OPTIMIZING FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA: MANAGING NEGATIVE SYMPTOMS, COGNITIVE IMPAIRMENT, AND ADVERSE EFFECTS

Learning Objectives

- Implement evidence-based strategies to address the negative symptoms of schizophrenia
- Examine evidence-based strategies to address the cognitive symptoms of schizophrenia
- Apply pre-emptive and monitoring strategies to mitigate the impact of adverse effects
- Evaluate the status of plasma monitoring and long-acting injectables (LAIs) with treatment adherence

Patients can't achieve functional outcomes without relief of negative symptoms.

Reduced speech

Limited eye contact

Reduced interest

- Difficulty forming a therapeutic alliance
- Impaired occupational functioning
  - Impaired social functioning
  - Impairment in relationships
    - Reduced quality of life

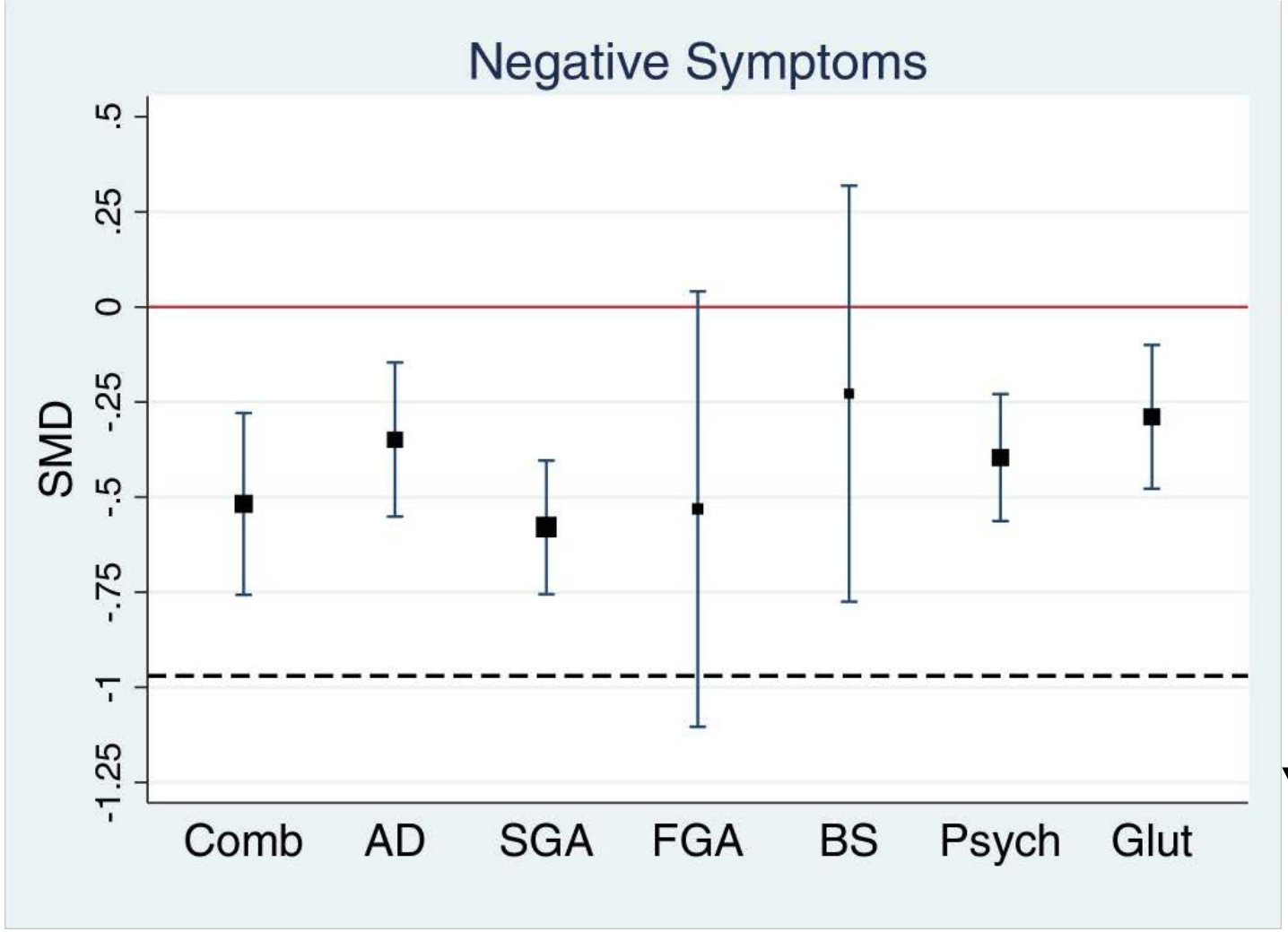
Poor grooming

Reduced emotional responsiveness

Reduced social drive

Velligan DI et al. J Clin Psychiatry 2009;70(suppl 4):1-46;
Milev P et al. Am J Psychiatry 2005;162:495-506.

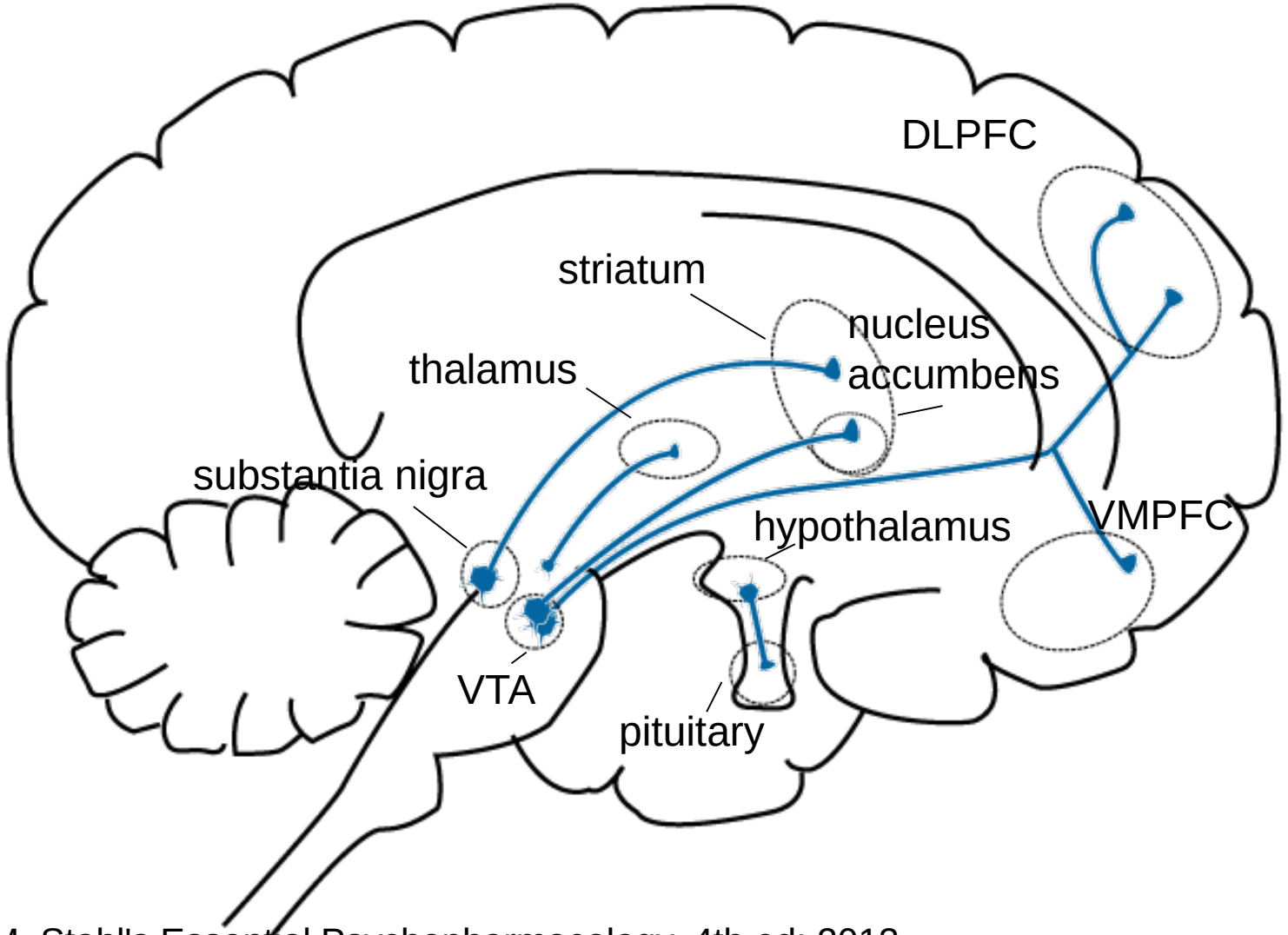
Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis



Fusar-Poli P et al. Schizophr Bull 2015;41(4):892-9.

Why aren't negative symptoms sufficiently improved with dopamine 2 antagonists?

