Neuroscience Education Institute

DOPAMINE PARTIAL AGONISTS: HOW THEY WORK AND WHY THEY DON'T ALWAYS PLAY NICE WITH OTHER ANTIPSYCHOTICS

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Presented at 2023 NEI Synapse.

Learning Objectives

- Describe how a D_2 partial agonist antipsychotic works
- Understand when and why it can be problematic to add a D_2 partial agonist antipsychotic to a dopamine D_2 antagonist
- Describe why the point of futility for a D_2 partial agonist is practically defined by the plasma level that achieves 100% D_2 receptor occupancy

Dopamine Partial Agonist Benefits

Agents and year of approval:

- Aripiprazole (2002)
- Aripiprazole monohydrate (2013)
- Aripiprazole lauroxil (2015)
- Brexpiprazole (2015)
- Cariprazine (2015)
- Aripiprazole lauroxil nanocrystal (2018)
  [in lieu of oral overlap when initiating or reinitiating treatment]
- Aripiprazole monohydrate 2 month (2023–pending)

- Fewer metabolic, endocrine, and movement disorder concerns compared to many other D_2 antagonist antipsychotics
- Aripiprazole, brexpiprazole, and cariprazine are approved as adjunctive agents to antidepressants for unipolar major depression
- Cariprazine is approved for bipolar I depression as monotherapy and has one study vs. risperidone showing benefit for negative symptoms[1]

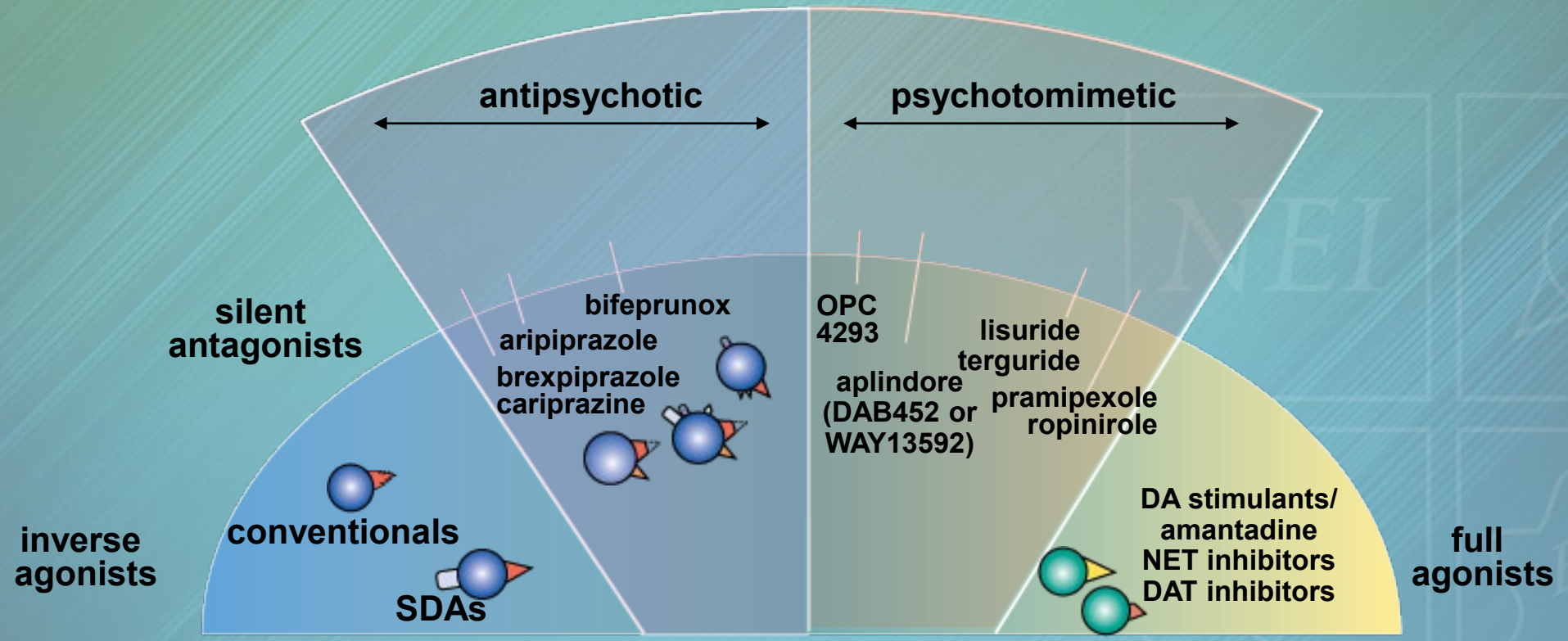
1. Nemeth G et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet 2017;389(10074):1103-13.

Partial Agonist APs Have Very High D_2 Affinity

	D_2 (Ki nM)	MAX STIMULATION AT D_2 RECEPTORS	M_1 (Ki nM)	H_1 (Ki nM)	α_1 (Ki nM)
Aripiprazole	0.34	**25%**	> 1000	61	26
Brexpiprazole	0.30	**18%**	> 1000	19	3.8
Cariprazine	0.49	**21%**	> 1000	23.2	155
Desmethylcariprazine (DCAR)	0.81	**??**	> 1000	18.4	97
Didesmethylcariprazine (DDCAR)	1.41	**10%**	> 1000	23.7	149
Haloperidol	1.2	**0%**	> 1000	1700	12

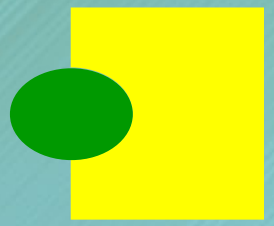
Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Ed; 2018:279-302.
Allergan USA Inc. Vraylar Package Insert. Madison, NJ 07940 2019.
Tadori Y et al. In vitro pharmacology of aripiprazole, its metabolite and experimental dopamine partial agonists at human dopamine D2 and D3 receptors. Eur J Pharmacol 2011;668(3):355-65.
Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels – Stahl's Handbooks. Cambridge University Press, 2021.

Dopamine 2 Receptor Partial Agonist (DPA) Spectrum

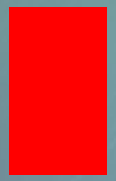


How Does a Partial Agonist Act?

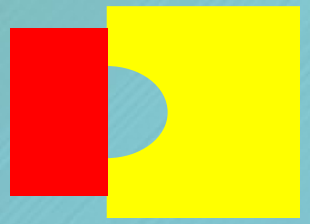
Full Agonist (dopamine)



Full Receptor Activation/Neurotransmission

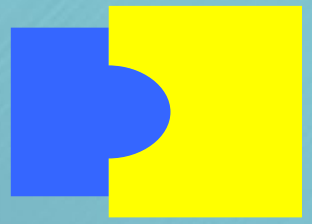


Antagonist (haloperidol, olanzapine, etc.)



No Receptor Activation/Neurotransmission

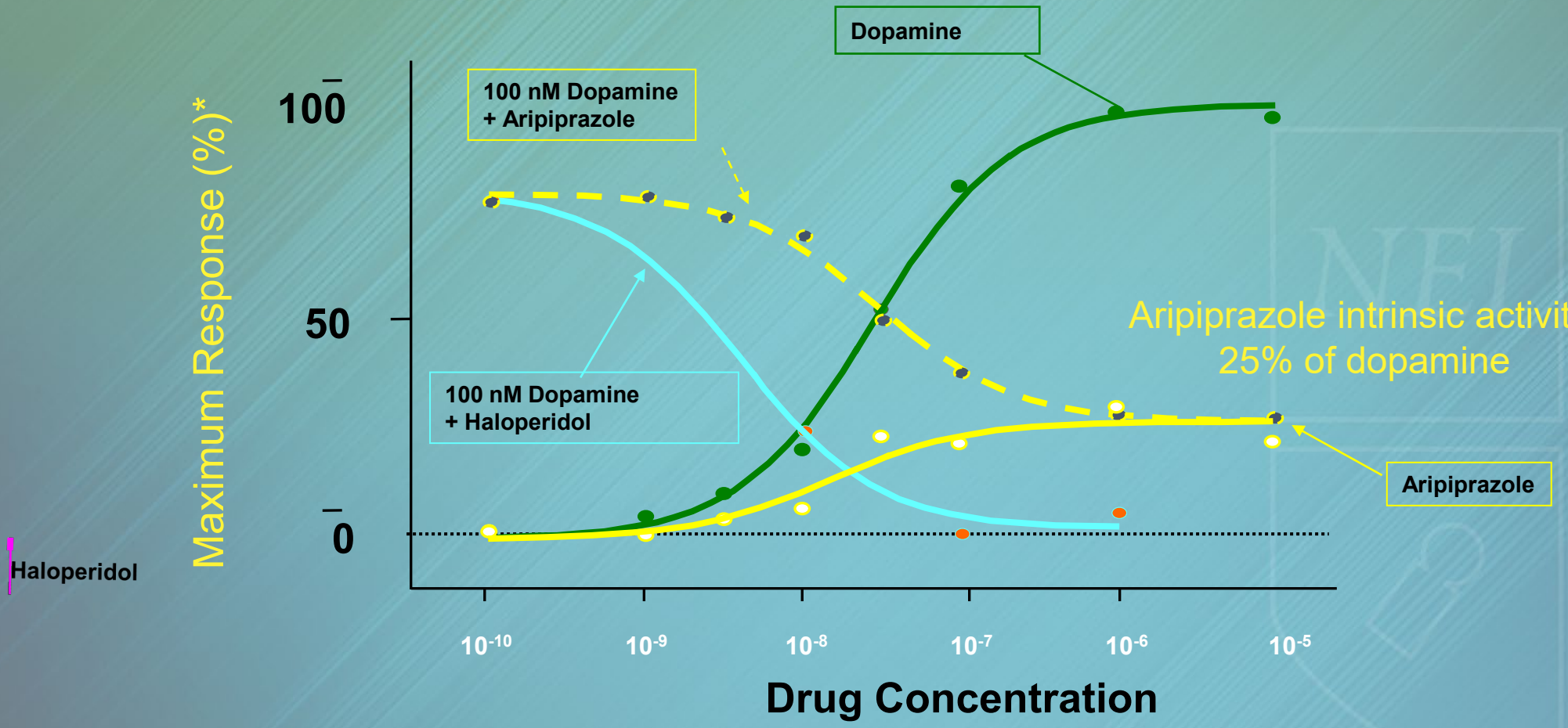
Partial Agonist (aripiprazole, brexpip-razole, cariprazine)



Partial Receptor Activation/ Neurotransmission

Tamminga CA et al. Curr Drug Target CNS Neurol Disord 2002;1(2):141.

