, worsening of psychosis (voices telling her that an old colleague has gotten a group of people together that want to "destroy her life"
- Olanzapine 20 mg restarted due to "failure of aripiprazole to maintain efficacy of olanzapine
- Lithium continued at 900 mg
- Further weight gain of 4 Kg, triglycerides: 280 mg/dL, glucose: 116 mg/dL

What can we learn from this case?

- Starting dose?
- Target dose?
- Titration?
- Cotreatment?
- Management of illness-related agitation, insomnia, anxiety?
- Management of "activation" possibly related to early sensitivity?
- When to give up?

Case 3: Switch – Scenario 2

- **Decision made to reattempt switch to aripiprazole**
- **Aripiprazole added at 10 mg/day x 1 week, then increased to 15 mg/day, at 2 weeks increased to 20 mg/day**
- **At 4 weeks, after 2 weeks of aripiprazole 20 mg/day, olanzapine reduced by 5 mg every 7 days (plateau switch)**
- **At 7 weeks, discontinue olanzapine**
- **No more sedation, more active, 3 kg weight loss, triglycerides: 155 mg/dL, glucose 100 mg/dL**

Summary and Conclusions

Conclusions

- Switching and dosing can be optimized taking into account relevant receptor binding potentials of both the previous and the new antipsychotic
- In general, abrupt switching of antipsychotics is neither advisable nor necessary
- A lower starting dose of aripiprazole can minimize initial partial agonism-related effects, such as restlessness, akathisia and nausea
- Rebound and withdrawal phenomena can complicate switching when the new antipsychotic has
  - less sedating or anticholinergic properties
  - partial dopamine agonism
  - a longer half life
- Temporary “rescue” medications / targeted sedation can help optimizing the initial start or switch

Oral Aripiprazole: Lessons Learned

- A partial D2 agonist is not just a "Me-too-D2" antipsychotic
- A starting dose that is too high can cause restlessness that is D2 agonism-related (self-limited "pseudo-akathisia")
- Too abrupt switching from a full D2 antagonist to a D2 partial agonist can cause rebound phenomena (restlessness, akathisia, potentially worsening of psychotic symptoms)
- Too abrupt switching from a more sedating and/or more anticholinergic D2 antagonist ("pine") to aripiprazole can cause rebound phenomena (anxiety, insomnia, restlessness, akathisia)
- Too abrupt switching from a shorter half-life D2 antagonist (all antipsychotics, except sertindole) to aripiprazole can cause rebound phenomena (anxiety, insomnia, restlessness, akathisia, worsening of psychotic symptoms)
- Based on the above, plateau cross-titration is the best strategy
- Benzodiazepines can optimize efficacy and effectiveness in the early/acute treatment phase (also minimizing rebound during switching)
- Higher doses of a partial agonist result in lower partial agonism, which some patients require (10 mg aripiprazole is the absolute minimum for schizophrenia)

Adapted from: Correll CU. European Psychiatry 2010;25 (Suppl 2):S12-21

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