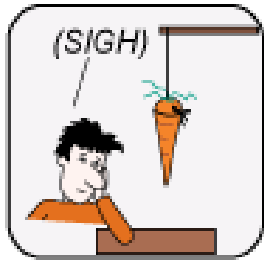
mesolimbic



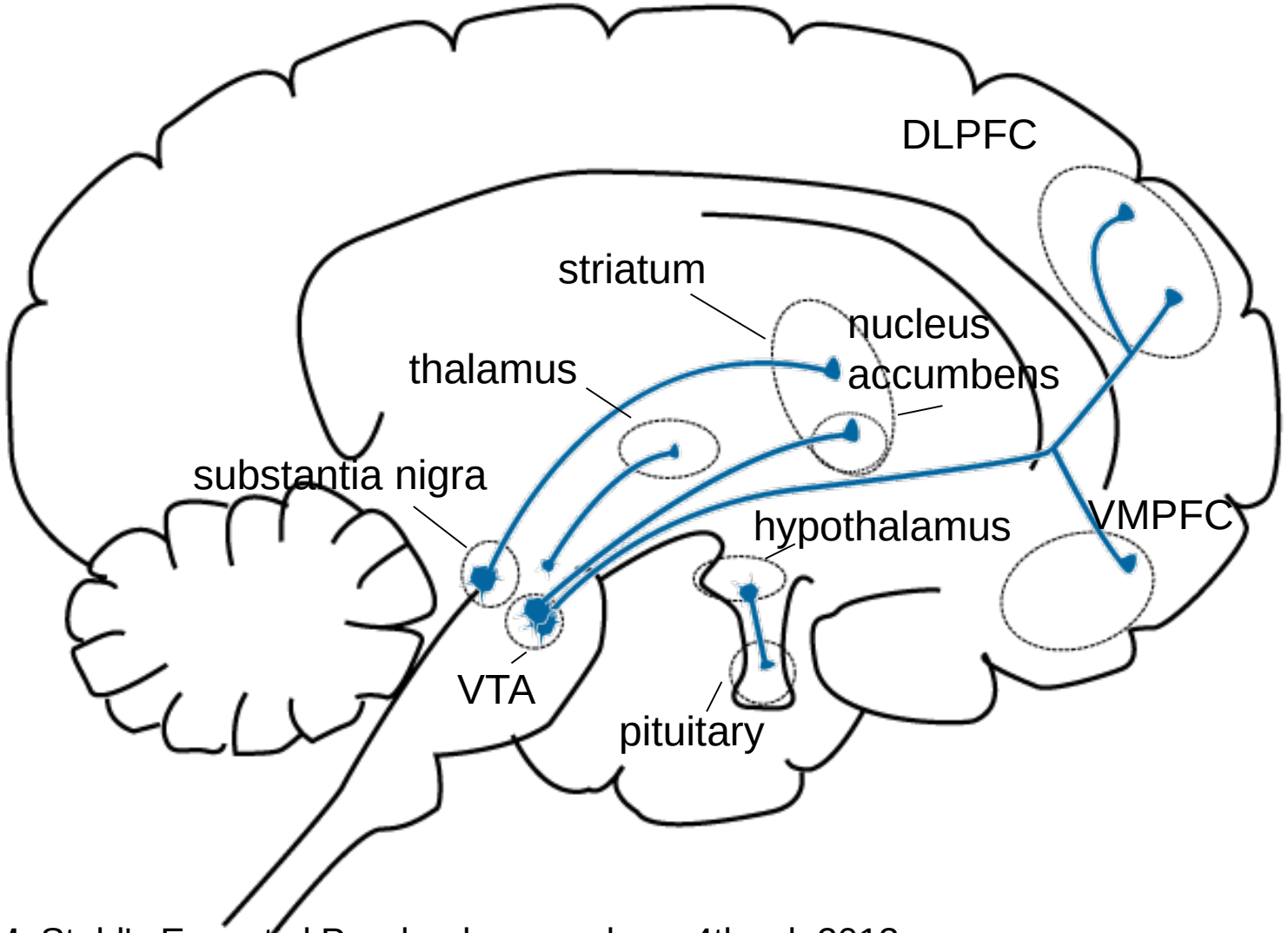
Stahl SM. Stahl's Essential Psychopharmacology. 4th ed; 2013.

Why aren't negative symptoms sufficiently improved with dopamine 2 antagonists? (cont.)

mesolimbic



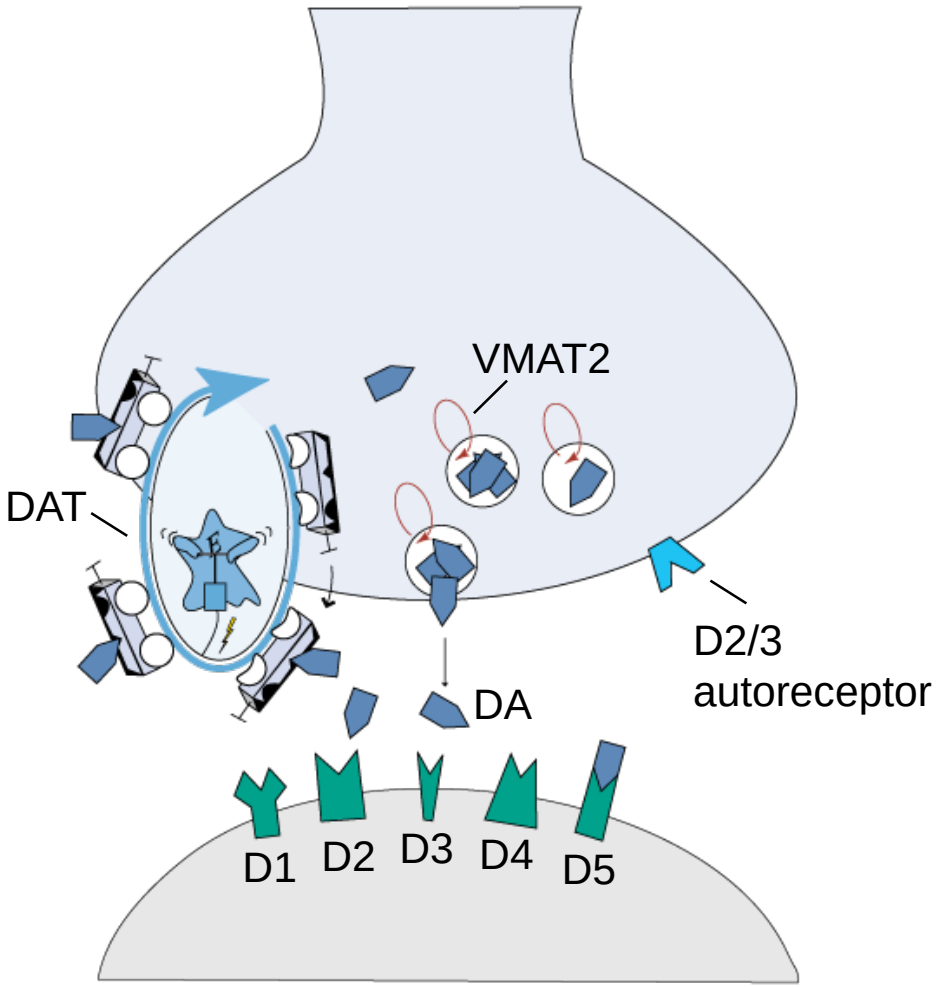
mesocortical reward circuits



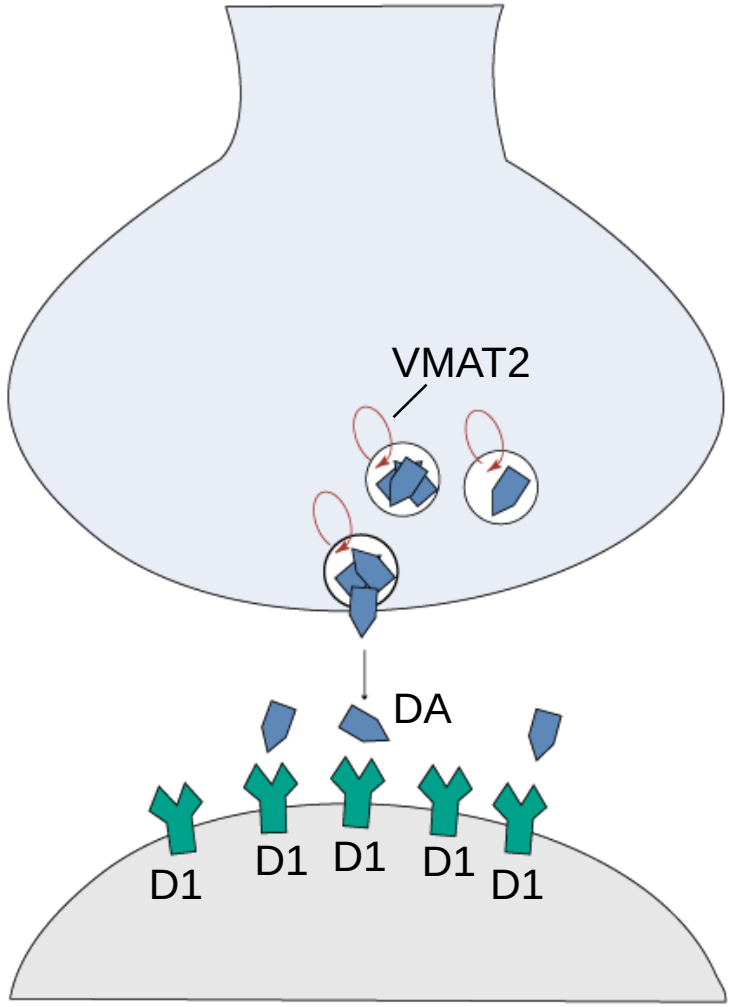
Stahl SM. Stahl's Essential Psychopharmacology. 4th ed; 2013.