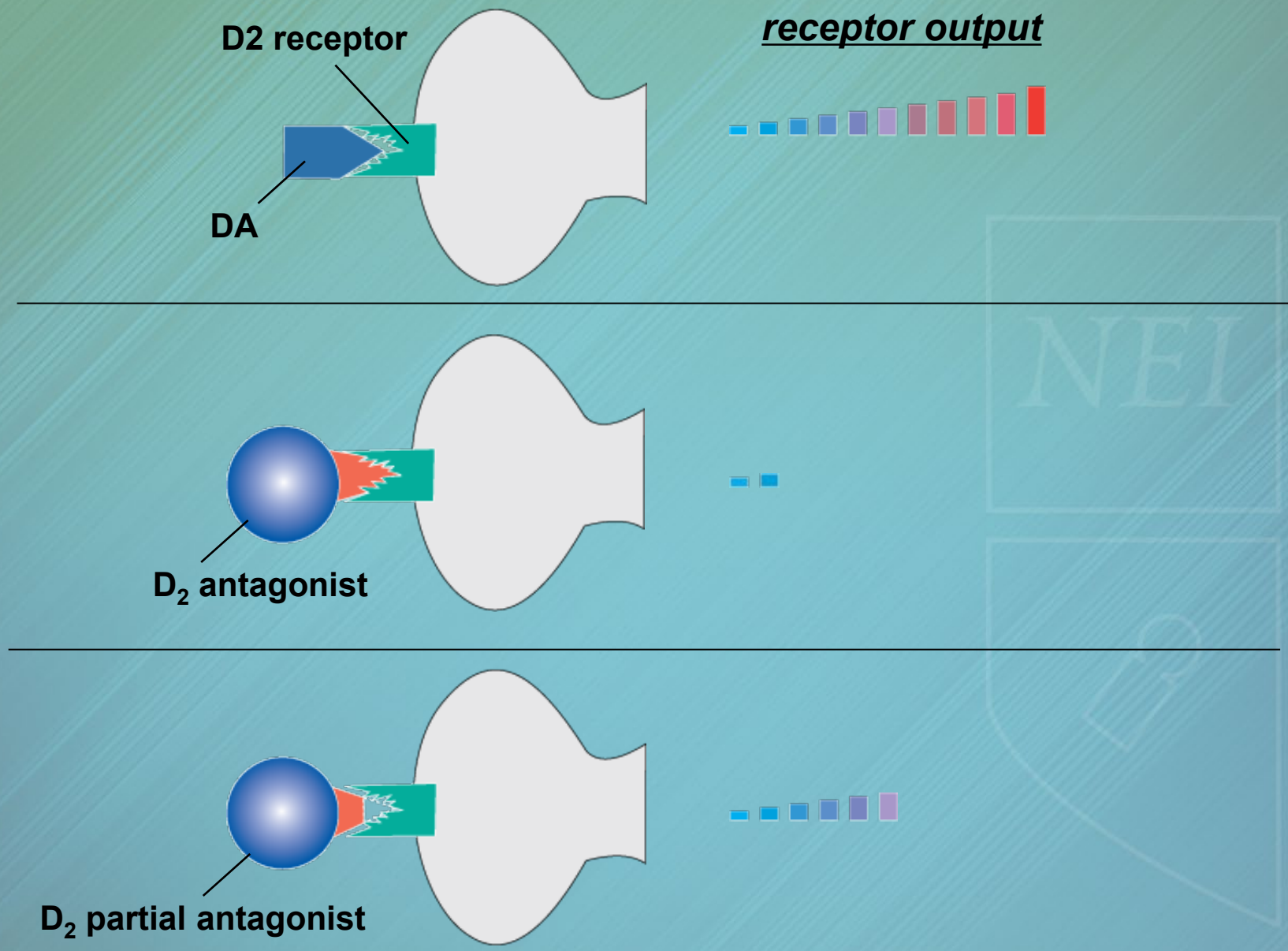
D_2 Activity in the Presence of Dopamine and an Antagonist or Partial Agonist



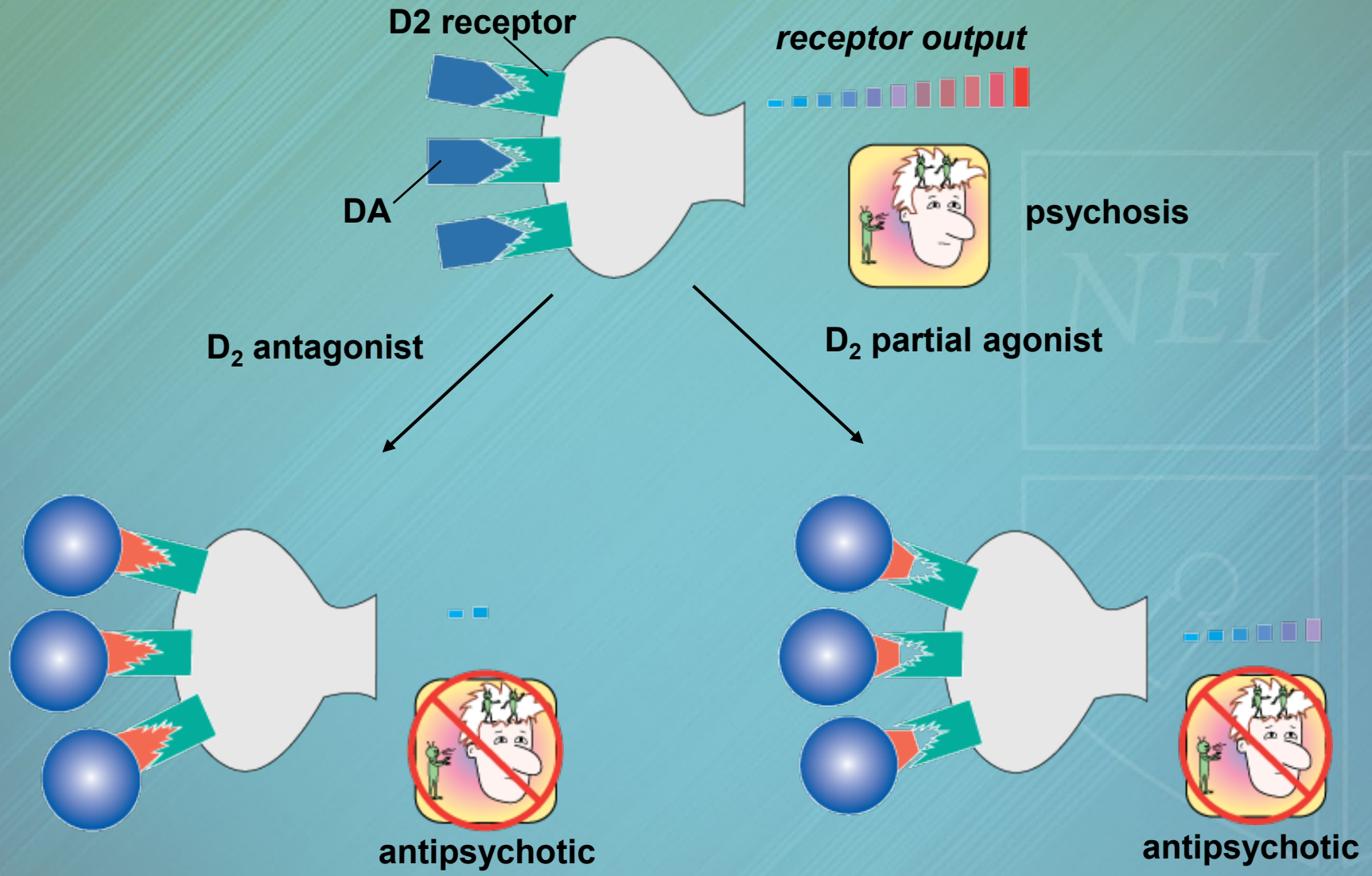
*Receptor activity measured as inhibition of forskolin-induced cAMP accumulation in CHO cells transfected with human D_{2L} DNA.

Burris KD et al. J Pharmacol Exp Ther 2002;302(1):381-9.

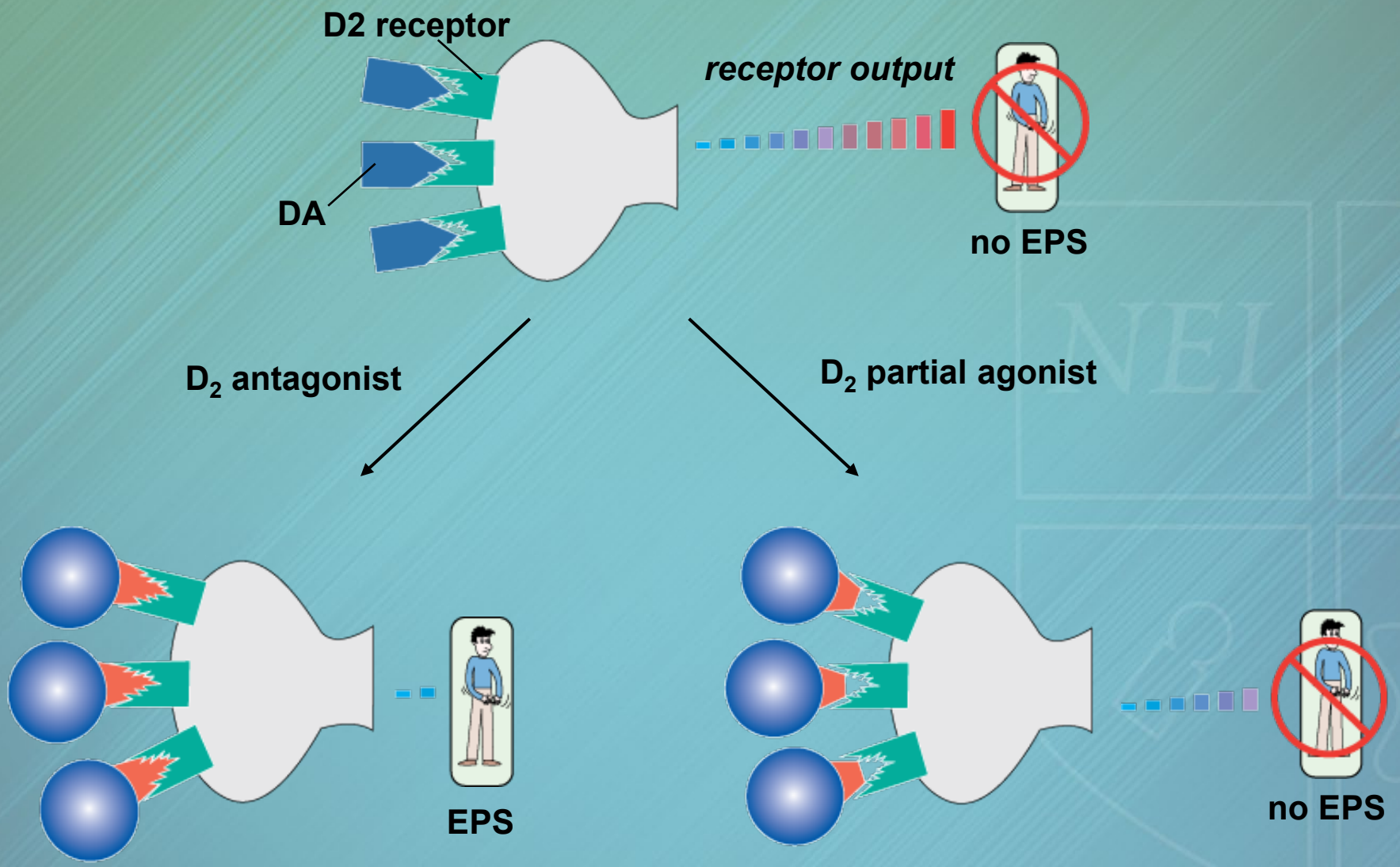
Postsynaptic Activity: Antagonist vs. Partial Agonist