Overview of the Dopamine Synapse

In the striatum

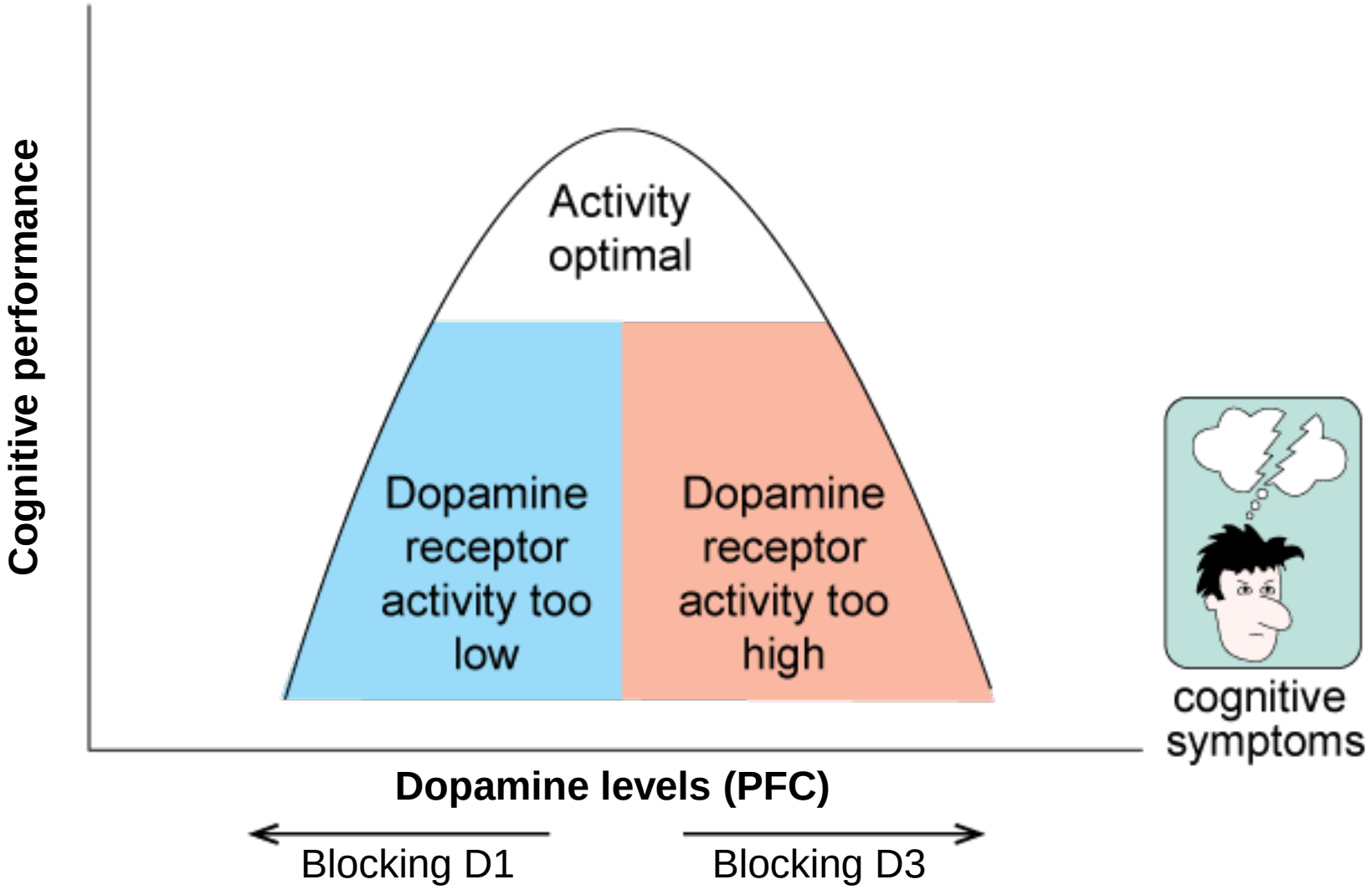


In the prefrontal cortex



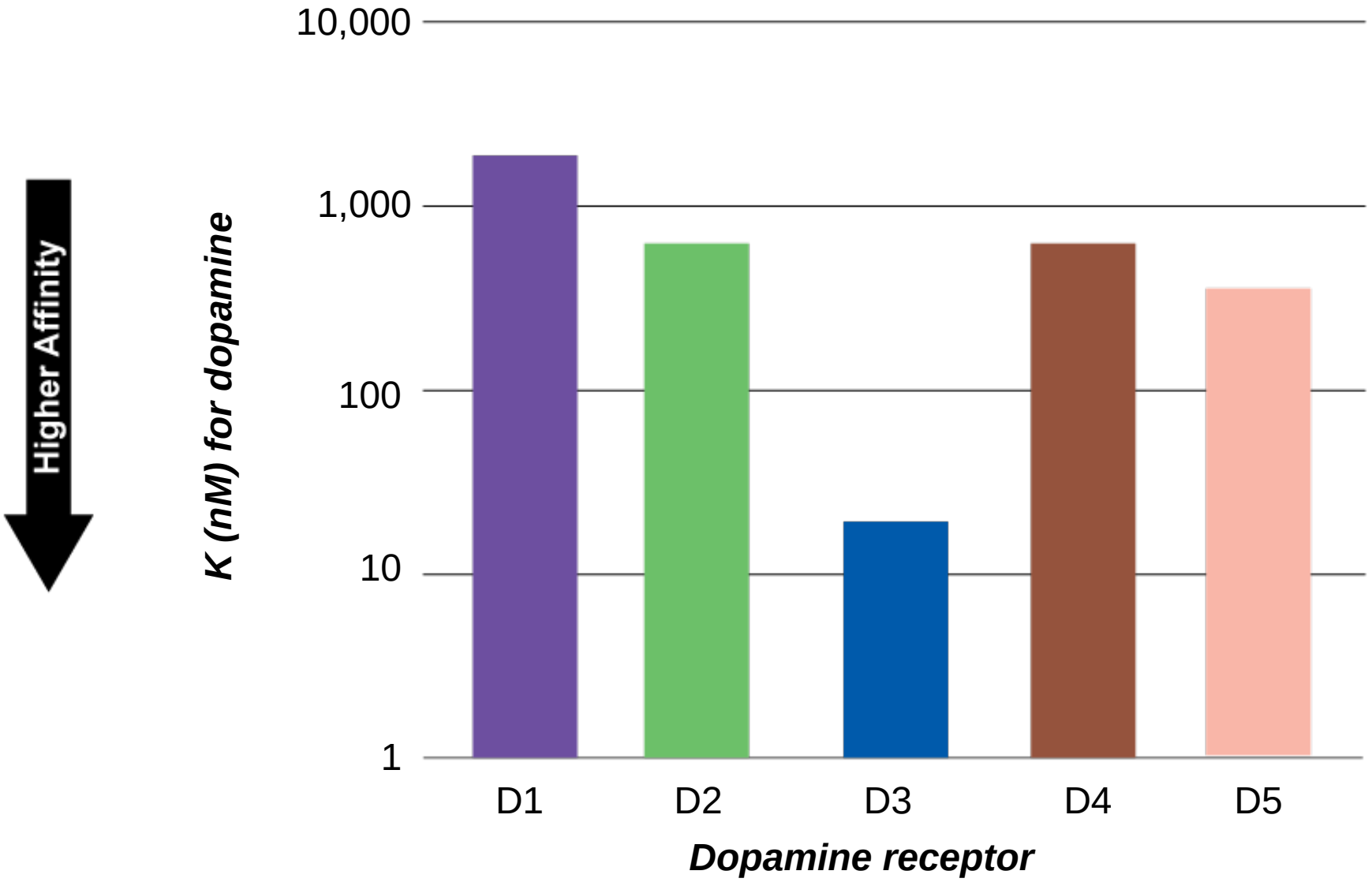
Stahl SM. CNS Spectrums 2017;22:305-11.

Functional Output of Cortical Dopamine and Cognition



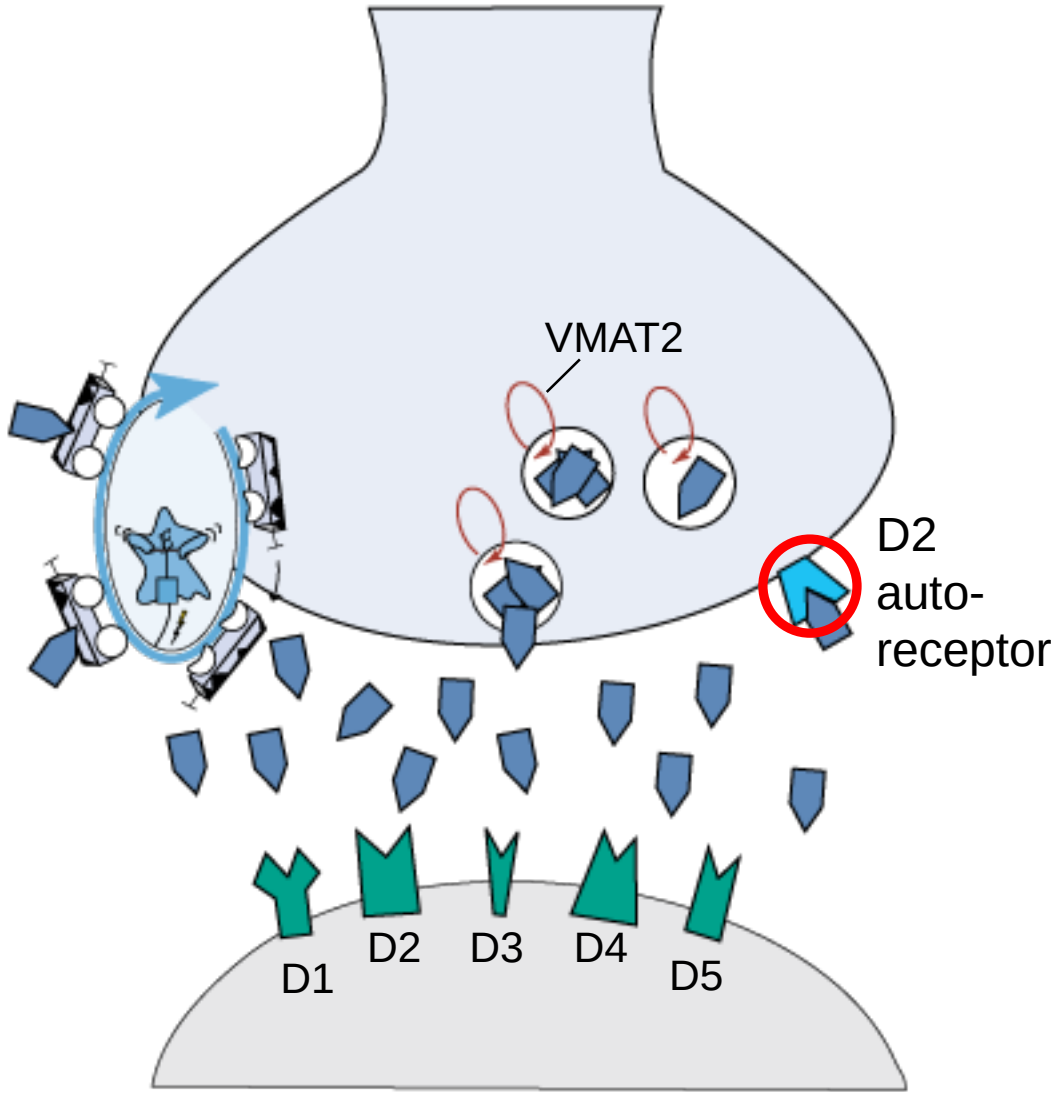
Stahl SM. CNS Spectrums 2017;22:305-11.

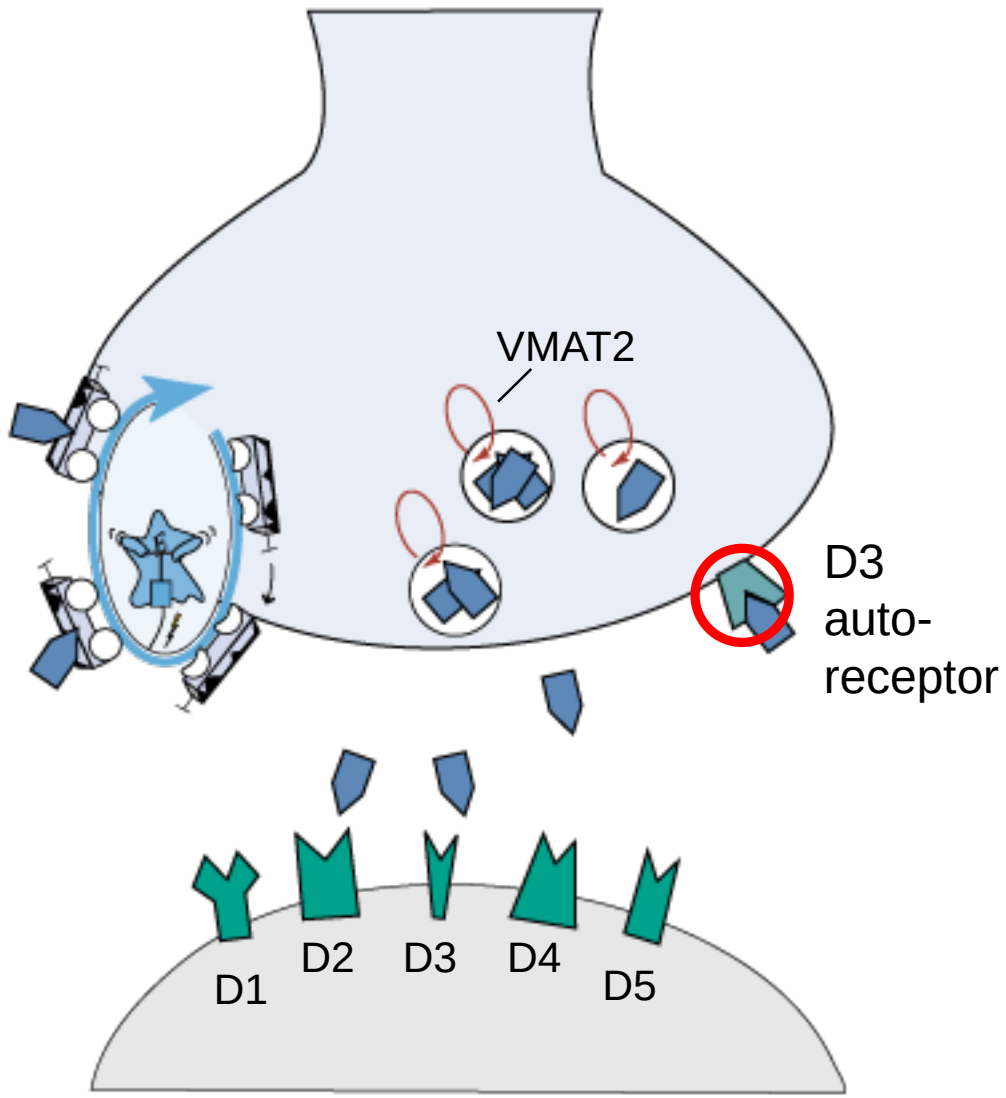
Dopamine Receptor Affinities



Stahl SM. CNS Spectrums 2017;22:305-11.

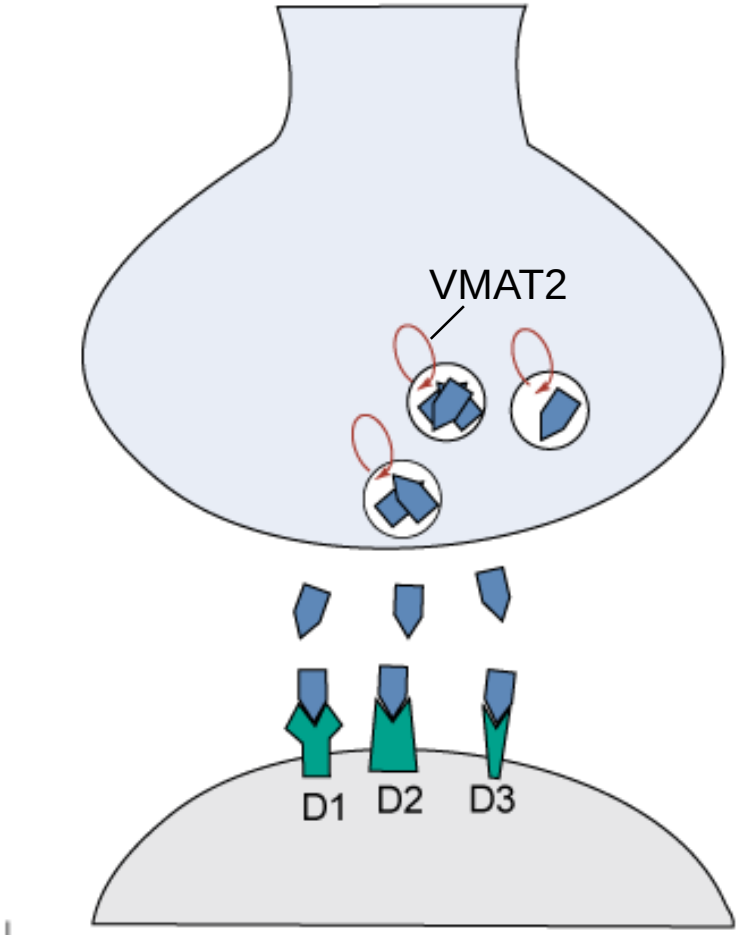
Regulation of Dopamine Levels at the Synapse





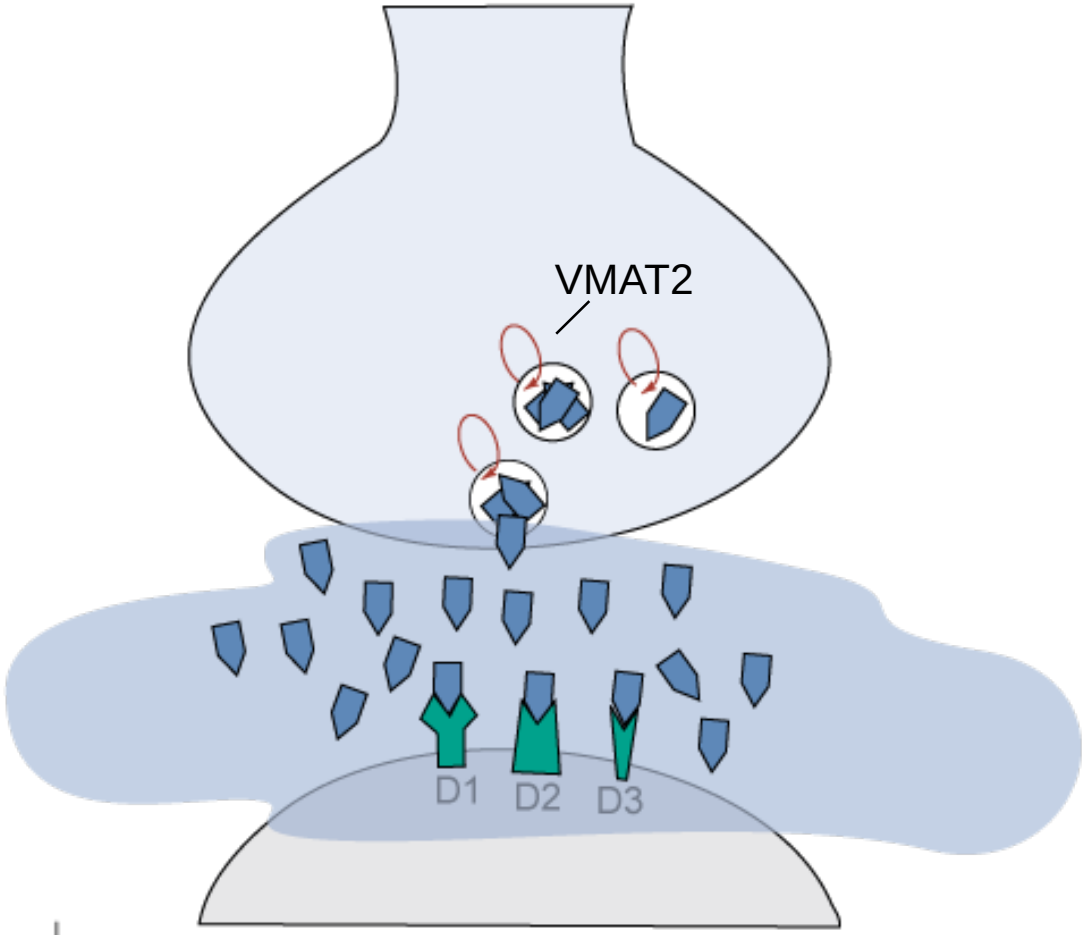
Stahl SM. CNS Spectrums 2017;22:305-11.

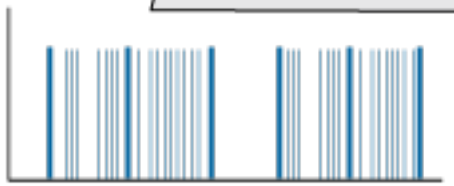
Receptor affinities dictate neuronal response to tonic and phasic firing.



- Slow, irregular
- Sets background DA level

Tonic firing

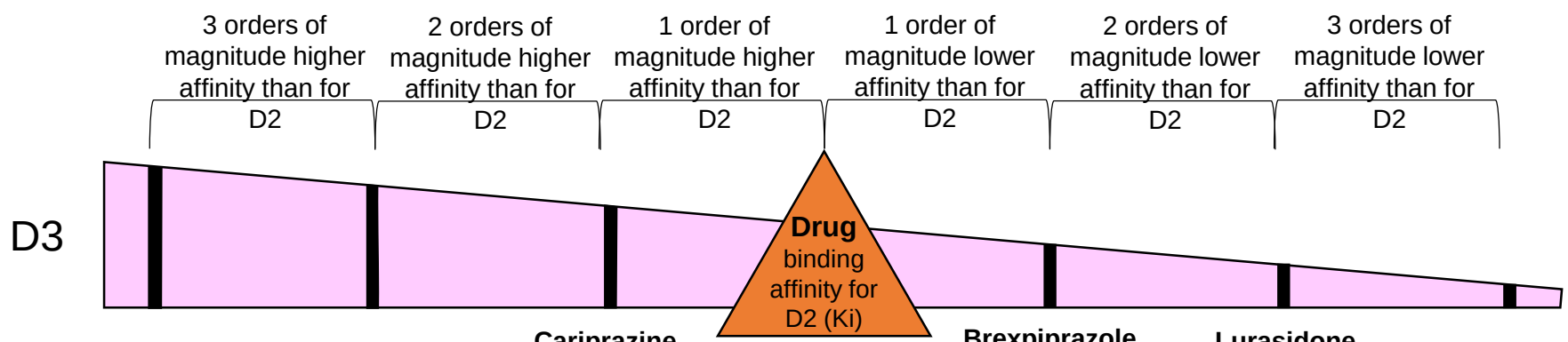




- Rapid, synchronous burst
- Spike in extracellular DA

Phasic firing

Stahl SM. CNS Spectrums 2017;22:305-11.



Cariprazine binding affinity for D3 (0.09nM)

Blonanserin binding affinity for D3 (0.49nM)

Asenapine binding affinity for D3 (1.8nM)

Paliperidone binding affinity for D3 (2.6nM)

Aripiprazole binding affinity for D3 (4.6nM)

Risperidone binding affinity for D3 (7.3nM)

Ziprasidone binding affinity for D3 (7.3nM)

Olanzapine binding affinity for D3 (38.1nM)

Clozapine binding affinity for D3 (310nM)

Quetiapine binding affinity for D3 (394nM)

Brexpiprazole binding affinity for D3 (1.1nM)

Iloperidone binding affinity for D3 (10.5nM)

Lurasidone binding affinity for D3 (15.7nM)