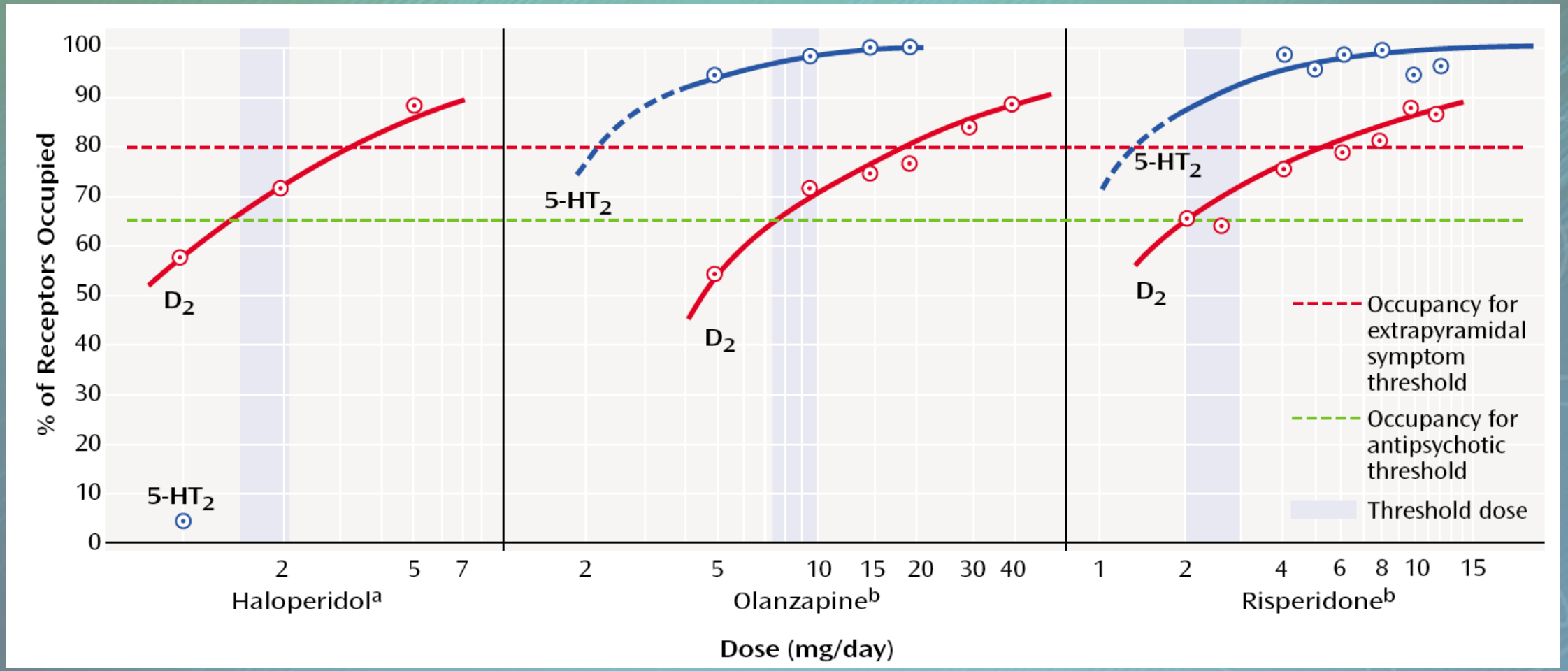
Associative Striatum Neuron Activity: Dopamine Antagonist or Partial Agonist



Nigrostriatal Dopamine Neurons: Antagonist vs. Partial Agonist

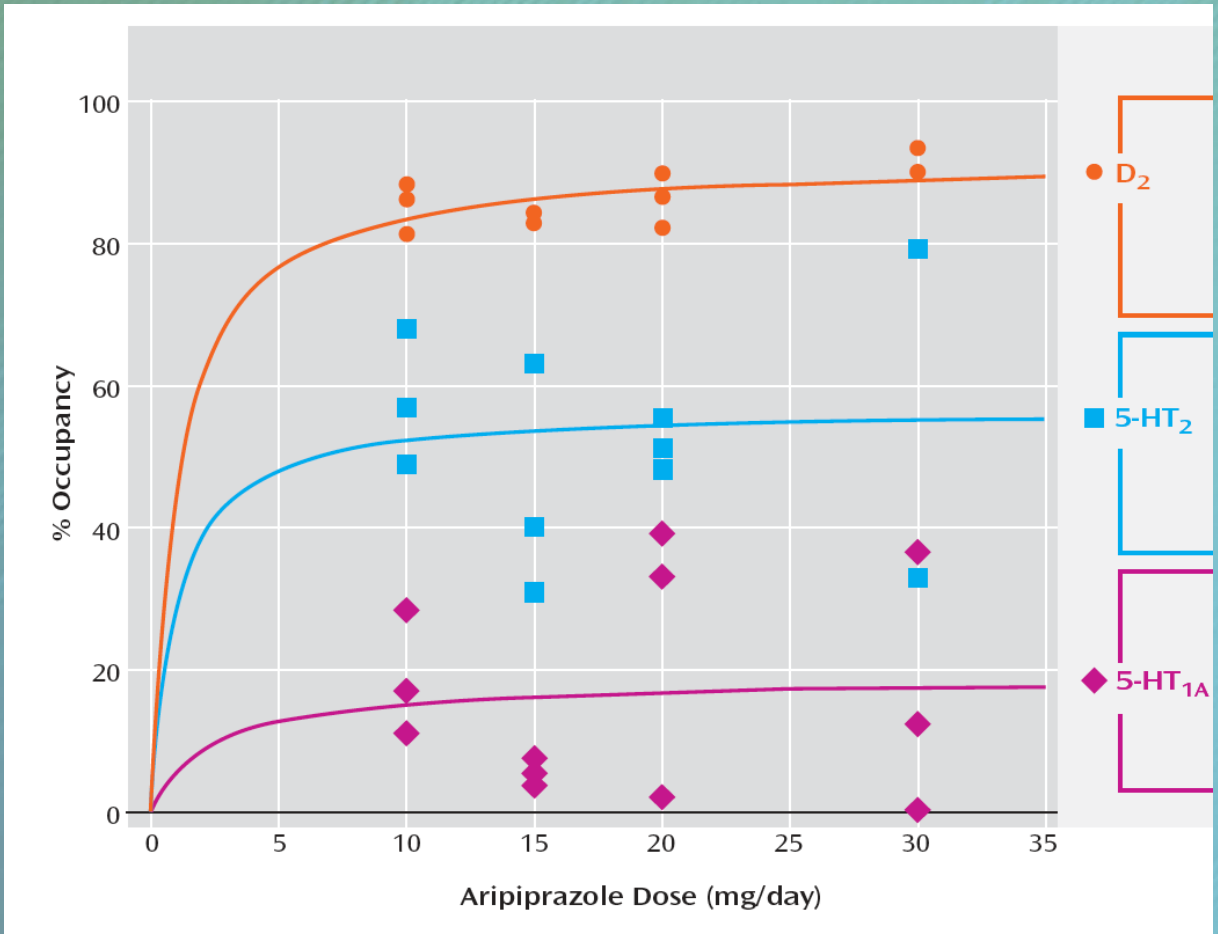


Response, Side Effects, and D_2 Occupancy For D_2 Antagonist Antipsychotics



Kapur S, Seeman P. Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics? - A New Hypothesis. Am J Psych 2001;158(3):360-9

Aripiprazole Is Effective at 85%–100% D_2 Receptor Occupancy



D_2 Occupancy by Dose	
0.5 mg	33.7%
1 mg	57.2%
2 mg	71.6%
10 mg	85.3%
30 mg	86.4%
40 mg	96.8%

Mamo D et al. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: a triple tracer PET study. Am J Psych 2007;164(9):1411-7. Sparshatt A, Taylor D, Patel MX, Kapur S. A systematic review of aripiprazole--dose, plasma concentration, receptor occupancy, and response: implications for therapeutic drug monitoring. J Clin Psychiatry 2010;71(11):1447-556.

How a Partial Agonist Works as an Antipsychotic at D_2 Receptors: Example of Aripiprazole vs Haloperidol

Scenario A: Dopamine binds to 100% of receptors = 100% postsynaptic DA activity

Scenario B: Haloperidol binds to 90% of receptors = 10% postsynaptic DA activity (i.e., 90% reduction in postsynaptic DA signal)

Scenario C: Aripiprazole binds to 90% of receptors

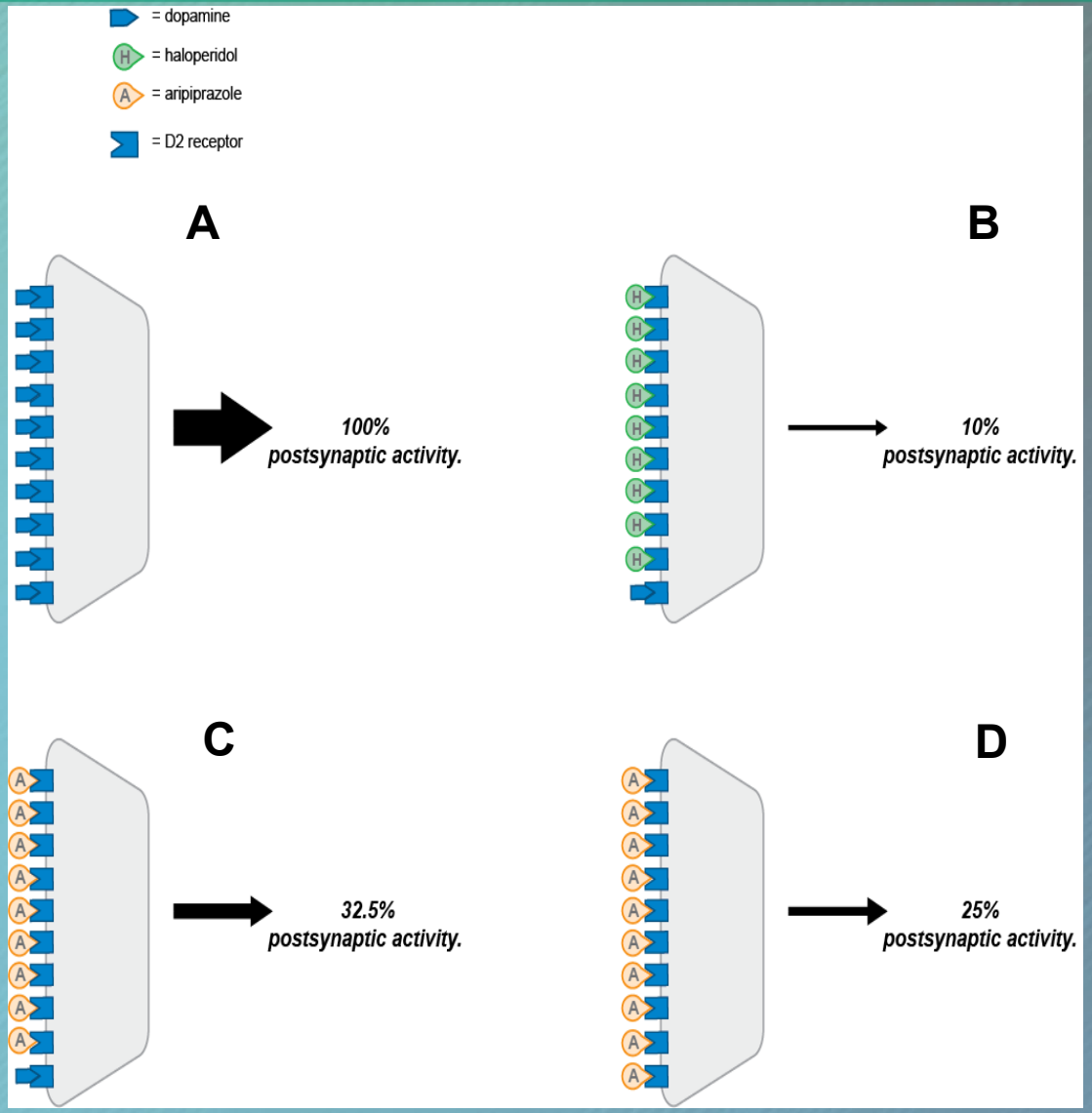
Aripip has 25% DA activity: 25% activity at 90% of the receptors = 22.5% postsynaptic DA activity

DA is still active at 10% of receptors

Net result: 22.5% + 10% = 32.5% postsynaptic DA activity (i.e., 67.5% reduction in postsynaptic DA signal)

Scenario D: Aripiprazole binds to 100% of receptors

Aripip has 25% DA activity: 25% activity at 100% of the receptors = 25% postsynaptic DA activity **(i.e., 75% reduction in DA signal)**



Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels – Stahl's Handbooks. Cambridge University Press; 2021.

Aripiprazole Binding Profile and Basic Info

	D_2 (Ki nM)	MAX STIMULATION AT D_2 RECEPTORS	M_1 (Ki nM)	H_1 (Ki nM)	α_1 (Ki nM)
ARIPIPRAZOLE	0.34	26%	> 1000	61	26
HALOPERIDOL	1.2	0%	> 1000	1700	12

Low affinity for H1, M1, α1-adrenergic receptors. Associated with low risk of sedation/wt gain, anticholinergic effects, and orthostasis.

FORMULATIONS: Tablets, ODT, Solution, LAI (aripip monohydrate, aripip lauroxil)

KINETICS: $T_{1/2}$ 75 hours; T_{Max} 3–5 hours

METABOLISM: CYP 2D6 and 3A4

- Strong 2D6 inhibitors increase aripiprazole exposure by 112%; decrease dose by 50%
- 2D6 poor metabolizers experience 80% increase in aripiprazole exposure, and the half-life is 146 hrs — also decrease the dose by 50%
- Strong 3A4 inhibitors only increase aripiprazole exposure by 63%; decrease the dose by 50%
- Strong 3A4/PGP inducers decrease aripiprazole exposure by 70%; double the dose

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Ed; 2022:357-84.
Otsuka America Pharmaceutical Inc. Abilify Package Insert. 2020.

Aripiprazole Oral Dose–Plasma Level Relationships

Aripiprazole Level = 11 x oral dose (mg/d)

Example: Patient is on aripiprazole 20 mg qhs, not getting better, and has no SEs. Is she taking it?

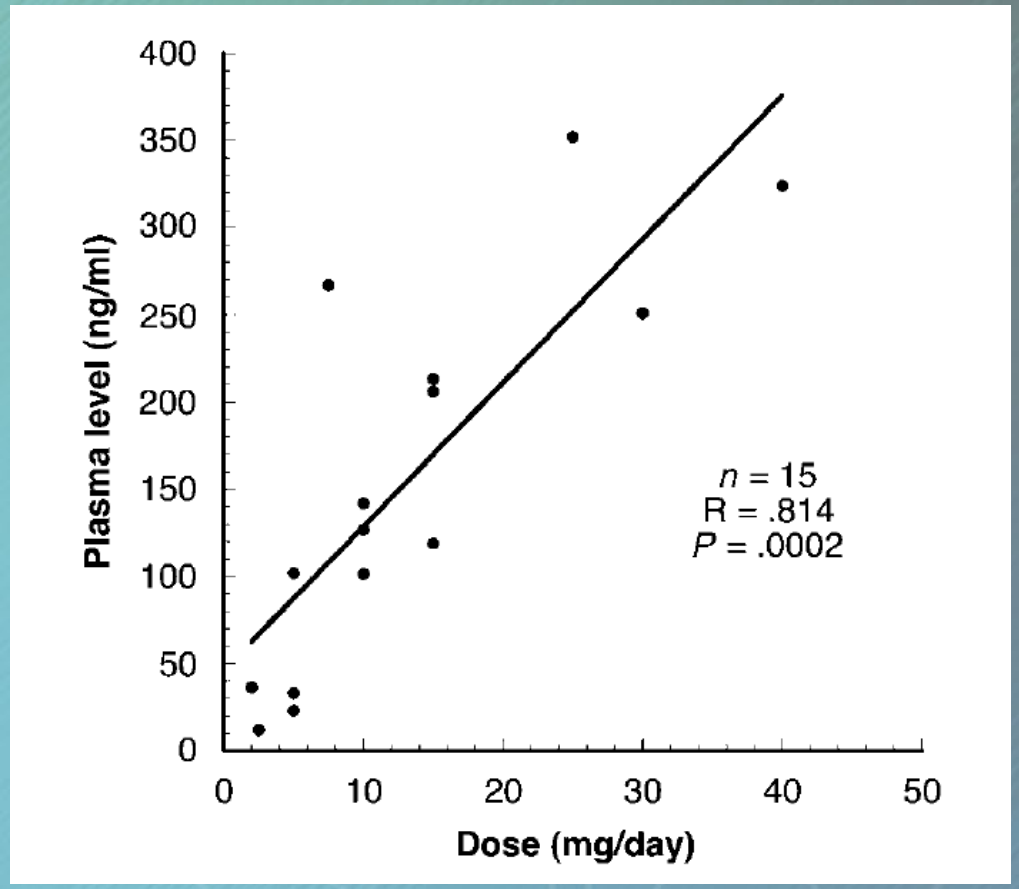
Expected level: 220 ng/ml

Actual level: 120 ng/ml

Response: **Do not make decisions based on one level for oral meds.** Explain to the patient that the level is not what you expected and check it again.

a. If next level is 220 ng/ml -> pt was nonadherent

b. If next level is 120 ng/ml -> pt probably an ultra-rapid metabolizer at 2D6 (if not on a CYP inducer)



Kegeles LS et al. Neuropsychopharmacology 2008;33(13):3111-25.
Meyer JM et al. Psychiatr Clin North Am 2016;39(4) 541-56.

Aripiprazole Therapeutic Plasma Level Range

Oral Dose correlation	Level of Evidence	Therapeutic Threshold	Level of Evidence	Point of Futility	Level of Evidence
10 mg = 110 ng/ml **Multiply oral dose by 11**	High	110 ng/ml	High	500 ng/ml	High

D_2 Occupancy By Dose	
0.5 mg	33.7%
1 mg	57.2%
2 mg	71.6%
10 mg	85.3%
30 mg	86.4%
40 mg	96.8%

- For partial agonist antipsychotics, the point of futility is defined by the plasma level that achieves ~100% D_2 receptor occupancy
- Based on the PET D_2 occupancy studies, a plasma level of 500 ng/ml will achieve close to 100% D_2 receptor occupancy
- 500 ng/ml divided by 11 = 45.45 mg/d

Sparshatt A et al. J Clin Psychiatry 2010;71(11):1447-556.
Meyer JM, Stahl SM Clinical Use of Antipsychotic Plasma Levels Cambridge Univ Press, 2021

Examples of Problems: Interactions With Aripiprazole

Can Aripiprazole Be Overlapped With Other Antipsychotics?

1. **Combining aripiprazole with modest doses of risperidone or quetiapine [1]**
   a. 16-week, double-blind, placebo-controlled adjunctive study of aripiprazole (2–15 mg) added to stable risperidone (n=187) or quetiapine (n=146). Mean doses: risperidone 4.7 mg; quetiapine 514 mg. (**Expected D_2 occupancy:** for risperidone 4.7 mg = 75%; for quet = 514 mg < 40%.).
   b. Mean endpoint aripiprazole dose: 10.4 mg in the risperidone group, and 10.2 mg for the quetiapine cohort.
   c. **Efficacy:** No difference in mean change from baseline PANSS in aripip or PBO groups (-8.8 vs. -8.9 points, p=.942). When compared by subgroup (risperidone or quetiapine) there were no significant differences in PANSS change.
   d. **Conclusions: Aripiprazole can be added to modest D_2 blockade without adverse consequences, though without significant benefit.**

2. **Overlapping aripiprazole with high levels of D_2 blockade [2]**
   - Numerous case reports exist of exacerbation when aripiprazole added to patients receiving other antipsychotics, primarily high potency typicals, or higher doses of more potent D_2 antagonist atypicals (e.g., risperidone ≥ 6 mg/d, paliperidone palmitate ≥ 234 mg/month).

1. Kane JM et al. J Clin Psychiatry 2009;70(10):1348-57.
2. Takeuchi H, Remington G. Psychopharmacology (Berl) 2013;228(2):175-85.

Case Reports of Aripiprazole Worsening Psychosis

2013 literature review covering case reports through August 2012. Case inclusion criteria:

- Dx: schizophrenia or schizoaffective disorder
- Worsening of psychosis on aripiprazole, and the oral aripiprazole daily dose was ≤ 30 mg

Findings:

- **22** cases: 8 were switched to aripiprazole, 14 aripiprazole was added to the current antipsychotic
- 11/22 cases demonstrated a strong relationship between aripiprazole and worsening psychosis
- 4/4 “rechallenge” cases worsened when aripiprazole added to current regimen and resolved when aripiprazole discontinued
- 8/22 psychosis worsened after adding aripiprazole to current treatment regimen: **ALL** resolved by discontinuing aripiprazole
- Doses of aripiprazole associated with worsening of psychotic symptoms ranged from 5 to 30 mg/day

Takeuchi H, Remington G. Psychopharmacology (Berl) 2013;228(2):175-85.