Conclusions

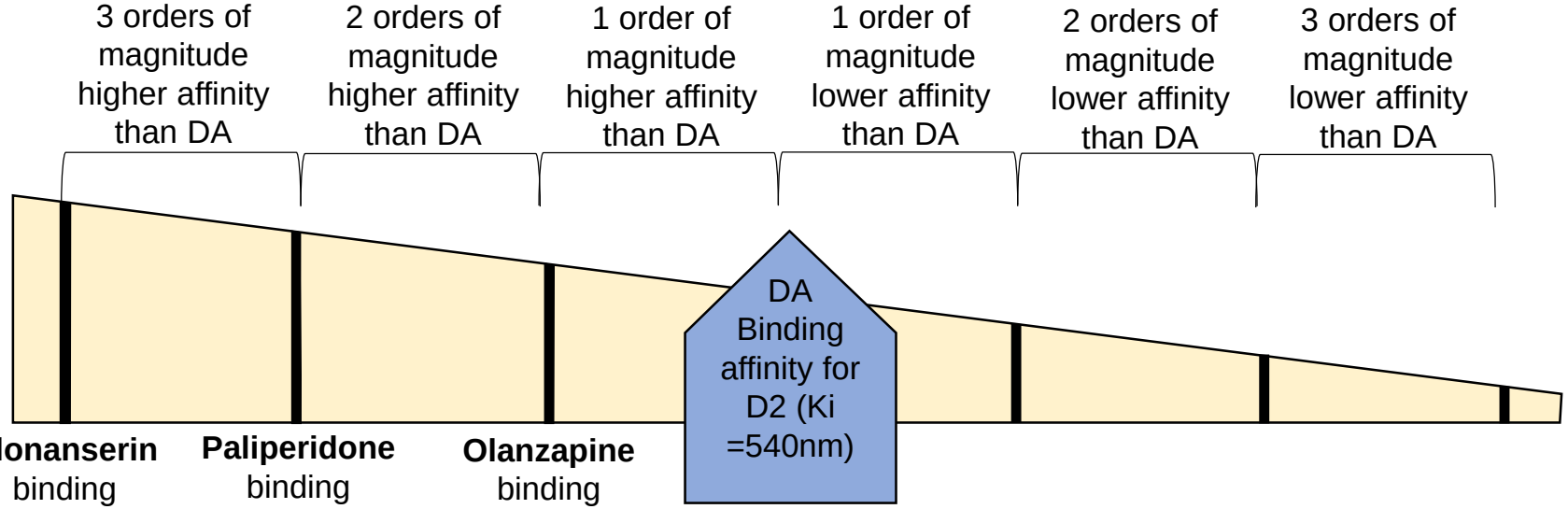
- Most antipsychotics have about the same affinity for D3 receptors as they have for D2 receptors
- Cariprazine has somewhat higher affinity for D3 receptors than for D2 receptors
- Lurasidone, brexpiprazole, and iloperidone have lower affinity for D3 receptors than for D2 receptors

So what?

- It’s not about an antipsychotic’s relative affinities for D1 and D3 receptors compared to D2 receptors

- At antipsychotic doses, and in the presence of dopamine…it’s about an antipsychotic’s relative affinity for dopamine receptors compared to **Dopamine’s** affinity for those receptors

- The one with the highest affinity “wins”



Blonanserin binding affinity for D2 (0.14nM)

Brexpiprazole binding affinity for D2 (0.3nM)

Cariprazine binding affinity for D2 (0.49nM)

Lurasidone binding affinity for D2 (0.66nM)

Paliperidone binding affinity for D2 (1.4nM)

Asenapine binding affinity for D2 (1.7nM)

Aripiprazole binding affinity for D2 (2.3nM)

Risperidone binding affinity for D2 (3.7nM)

Ziprasidone binding affinity for D2 (4.75nM)

Iloperidone binding affinity for D2 (8.3nM)

Olanzapine binding affinity for D2 (30.8nM)

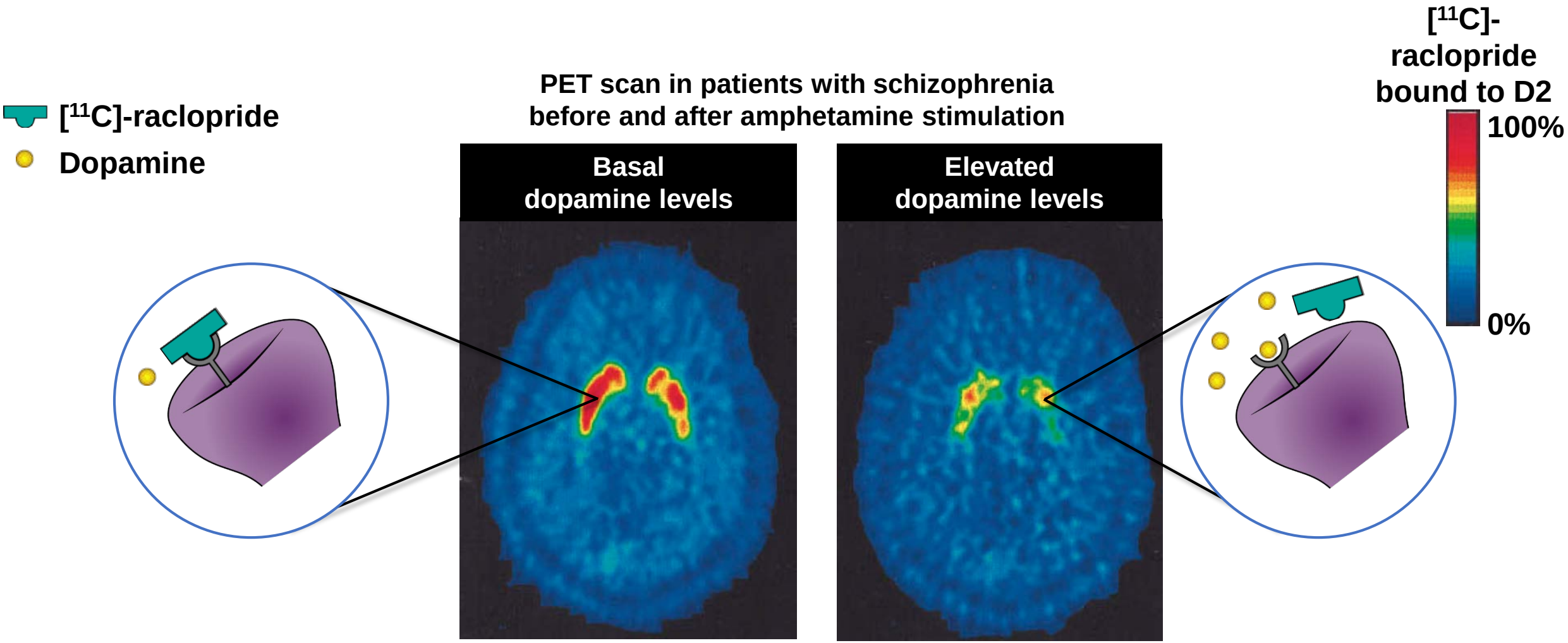
Clozapine binding affinity for D2 (147nM)

Quetiapine binding affinity for D2 (437nM)

Conclusions

- Every antipsychotic has the same or higher affinity for D2 receptors as dopamine has for D2 receptors
- Not surprising, because if they didn’t they wouldn’t be antipsychotics
- However…

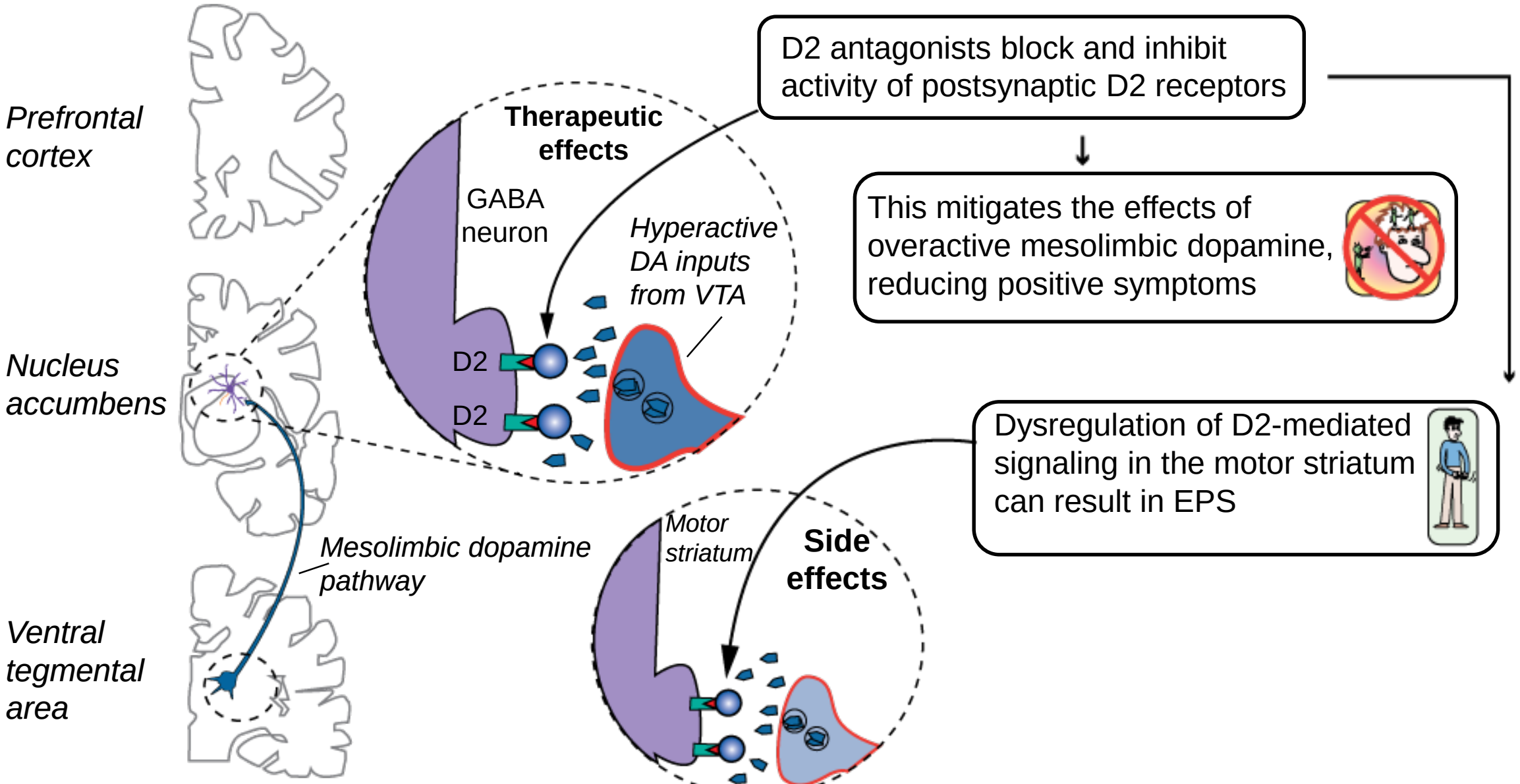
Dopamine can displace antipsychotics from D2.



Dopamine overflow was stimulated by amphetamine injection (0.2 mg/kg) in schizophrenia patients

Breier A et al. PNAS 1997;94:2569-74.