State Hospital Case #1: Oral Aripiprazole Interfering With Haloperidol

Clinical Comments

- 68 yo male with SCZ developed parkinsonism on risperidone 8 mg qhs. Switched to aripiprazole to mitigate this adverse effect and titrated over 7 months to 30 mg/d.
- Insufficient control of positive symptoms on aripiprazole **30 mg/d**. Haloperidol then added to aripiprazole **(starting May 6, 2014)** in increasing dosages.
- The referring clinicians were perplexed when the patient did not improve, and also did not develop parkinsonism on **haloperidol 30 mg BID** when combined with aripiprazole 30 mg/d.
- Psychopharmacology consultation requested 10/20/2014

Drug	Eff. Date	D/C Date	Dose	Schedule	Drug	Eff. Date	D/C Date	Dose	Schedule
Risperidone	06/15/12	07/25/12	6	QHS	Haloperidol	05/06/14	05/07/14	5	BID
Risperidone	07/25/12	09/28/12	6	QHS	Haloperidol	05/07/14	05/14/14	10	BID
Risperidone	04/22/13	05/06/13	4	QHS	Haloperidol	05/08/14	05/14/14	15	BID
Risperidone	05/06/13	05/08/13	5	QHS	Haloperidol	05/14/14	05/22/14	20	BID
Risperidone	05/08/13	05/16/13	6	QHS	Haloperidol	05/22/14	06/04/14	25	QHS
Risperidone	05/16/13	05/29/13	6	QHS	Haloperidol	05/22/14	06/04/14	20	QD
Risperidone	05/29/13	05/30/13	6	QHS	Haloperidol	06/04/14	06/04/14	30	QHS
Risperidone	05/29/13	06/13/13	6	QHS	Haloperidol	06/04/14	06/27/14	25	QD
Risperidone	06/13/13	06/17/13	8	QHS	Haloperidol	06/04/14	06/04/14	25	QD
Risperidone	06/17/13	07/03/13	8	QHS	Haloperidol	06/04/14	06/27/14	30	QHS
Risperidone	06/17/13	06/17/13	8	QHS	Haloperidol	06/27/14	08/13/14	25	BID
Risperidone	07/03/13	07/09/13	2	QD	Haloperidol	08/13/14	08/13/14	30	BID
Risperidone	07/10/13	08/29/13	4	BID	Haloperidol	08/13/14	10/22/14	30	BID
Risperidone	08/29/13	10/23/13	5	BID	Haloperidol	10/22/14	11/05/14	15	BID
Risperidone	10/23/13	11/06/13	2	BID	Haloperidol	11/05/14	12/03/14	20	BID
Risperidone	11/06/13	11/19/13	2	QHS	Haloperidol	12/03/14	03/03/15	25	BID
Risperidone	11/19/13	11/19/13	2	QD	Haloperidol	03/03/15	03/10/15	15	QHS
Aripiprazole	10/23/13	10/29/13	2.5	QHS	Haloperidol	03/03/15	03/10/15	10	QD
Aripiprazole	10/24/13	10/29/13	2	QHS	Haloperidol	03/10/15	03/13/15	5	BID
Aripiprazole	10/29/13	11/06/13	5	QHS					
Aripiprazole	11/06/13	11/19/13	2	BID					
Aripiprazole	11/19/13	11/25/13	2	QD					
Aripiprazole	11/19/13	11/25/13	5	QHS					
Aripiprazole	11/25/13	12/04/13	2	QD					
Aripiprazole	11/25/13	12/19/13	2	QD					
Aripiprazole	11/25/13	12/19/13	5	QHS					
Aripiprazole	12/19/13	01/21/14	5	BID					
Aripiprazole	01/21/14	02/18/14	10	QHS					
Aripiprazole	01/21/14	02/18/14	5	QD					
Aripiprazole	02/18/14	03/25/14	10	BID					
Aripiprazole	03/25/14	05/02/14	10	BID					
Aripiprazole	05/02/14	08/18/14	15	BID					
Aripiprazole	08/18/14	03/04/15	15	QD					
Aripiprazole	03/04/15	03/10/15	5	QD					

State Hospital Case #1—Oral Aripiprazole Interfering With Haloperidol: Psychopharmacology Consultation Recommendations

1. Noted that at 30 mg/d the aripiprazole D_2 receptor occupancy likely exceeded 85%. Haloperidol had limited access to the D_2 receptor.
2. Recommended to discontinue oral aripiprazole, noting that it will self-taper over 2 weeks due to the 75h half-life.
3. As the aripiprazole level drops there will be incrementally more D_2 receptors available for the antagonist antipsychotic to access.
4. Since the patient previously experienced parkinsonism on risperidone 8 mg qhs, haloperidol doses > 7.5 mg will likely be poorly tolerated once aripiprazole is washed out. Suggested decreasing the haloperidol dose to 7.5 mg qhs from 30 mg BID now, and then reassessing in 3 weeks.

State Hospital Case #2—Problems Caused by Aripiprazole LAI

Reason for consult: 37 yo male with working Dx of schizophrenia and alleged haloperidol allergy, admitted as incompetent to stand trial, overtly manic and psychotic. Patient not responding to current meds 1 month after admission.

- **Prior Hx:** Refused to eat or drink in jail, was treated for dehydration and started on aripiprazole monohydrate 400 mg IM qmonth.
- **Presentation:** Upon state hospital admission was disorganized with inappropriate smiling, making dancing movements, mumbling, and difficult to understand. Refused to leave Tx room or day hall, required physical escort to side room. During attempts to physically escort him, he tried to bite and swing at staff with a closed fist without contact. He also made verbal threats to kill others while shaping his hands as if to choke staff.
  - **Subsequent Incidents:** 2 days after admission refused scheduled meds and did a "slow karate kick" towards staff's face without making contact. Continued very disorganized, delusional, grandiose, with poor social boundaries, and required frequent redirection. He received multiple PRNs due to agitation and disorganized thoughts. He was urinating in his room and was sexually inappropriate. He stated, “You will go to federal prison, you are injecting me with HIV. I am God, king of heaven, I made the planet, you can call NASA…”

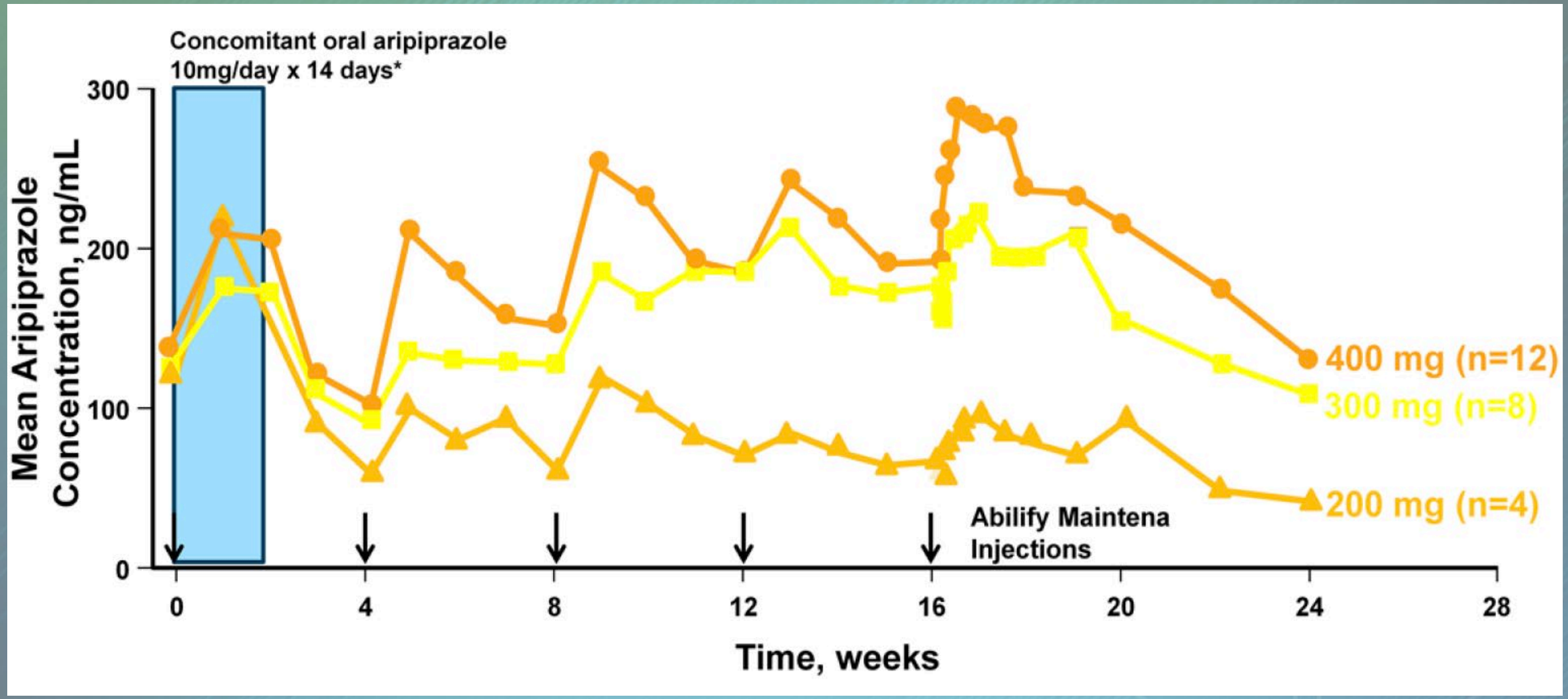
Aripiprazole LAI Kinetics

Preparation	Diluent	Dosage	T_{max} (days)	Steady State $T_{1/2}$ (days)	Able To Be Loaded
Aripiprazole Monohydrate	Water	300–400 mg/4 weeks	6.5 – 7.1	**29.9 – 46.5**	No (14 days oral overlap)
Aripiprazole Monohydrate (2-month—pending)	Water	720–960 mg/8 weeks **Max:** 960 mg/8 weeks	28 days	???	No * (7 days oral overlap)
Aripiprazole Lauroxil	Water	441–882 mg/4 weeks 882 mg/6 weeks 1064/8 weeks	41 (single dosing) 24.4 – 35.2 (multiple dosing)	**53.9 – 57.2**	No *
Aripiprazole Lauroxil Nanocrystal	Water	675 mg once	27 (range 16 – 35)	15 – 18 (single dose)	Only for initiation or resumption (always given with maintenance dose of aripiprazole lauroxil

* Start therapy with 21 days oral overlap or one aripiprazole lauroxil nanocrystal injection + a single 30 mg oral dose in addition to the clinician determined dose of aripiprazole lauroxil.

Meyer JM. CNS Spectr 2013;18(Suppl 1):58-67.
Jain R et al. CNS Spectr 2020;32(3):323-30.