Antagonist/Partial Agonist Effects at D2 Dopamine Receptors

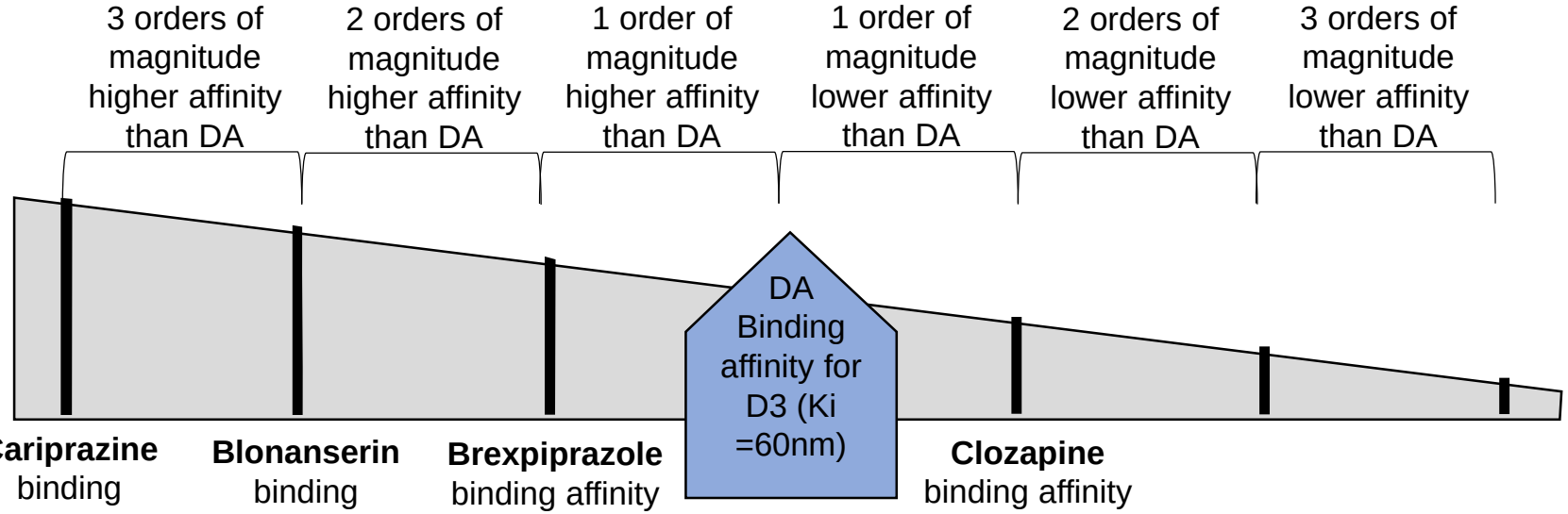


D2 antagonists block and inhibit activity of postsynaptic D2 receptors

This mitigates the effects of overactive mesolimbic dopamine, reducing positive symptoms

Dysregulation of D2-mediated signaling in the motor striatum can result in EPS

Stahl SM. CNS Spectrums 2017;22:375-84.



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Risperidone binding affinity for D3 (7.3nM)

Ziprasidone binding affinity for D3 (7.3nM)

Iloperidone binding affinity for D3 (10.5nM)

Lurasidone binding affinity for D3 (15.7nM)

Olanzapine binding affinity for D3 (38.1nM)

Clozapine binding affinity for D3 (310nM)

Quetiapine binding affinity for D3 (394nM)

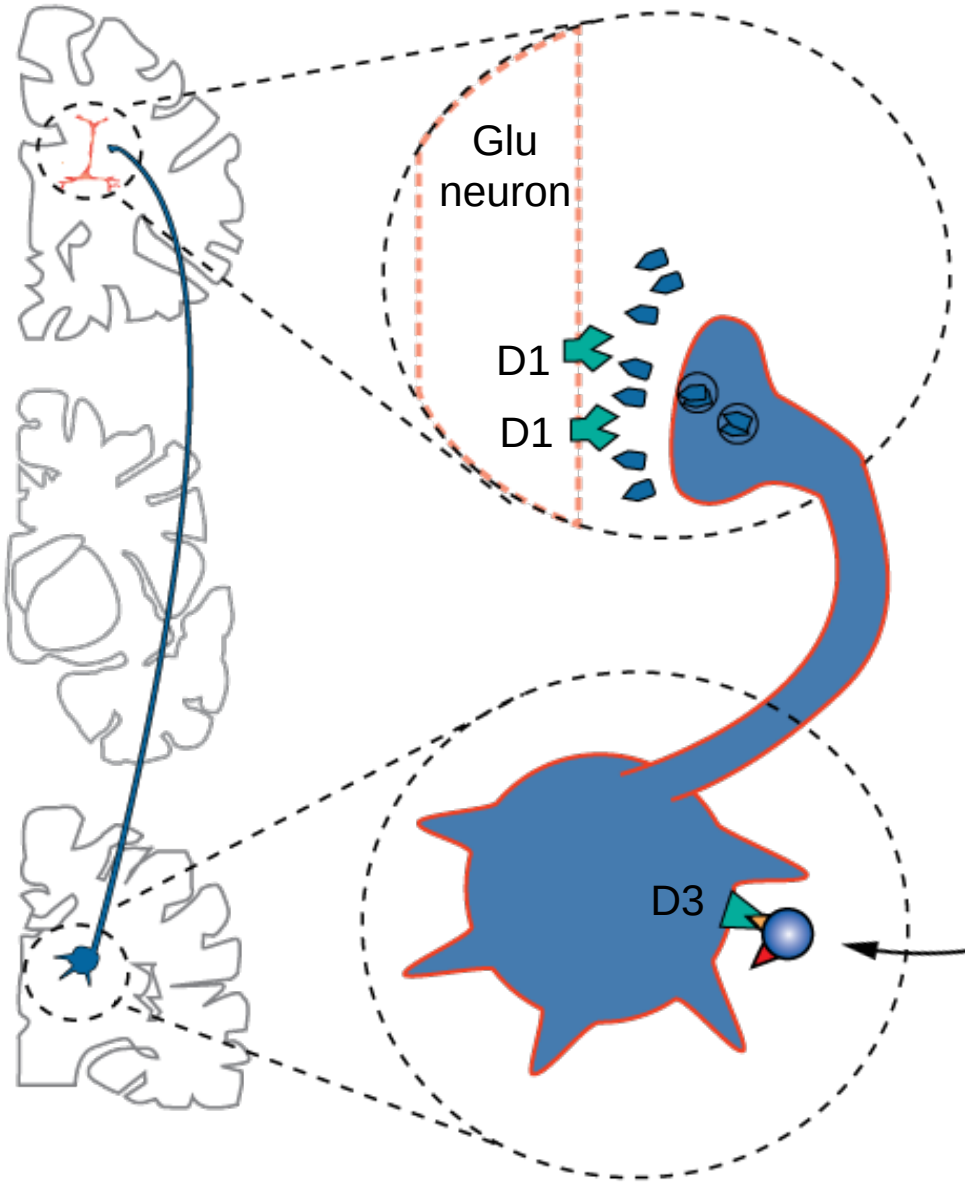
Conclusions

- Almost all antipsychotics have about the same affinity for D3 receptors as dopamine, resulting in little net D3 blockade in the presence of dopamine and at antipsychotic doses
- However, two antipsychotics have even higher affinity for D3 receptors than dopamine does, and do result in net blockade of D3 receptors
  - cariprazine > blonanserin

Who cares if you block D3 receptors?

- Increased dopamine delivery to prefrontal cortex and possibly limbic striatum
- Disinhibition of D3 autoreceptors, especially in the VTA/SN
- Enhancement of mood, cognition, negative symptoms, apathy, anhedonia?

Antagonist/Partial Agonist Effects at D3 Dopamine Receptors



Increased DA release in the PFC re-regulates aberrant cortical activity and could theoretically improve negative symptoms and cognitive impairment

↑

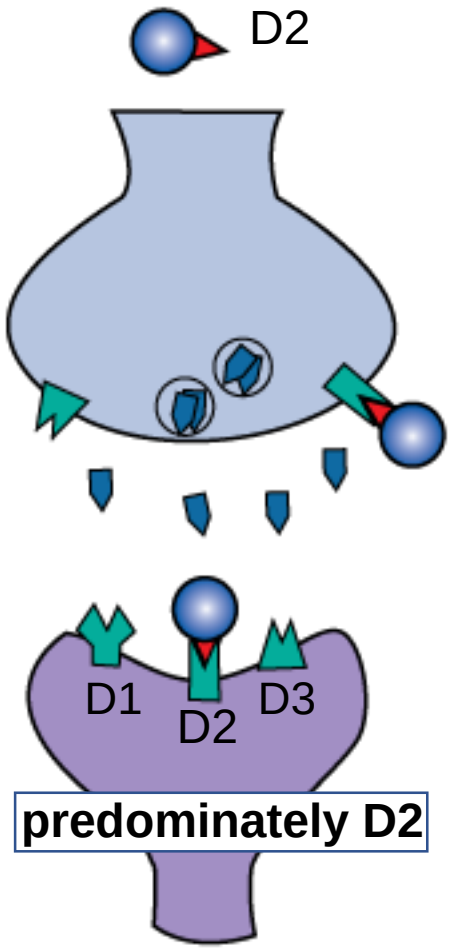
This results in an increase in DA release in the PFC

↑

D3 antagonists/partial agonists block and inhibit the activity of somatodendritic D3 receptors

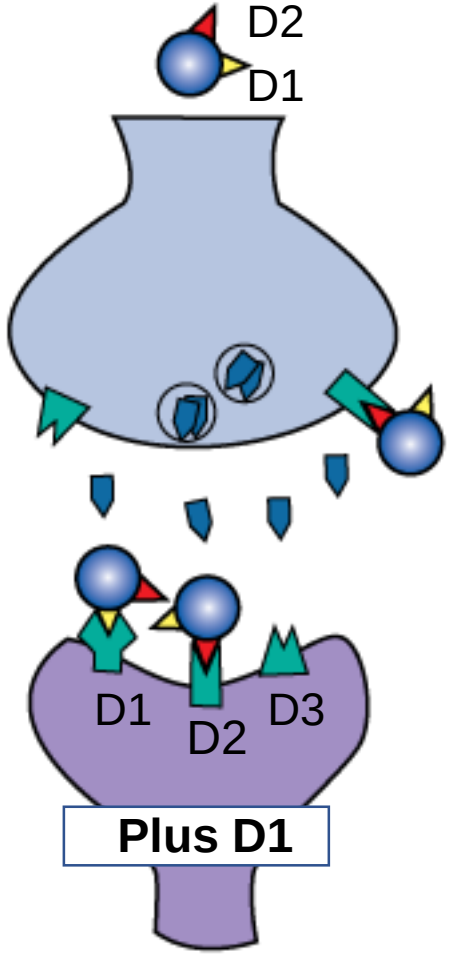
Stahl SM. CNS Spectrums 2017;22:375-84.