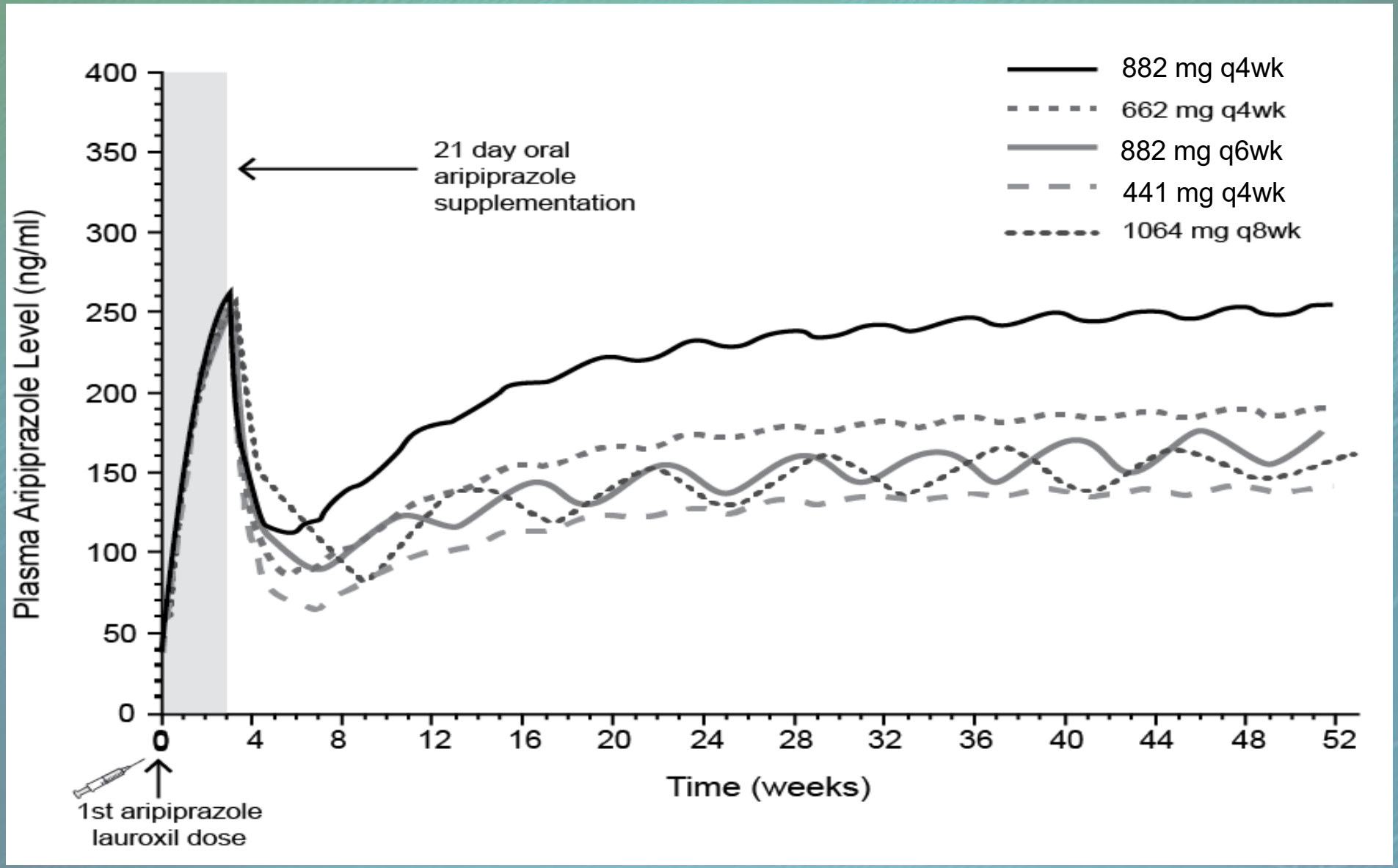
Aripiprazole Monohydrate Kinetics



400 mg dose achieves steady state levels equivalent to 20 mg oral

Meyer JM. CNS Spectrums 2013;18(Suppl 1):58-67.

Aripiprazole Lauroxil Steady-State Levels



Meyer JM. Curr Psychiatry 2018;17(11):34-40.

State Hospital Case #2: Medications and Psychopharmacology Consultation Recommendations

Medications:

- Aripiprazole monohydrate (Abilify Maintena®) 400 mg IM q month
- Olanzapine 60 mg/d with risperidone added up to 4 mg/d recently

Prior state hospital med Hx: During prior admission, this patient was restored to competency on risperidone 6 mg/d monotherapy.

Assessment: Patient is an inadequate responder to aripiprazole, and the presence of aripiprazole is interfering with the D_2 antagonists olanzapine and risperidone.

Recommendations:

- Discontinue aripiprazole LAI. It will self-taper over months. After ~ 8 weeks the level will drop 50%, but the remaining aripiprazole level will still generate > 85% D2 occupancy.
- As the aripiprazole level drops there will be incrementally more D_2 receptors available for antagonist antipsychotics to access. Since the patient previously responded to risperidone 6 mg qhs, resume this for now. Higher doses will NOT be more effective while aripiprazole is present. One must wait.

Brexpiprazole Binding Profile and Basic Info

	D_2 (Ki nM)	MAX STIMULATION AT D_2 RECEPTORS	M_1 (Ki nM)	H_1 (Ki nM)	α_1 (Ki nM)
ARIPIPRAZOLE	0.34	26%	> 1000	61	26
BREXPIPRAZOLE	0.30	18%	> 1000	19	3.8

Low affinity for M1, α1-adrenergic receptors, modest for H1. Associated with low risk of sedation, anticholinergic effects, and orthostasis, but possibly more wt gain than aripiprazole.

FORMULATIONS: Tablets

KINETICS: $T_{1/2}$ 91 hours; T_{Max} 4 hours

METABOLISM: CYP 2D6 and 3A4

- Strong 2D6 or 3A4 inhibitors increase $AUC_{0\text{-}24H}$ 2-fold. Decrease dose by 50%.
- Combined use of a strong 3A4 and 2D6 inhibitor (or with 2D6 PM) increases $AUC_{0\text{-}24H}$ 4.8 – 5.1 fold. Decrease dose by 75%.
- Strong 3A4/PGP inducers decrease $AUC_{0\text{-}24H}$ exposure by 70%. Double the dose.

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Ed; 2018:279-302.
Otsuka America Pharmaceutical Inc. Rexulti Package Insert 2020.

Outpatient Case: Cariprazine vs. Fluphenazine

Reason for consult: 42 yo male with prior history of responding to risperidone 6 mg BID but who was repeatedly nonadherent in part due to endocrine related adverse effects (e.g., sexual dysfunction). He has refused LAI medications in the past.

Clinician decision: Since this patient was refusing an LAI, cariprazine seemed an appealing option because its active metabolite DDCAR has a half-life of 13–18 days, with studies showing reduced relapse rates following abrupt discontinuation compared to agents with shorter half-lives. [1]

Subsequent course:

- Patient titrated up to cariprazine 6 mg and risperidone tapered off. Over the next 6 weeks the patient's positive symptoms slowly worsened.
- The patient refused to reconsider risperidone or to add risperidone to the cariprazine but did allow the clinician to add fluphenazine. This was titrated to 20 mg BID with no benefit on the positive symptoms and no adverse effects.

WHAT TO DO??

1. Correll CU et al. Neuropsychiatr Disease Treat 2019:15 2537-550.

Cariprazine Binding Profile

	D_2 (Ki nM)	MAX STIMULATION AT D_2 RECEPTORS	M_1 (Ki nM)	H_1 (Ki nM)	α_1 (Ki nM)
ARIPIPRAZOLE	0.34	26%	> 1000	61	26
BREXPIPRAZOLE	0.30	18%	> 1000	19	3.8
CARIPRAZINE	0.49	21%	> 1000	23.2	155
DESMETHYLCARIPRAZINE (DCAR)	0.81	??	> 1000	18.4	97
DIDESMETHYLCARIPRAZINE (DDCAR)	1.41	10%	> 1000	23.7	149

Low affinity for M1, α1-adrenergic receptors, modest for H1. Associated with low risk of sedation, weight gain, anticholinergic effects, and orthostasis.

Allergan USA Inc. Vraylar Package Insert. Madison, NJ 07940 2019

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Ed; 2018:279-302.

Tadori Y et al. In vitro pharmacology of aripiprazole, its metabolite and experimental dopamine partial agonists at human dopamine D2 and D3 receptors. Eur J Pharmacol 2011;668(3):355-65.

Cariprazine Kinetic Info

FORMULATIONS: Capsules

METABOLISM: CYP 3A4 converts cariprazine to active metabolites DCAR & DDCAR. CYP 2D6 is a minor pathway.

- Strong 3A4 inhibitors—decrease dose by 50%. No impact of strong 2D6 inhibitors.
- No info on use with strong 3A4/PGP inducers. Do not combine with cariprazine (until more info available.)

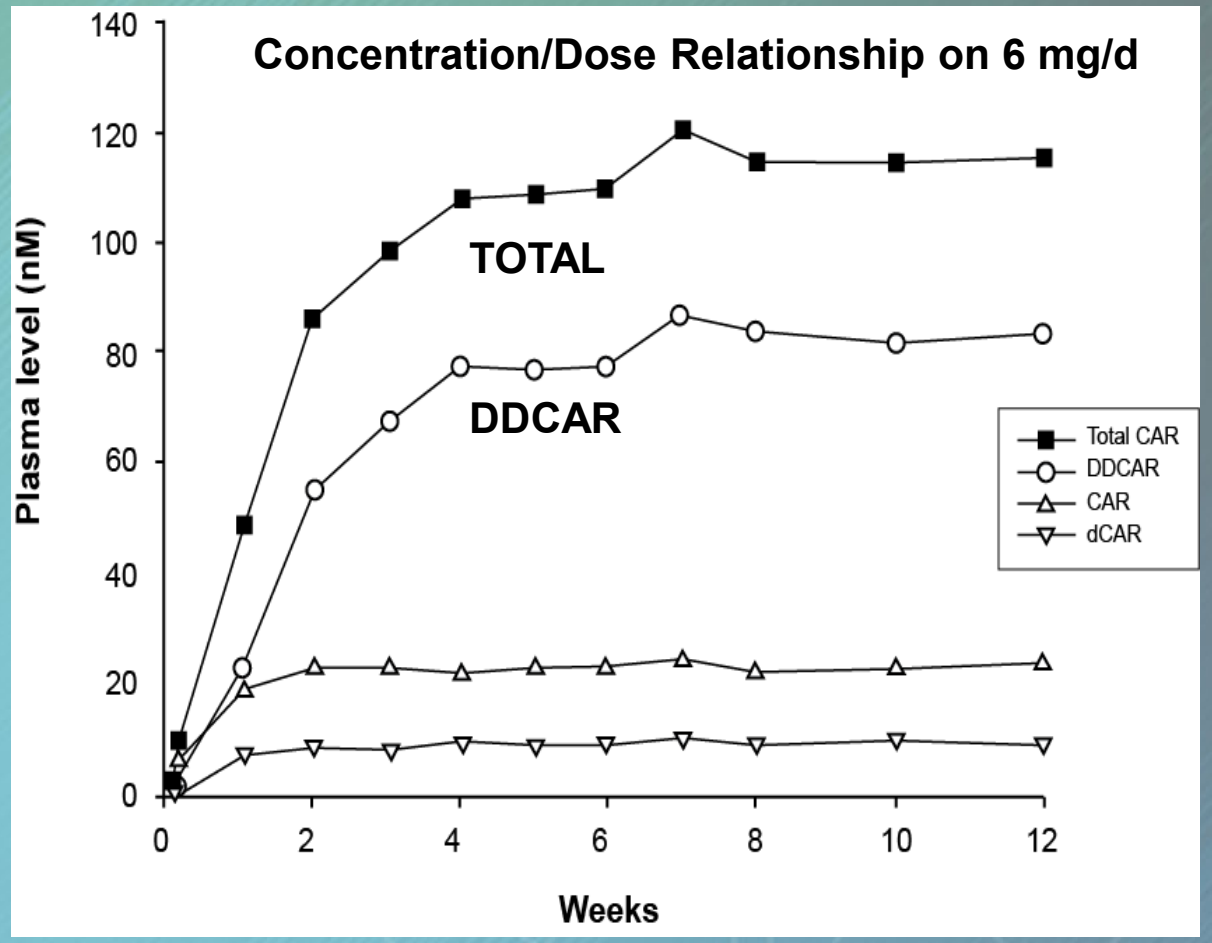
KINETICS: T_{Max} 3–6 hours

$T_{1/2}$ 31.6 – 68.4 hrs (Cariprazine)

$T_{1/2}$ 29.7 – 39.5 hrs (DCAR)

$T_{1/2}$ 314 – 446 hrs (DDCAR) [13.08 – 18.58 days]

At steady state on 6 mg/d the active moiety is: cariprazine 28%, DCAR 9%, and DDCAR 63%.



Comment: Due to the very long half-life of DDCAR, 50% is still present 1 week after discontinuation. At steady state it may take a month or more after discontinuation to allow another antipsychotic access to the D_2 receptor.

Allergan USA Inc. Vraylar Package Insert. Madison, NJ 07940, 2019.

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Ed; 2018:279-302.

Brexpiprazole and Cariprazine Are Effective at 80%–100% D_2 Receptor Occupancy

Figure 17.11 Fitted D_2 receptor occupancy curve for brexpiprazole [72]

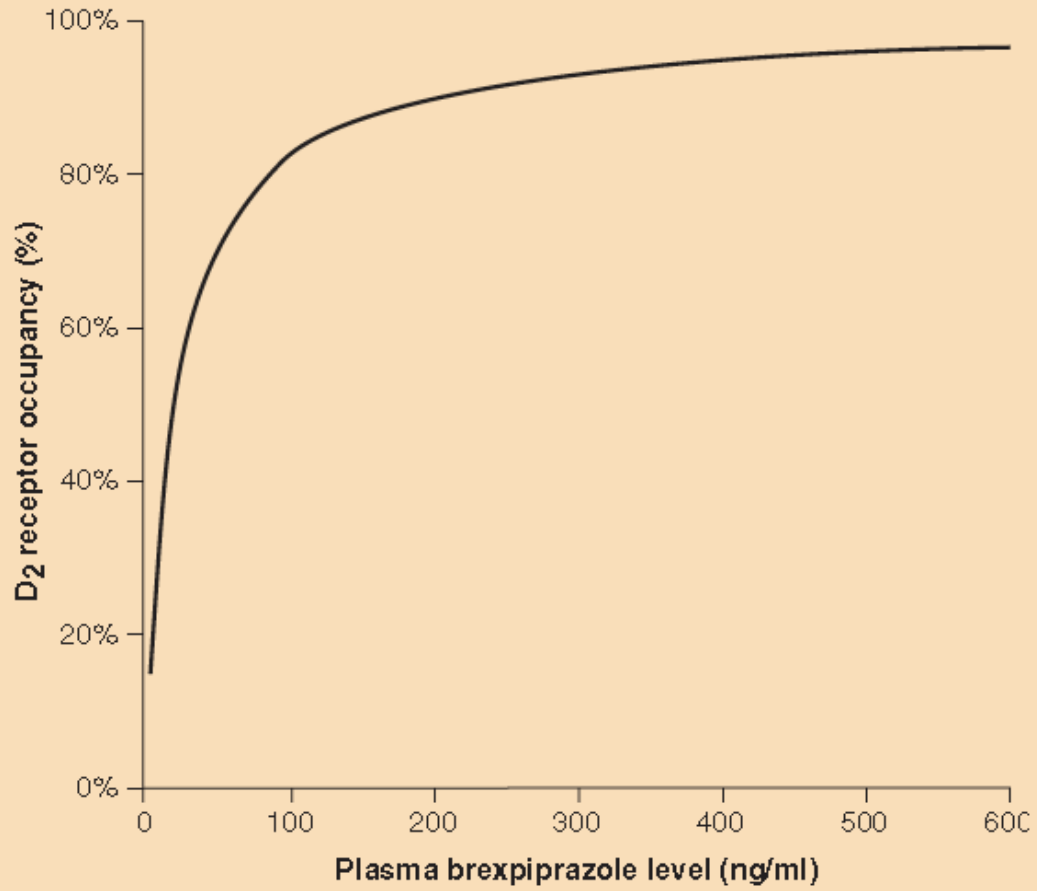
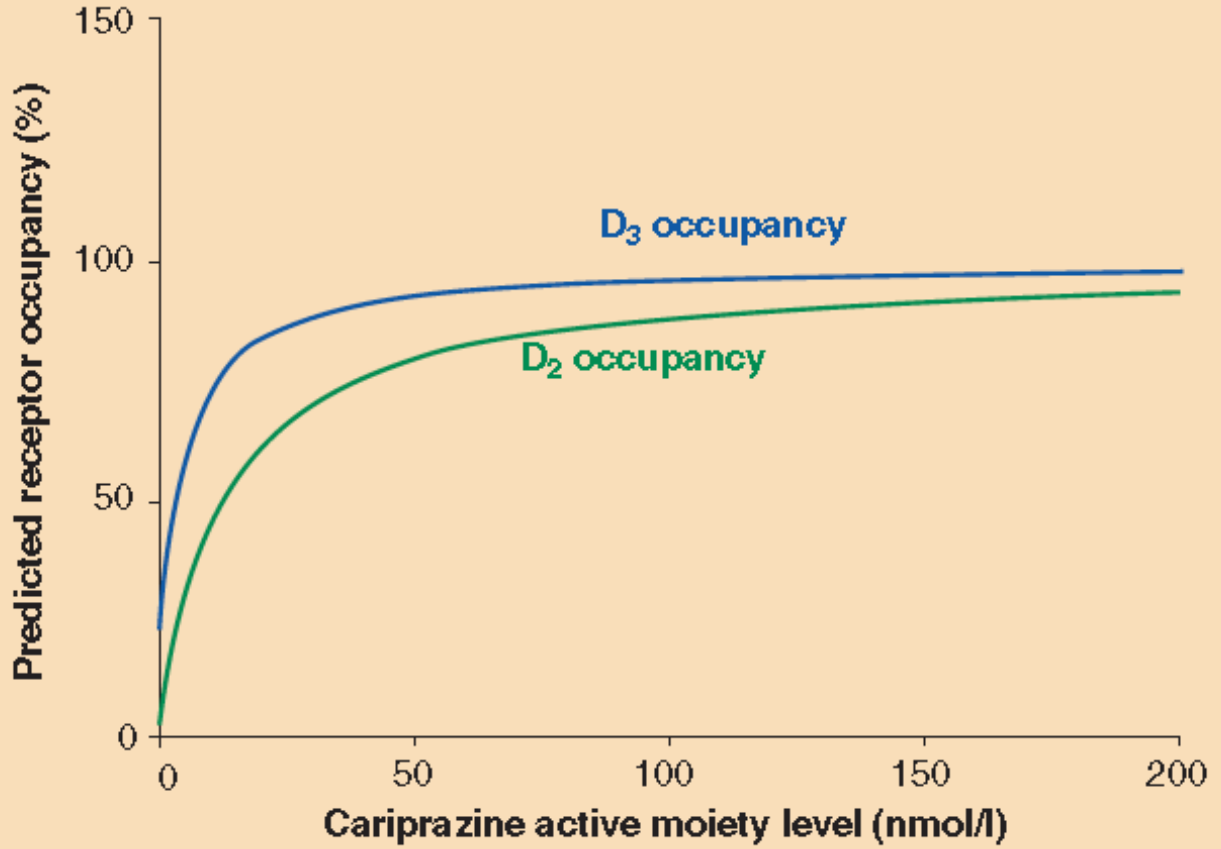


Figure 17.13 Fitted D_2 and D_3 receptor occupancy curve for cariprazine active moiety levels [76]



Meyer JM, Stahl SM Clinical Use of Antipsychotic Plasma Levels Cambridge Univ Press, 2021.

Outpatient Case: Cariprazine vs. Fluphenazine - Recommendations

1. Noted that at 6 mg/d the cariprazine D_2 receptor occupancy likely exceeded 85%. Fluphenazine had limited access to the D_2 receptor.
2. Recommended to discontinue cariprazine, noting that it will self-taper over **2 months** due to the long DDCAR half-life.
3. As the level of cariprazine and DDCAR drop there will be incrementally more D_2 receptors available for the antagonist antipsychotic to access.
4. Since the patient previously required risperidone 12 mg/d, a reasonable target fluphenazine dose is 10 mg qhs. Suggested decreasing the fluphenazine to 10 mg qhs and letting the patient know it will take1–2 months for his positive Sx to improve.

Switching Between Partial Agonist and Antagonist Antipsychotics

Switching From a D_2 Antagonist to a D_2 Partial Agonist

Critical Issues:

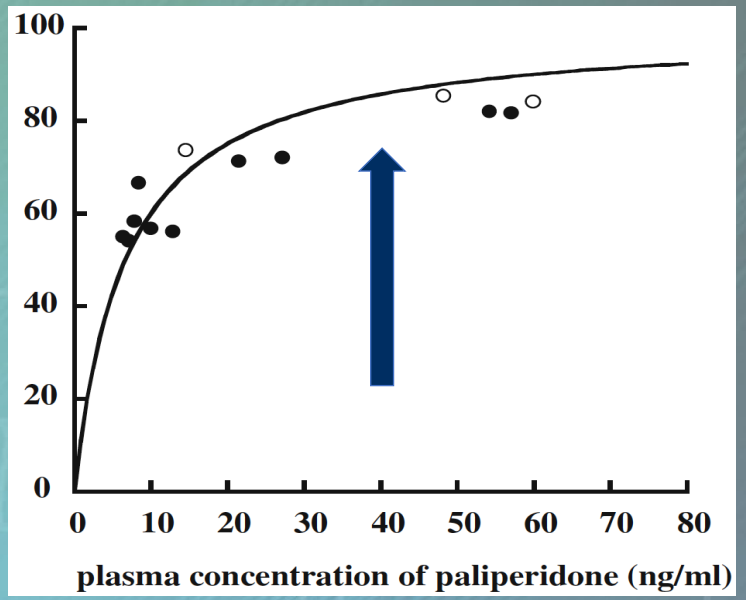
1. **Pharmacodynamic considerations:** Partial agonist APs can only provide up to 80% reduction in D_2 related neurotransmission. Some patients need a full antagonist that can reduce postsynaptic activity more than 80%. **Whether the partial agonist AP will work out can be estimated before the switch. If deemed feasible, the switch will proceed by adding the partial agonist and seeing what happens as it displaces the antagonist AP.**
2. **Pharmacodynamic & kinetic considerations:** Before committing a patient to an LAI form of aripiprazole ideally confirm that they are a responder. Partial agonist APs have very high D_2 affinities; it is hard to override them even with an FGA if the patient is a nonresponders—one must allow a number of weeks to wash out the aripiprazole before the antagonist AP will work. Cariprazine has a metabolite with a 13–18 d half-life (DDCAR), so a similar scenario may occur in nonresponders—one may need to wait 4 weeks or more to wash out enough DDCAR to allow an antagonist AP access to the D_2 receptor.
3. **Pharmacodynamic considerations:** Need to have a mechanism for rescue sleep meds to replace what is lost from the first agent if it is sedating, since the partial agonist APs are not sedating.

Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels – Stahl's Handbooks. Cambridge University Press, 2021.

Example: Switching From Paliperidone to Aripiprazole

Step 1: Determine feasibility of responding to a partial agonist based on current requirements for D_2 blockade, bearing in mind that aripiprazole may reduce D_2 neurotransmission at most by 75%.

Example: The mean steady state trough plasma level for paliperidone palmitate 234 mg/month is 38.5 ng/ml ***on average***. If the measured plasma paliperidone level were < 40 ng/ml in your patient, aripiprazole should work out since we need ~75% reduction in postsynaptic activity.