Summary:
Antipsychotic Binding at Dopamine Receptors



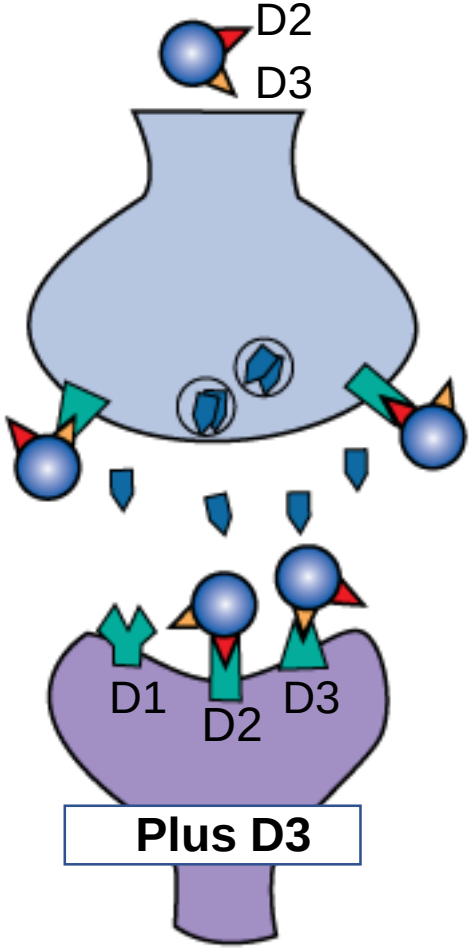
predominately D2

brexpiprazole
paliperidone
aripiprazole
risperidone
ziprasidone
iloperidone
lurasidone
quetiapine



Plus D1

asenapine
olanzapine
clozapine

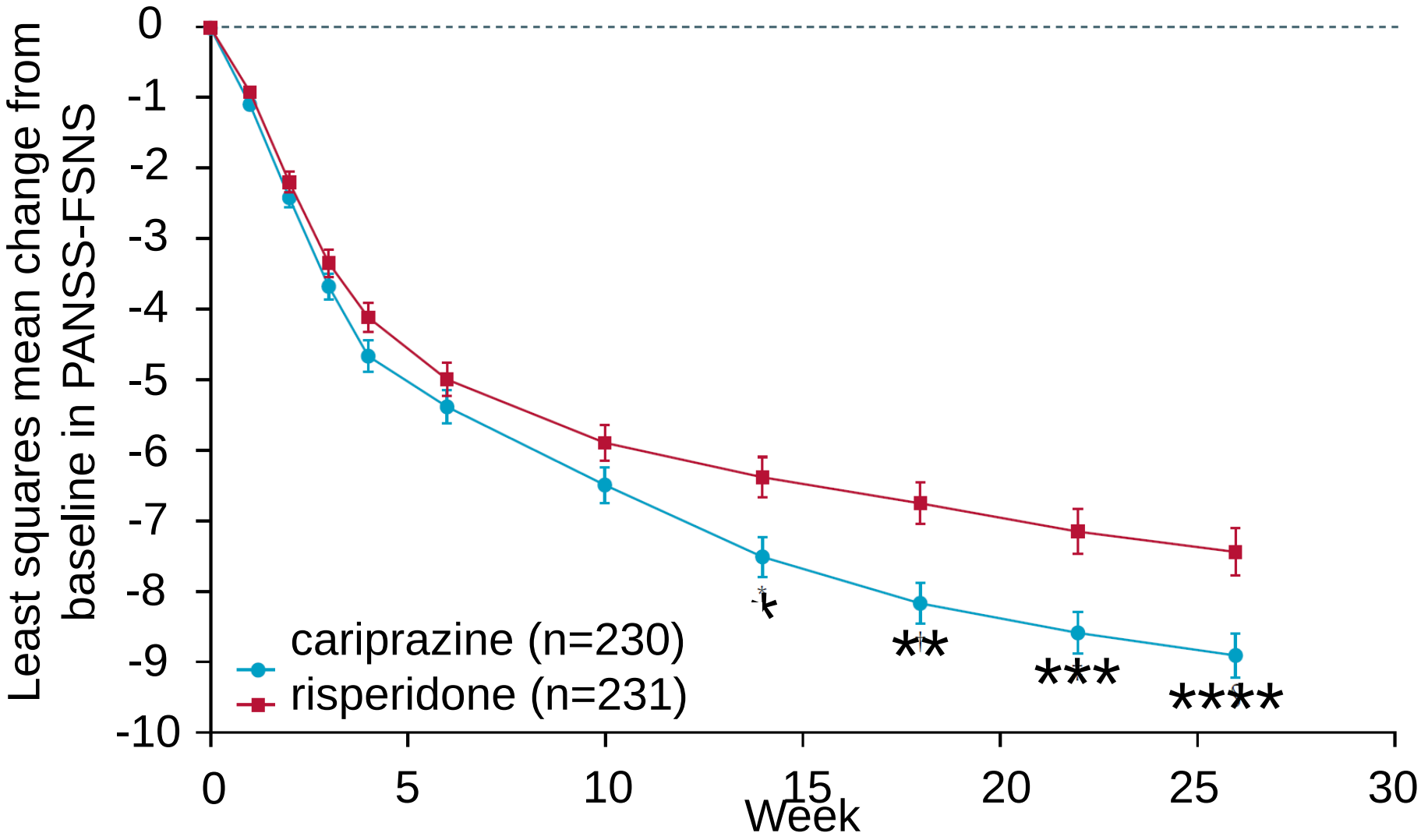


Plus D3

cariprazine
blonanserin

Stahl SM. CNS Spectrums 2017;22:375-84.

D3 (Cariprazine) vs. D2 (Risperidone) for Negative Symptoms

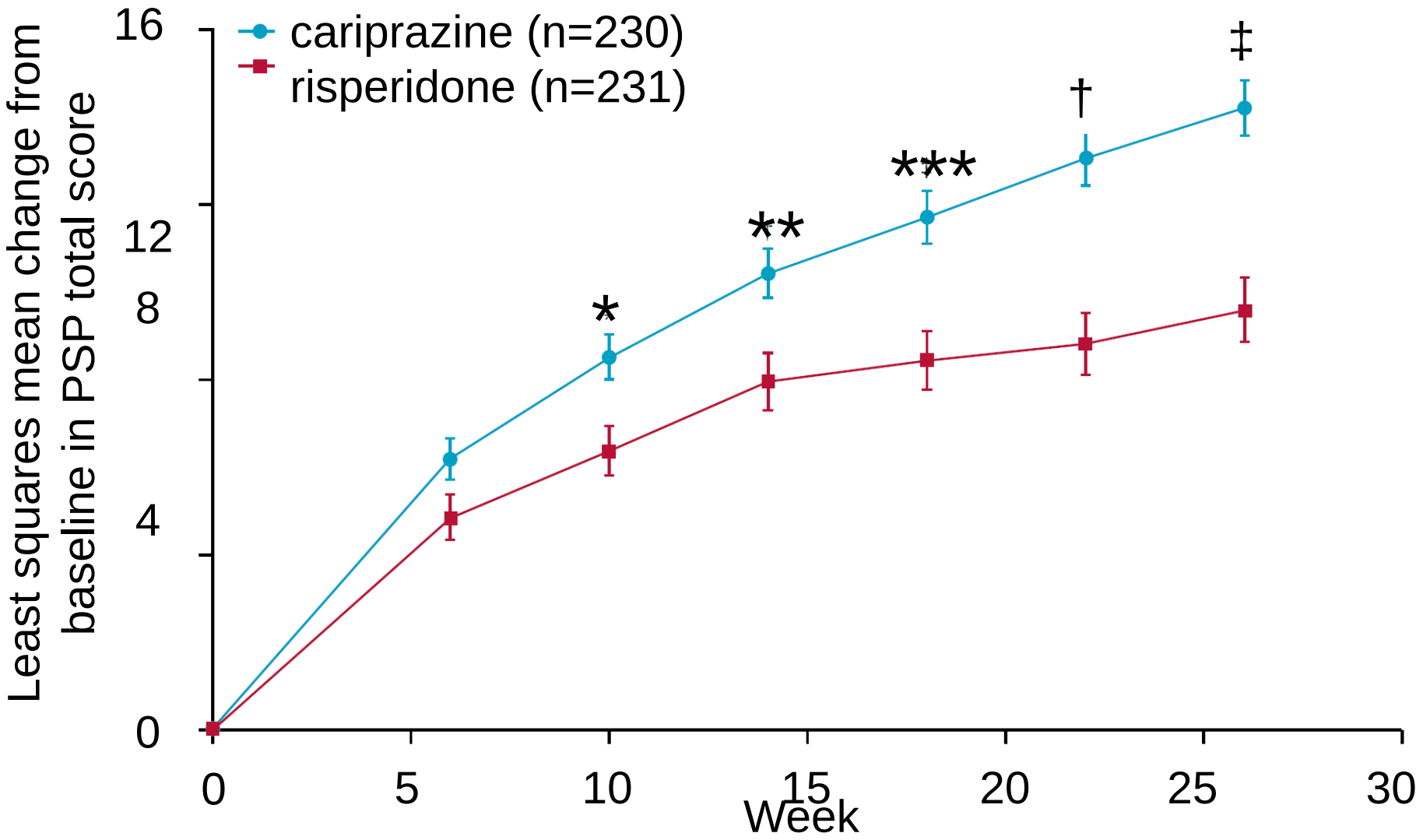


*p=0.0079
**p=0.0011
***p=0.0016
****p=0.0022

p=0.0092 for the overall treatment effect of cariprazine versus risperidone

Nemeth G et al. Lancet 2017;389:1103-13.

D3 (Cariprazine) vs. D2 (Risperidone) for Negative Symptoms (cont.)



*p=0·0053.
**p=0·0046.
***p=0.0004
† p<0.0001
‡ p<0.0001

PSP: Personal and social performance

Nemeth G et al. Lancet 2017;389:1103-13.

Treatment of Negative Symptoms: Other Strategies

- **Exercise** - Meta-analyses show moderate effect of aerobic exercise and yoga
- **Music therapy** - Meta-analysis show large significant effect compared to treatment as usual (TAU)
- **Cognitive behavioral therapy** - Recent meta-analysis of 30 studies did not find beneficial effect
- **Cognitive remediation therapy (CRT)**
- **High frequency repetitive transcranial magnetic stimulation (HF-rTMS)**

Veerman SRT et al. Drugs 2017;77:14723-59. Cella M et al. Clin Psych Rev 2017;52:43-51.

CRT Effectiveness

- Current evidence suggests that CRT is associated with both neurobiological and cognitive improvement in patients with schizophrenia
- Studies indicate that CRT affects several brain regions and circuits, including prefrontal, parietal, and limbic areas, both in terms of activity and structure
- Changes to prefrontal areas are the most reported finding, fitting to previous evidence of dysfunction in this region

Thorsen et al. Frontiers in Psychiatry 2014;5(103):1-9.