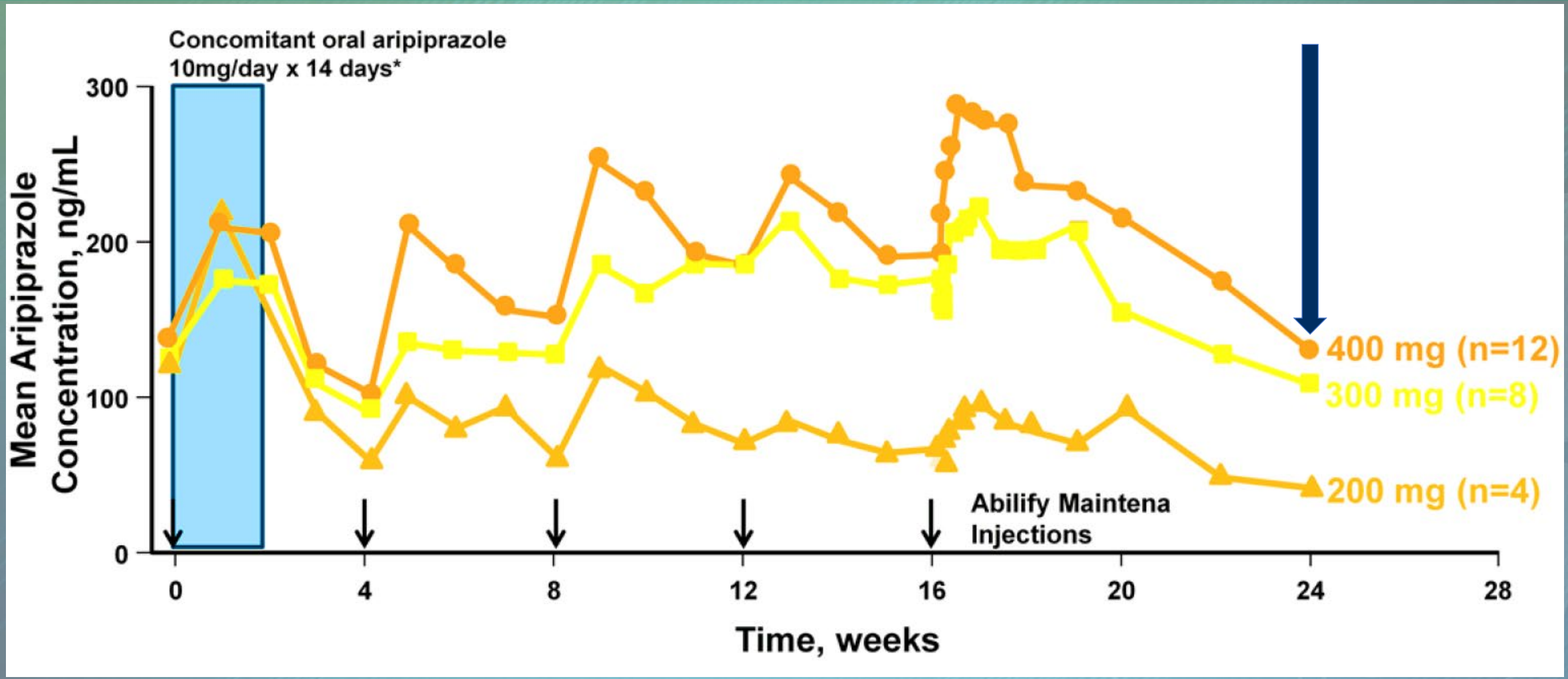


Step 2: Add oral aripiprazole to the existing AP, allow it to displace the existing AP from the D_2 receptor, and see what happens

- Since the D_2 neurotransmission curve for aripiprazole is very flat from 10–30 mg, aim for 20 mg. This dose also represents the max amount deliverable via an LAI form of aripiprazole. Titrate over 1–2 weeks.
- Oral aripiprazole will be at steady state in 15.63 days. If no exacerbation occurs, then one could reasonably commit to an LAI formulation that equals 20 mg/d (e.g., aripiprazole monohydrate 400 mg/mo, aripiprazole lauroxil 882 mg/mo). **If in doubt, wait another few weeks to be certain the patient is an aripiprazole responder.**
- Once an aripiprazole responder, the primary AP can be tapered off quickly if nonsedating (or stopped abruptly if an LAI — it will self-taper). If sedating, then taper slowly to avoid rebound insomnia.

Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels – Stahl's Handbooks. Cambridge University Press, 2021.

Aripiprazole Monohydrate Kinetics



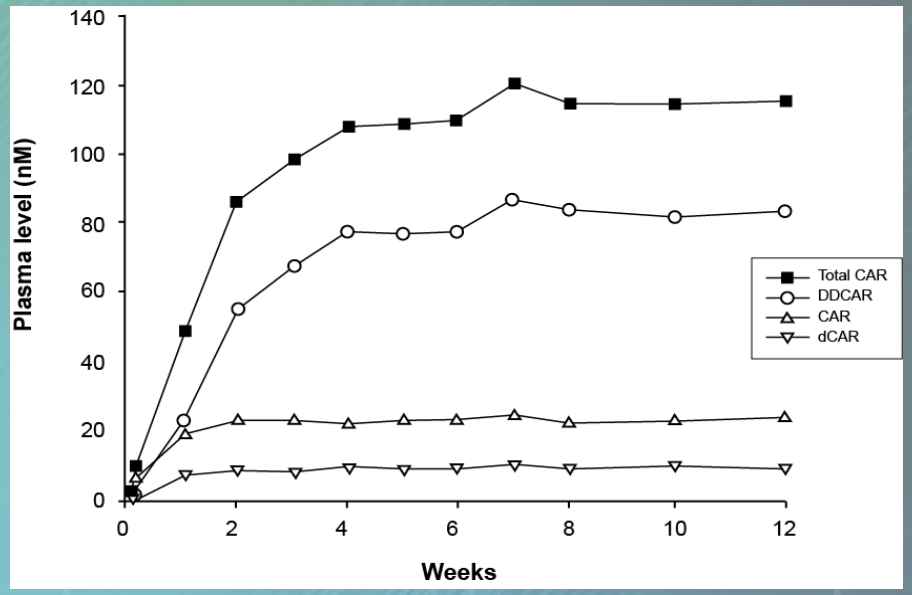
Note: Even 8 weeks after the last injection of 400 mg the plasma aripiprazole level = 120 ng/ml, which is comparable to > 10 mg/d and ≥ 85% D_2 receptor occupancy

Meyer JM. CNS Spectr 2013;18(Suppl 1):58-67.

Example: Switching From Risperidone to Cariprazine

Step 1: Determine feasibility of responding to a partial agonist based on current requirements for D_2 blockade, bearing in mind that cariprazine may reduce D_2 neurotransmission less than an antagonist.

Example: A patient on risperidone 4 mg PO qhs has predominantly negative symptoms with good control of positive symptoms. Based on the results of a 26-week double-blind trial, cariprazine 4.2 mg was superior to risperidone 3.8 mg on the PANSS factor score for negative symptoms. [1]



Step 2: Add cariprazine to the existing AP and allow it to displace the existing AP from the D_2 receptor.

- **Target dose:** As cariprazine comes in 1.5 mg increments, 4.5 mg seems a reasonable target dose.
- **Kinetics:** Cariprazine has a $T_{1/2}$ of 31.6 – 68.4 hrs and will reach steady state sooner than DDCAR ($T_{1/2}$ 13.08 – 18.58 days). Cariprazine will be at steady state in 5 half-lives = 158 – 360 hours (6.6 – 20.5 days). If no exacerbation occurs during the first 3 weeks, then risperidone can be tapered off.
- Once a presumed cariprazine responder, risperidone can be tapered off quickly since it is nonsedating (i.e., over 1–2 weeks depending on patient preference, not kinetics).

1. Nemeth G et al. Lancet 2017;389(10074):1103-13.

Switching From a D_2 Partial Agonist to a D_2 Antagonist

Critical Issues:

1. **Pharmacodynamic considerations:** The partial agonist AP will occupy ≥ 80% of D_2 receptors at therapeutic concentrations. **Whether the antagonist AP will work out can only be seen once the partial agonist is almost completely washed out.**

2. **Dosing considerations:** Based on prior history of response, estimate the dose of the D_2 antagonist AP that should work once the partial agonist is washed out. **Do not attempt to override the partial agonist with heroic doses of the antagonist.**

    - **Clozapine is the exception: it is the one AP that can work in the presence of aripiprazole or other partial agonists since its magic efficacy properties do not depend on D_2 receptor binding.**

3. **Kinetic considerations:** It may be many, many weeks before enough LAI aripiprazole is washed out enough to see if the antagonist AP will work. Oral aripiprazole can be washed out in 2 weeks. Cariprazine will take longer than oral aripiprazole (4 weeks or more) but not as long as an aripiprazole LAI to wash out and allow an antagonist AP access to the D_2 receptor.

Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels – Stahl's Handbooks. Cambridge University Press, 2021.

Example: Switching From LAI Aripiprazole to LAI Paliperidone or Risperidone

Step 1: Determine target dose: Based on this patient's prior history, they responded at one point to risperidone 5 mg/d PO at a time when there was reasonable evidence of oral adherence (e.g., in an inpatient unit). This will be the initial target risperidone dose.

Step 2: Since one is going from one LAI to the other, one has two options:

a. **As of 2022:** Start paliperidone palmitate monthly (PP1M) using the loading regimen of 234 mg IM (deltoid) followed by 156 IM (deltoid) 1 week later. The closest maintenance dose of PP1M to 5 mg risperidone is 234 mg**.** The dose could be lowered for tolerability reasons to 156 mg.

b. **The future (!!):** A new subcutaneous (SC) risperidone (Uzedy) is under FDA review; the kinetic profile does not require loading and provides 1- or 2-month coverage. The proposed Uzedy dose equal to 5 mg/d oral risperidone is either 125 mg/1 month or 250 mg/2 months.

c. **D/C LAI aripiprazole:** This will self-taper over many weeks and eventually allow the new AP access to the D_2 receptor.

d. **Continue to administer LAI paliperidone or risperidone on schedule. Be patient: Whether the dose you have chosen is correct may not be apparent for a long time.**

Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels – Stahl's Handbooks. Cambridge University Press, 2021.

Summary

- Dopamine partial agonists have high affinities for the dopamine D_2 receptor and can render those receptors inaccessible to D_2 antagonist antipsychotics.
- Attempting to override a partial agonist with an antagonist, even a potent one, often does not achieve the intended therapeutic outcome.
  - The presence of the partial agonist may be a reason why the patient is not responding to a 2nd antipsychotic. Combining a partial agonist and an antagonist does not make pharmacological sense. Partial agonists can be combined with clozapine (whose benefit does not rest on D_2 receptor blockade).
  - Try not to commit a patient to an LAI form of aripiprazole unless you have evidence that they respond to aripiprazole as antipsychotic monotherapy.
  - Oral cariprazine presents similar kinetic issues but to a somewhat lesser extent. Once a patient is on cariprazine for 2 months, it will take 1–2 months to wash out.

Posttest Question 1

Which of the following has the lowest *in vitro* D_2 receptor affinity?

1. Aripiprazole
2. Brexpiprazole
3. Cariprazine
4. Haloperidol

Posttest Question 2

As a partial agonist, it is estimated that aripiprazole has approximately 25% of the intrinsic activity of dopamine. When aripiprazole levels are pushed to the point where aripiprazole occupies 100% of D_2 receptors, what is the expected postsynaptic dopamine signal?

1. 0%
2. 10%
3. 25%
4. 75%
5. 100%

Posttest Question 3

Over 60% of cariprazine's active moiety is from the metabolite DDCAR. What is its half-life?

1. 1–2 days
2. 3–6 days
3. 7–12 days
4. 13–18 days