Neuroimaging and CRT

- CRT group exhibited significantly greater improvements than the TAU group in verbal fluency (p=0.012)
- CRT group demonstrated significantly greater improvements than the TAU group in global cognitive scores (p=0.049)
- CRT group also exhibited significantly greater hippocampal volume than in the TAU group (p <0.001)
- Changes in verbal fluency scores and right hippocampal volumes were positively correlated
- Results suggest that CRT induces cognitive improvement through hippocampal plasticity

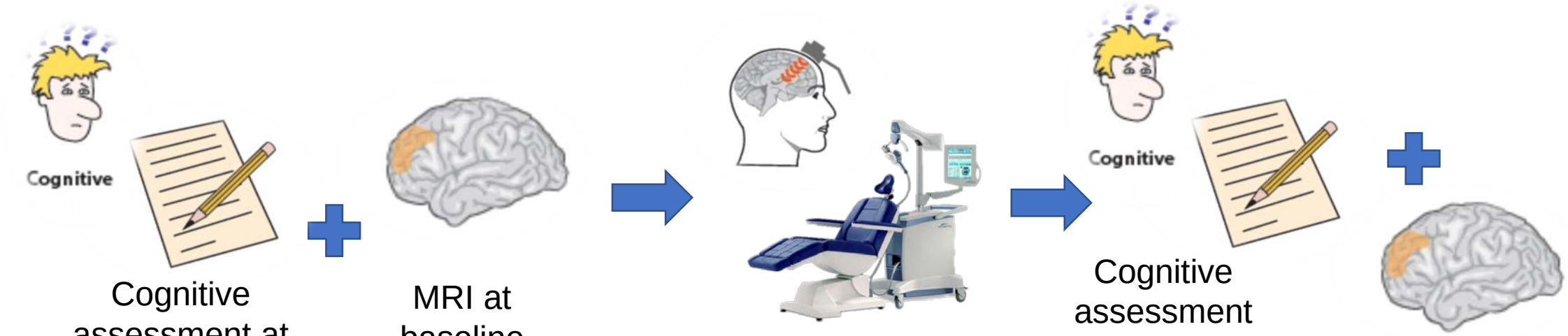
Morimoto et al., BMC Psychiatry 2018;18(83):1-8.

Transcranial Magnetic Stimulation for Treatment of Schizophrenia

- Recent pilot study: bilateral high frequency repetitive transcranial magnetic stimulation (HF-rTMS) on cognitive function in patients with early-phase psychosis
- Over 2 weeks, 21 subjects underwent ten sessions of HF, bilateral, sequential rTMS over the dorsolateral prefrontal cortex (DLPFC) or sham
- Participants completed a cognitive assessment and MRI prior to and after completion of the study
- Those who received rTMS displayed improvement on a standardized cognitive battery test both immediately following the course of study treatment and at follow-up two weeks later
- MRI results indicated that left frontal cortical thickness at baseline was correlated with treatment response
- Study treatment was safe and well tolerated
- rTMS may be an effective treatment of cognitive dysfunction in the early phase of psychosis

Francis et al. Brain Imaging Behavior 2018; doi.org/10.1007/s11682-018-9902-4.

Transcranial Magnetic Stimulation for Treatment of Cognitive Impairment in Schizophrenia



Cognitive assessment at baseline

MRI at baseline

Pilot study: 21 participants

2 weeks; ten sessions
HF, bilateral sequential rTMS over DLPFC or sham

Cognitive assessment at end of study

MRI at end of study

Results:

- rTMS improved scores on standardized cognitive battery test both immediately after study treatment and at follow-up two weeks after
- MRI results indicated that left frontal cortical thickness at baseline was correlated with treatment response

Francis et al. Brain Imaging Behavior 2018; doi.org/10.1007/s11682-018-9902-4.

MANAGING ADVERSE EFFECTS

Monitoring Challenging Adverse Effects

- Antipsychotic (AP)-related weight gain
- Extrapyramidal Symptoms (EPS)
- Akathisia

Weight Gain & Antipsychotics

- Most antipsychotics
  - Younger and AP naive patients are more sensitive
- Tip: don’t just look at **mean** change in weight; also look at proportion of patients in each group who gained or lost ≥ 7% of baseline body weight
- Tip: **must compare to placebo**
- Mechanisms: H1 or 5HT2C blockade

Weight Gain Management: Let's Prescribe Metformin More Often

- Metformin reduces weight, BMI, fasting glucose, fasting insulin, triglycerides, and total cholesterol
- Of treatments for antipsychotic-induced weight gain/metabolic abnormalities, metformin was the most effective
- Average weight loss: 6.5 lbs
- Hypoglycemia is rare with metformin, and the risk of lactic acidosis is extremely low until eGFR is < 30 mL/min
  - Reevaluate metformin if eGFR < 45 mL/min, and stop if < 30 mL/min

Zheng et al., 2015 (PMID: 26280837). Maayan et al., 2010 (PMID: 20336059); Kirpichnikov et al., 2002 (PMID: 12093242); Lipska KJ Diabetes Care 2011; 34: 1431-37 (PMID 21617112).

Metformin: for Whom

- Metformin works whether or not there is increased blood sugar or hemoglobin A1C
- Who is most likely to respond?
    1. Younger patients
    2. Recently started on the antipsychotic
    3. Before weight gain (to prevent it)
    4. Early on if weight gain occurs

Standard titration: 500 mg qam the first week. Increase by 500 mg/wk if tolerated to 1000 mg BID. Use extended release formulation if GI adverse effects.

Jarskog et al., 2013 (PMID: 23846733);
Hasnain and Viewing, 2013 (PMID: 23659558).

Combination of Metformin and Lifestyle Intervention

- Recent meta-analysis of six RCTs: metformin, placebo, or metformin and lifestyle combination (MLC)
- MLC group had significant reduction in weight and body mass index
- Less frequent weight gain of ≥ 7% in the MLC group over placebo
- No other group differences in total adverse drug reactions, total psychopathology, and all-cause discontinuation
- Combining metformin and lifestyle intervention significantly reduces AP-related weight gain

Zheng et al. Pharmacopsychiatry 2018;Epub ahead of print.

Weight Gain Management: Topiramate

- Eight RCTs for weight gain on second-generation antipsychotics
- Mean decrease in weight: 6.2 lbs
- Which (again) means—many of the patients lost more than that

Mahmood et al., 2013 (PMID: 23277264).

Weight Gain Management: Topiramate Considerations

BUT:

- **Cognitive dulling**
- Risk of renal stones
- Drug interactions

Ellinger et al., 2010 (PMID: 20233913).

What are extrapyramidal signs (EPS) and extrapyramidal side effects (EPSE)?

- Movement disorders that occur with antipsychotics
- Thought to involve structures outside of the pyramidal tract
- Occur in acute and late (tardive) forms
- Reason for the older term "neuroleptic" to describe antipsychotics

Extrapyramidal Side Effects

- Acute extrapyramidal side effects
  - Dystonia
    - Disturbance in muscle tone leading to prolonged contractions of muscle groups
    - Occurs within 24–48 hours of antipsychotic initiation
    - Only acute EPS that is less common in the elderly
  - Parkinsonism
    - Classic triad of bradykinesia, rigidity, and tremor
    - Occurs within days of starting treatment or dose increase in 1/4 to 1/3 of patients
    - Can occur in up to 75% of older patients

Pathophysiology and Treatment

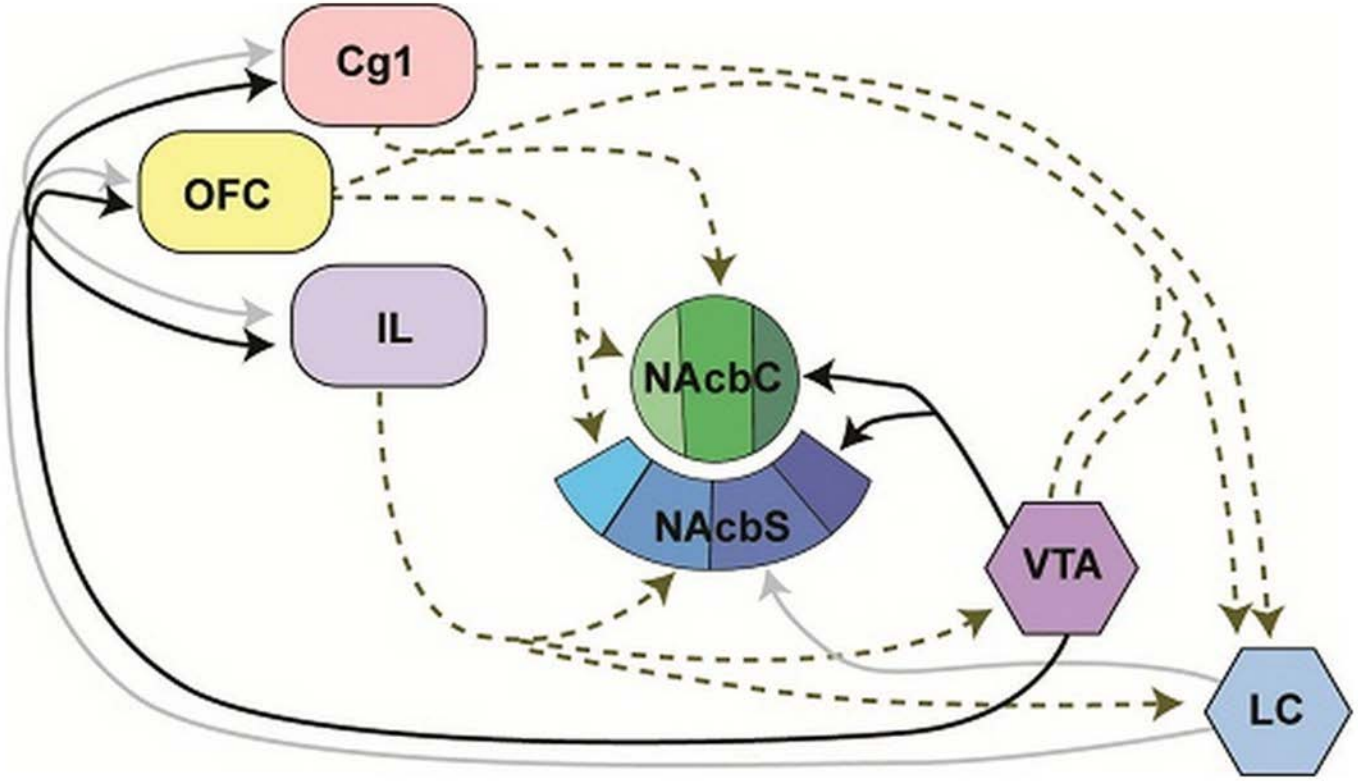
- Pathophysiology
  - Due to D2 blockade in the dorsal striatum

- Treatment
  - Reduction in dose
  - Anticholinergics and other antiparkinsonians (e.g., amantadine) until plasma antipsychotic levels have been reduced below the threshold for motor adverse effects
  - Chronic anticholinergic treatment should be avoided due to adverse cognitive effects and increased ileus risk

Akathisia: Subjective Symptoms

- Often extraordinarily difficult for the patient to describe, to some extent, because there are few subjective states to which it can be compared
- Patients often use terms such as "anxiety" or "itching," although these do not really capture the essence of the condition
- Since many clinicians have never experienced it, there is often a lack of common ground in communicating the problem

Hypothesized Mechanism of Akathisia: the Role of the Nucleus Accumbens



Cg1: cingulate gyrus, 1. OFC: orbitofrontal cortex. IL: infralimbic cortex.
NAcbC: nucleus accumbens core. NAcbS: nucleus accumbens shell.
VTA: ventral tegmental area. LC: locus coeruleus.
Stahl et al. CNS Spectrums 2011: www.neiglobal.com.

Akathisia: Rates in FDA Registrational Trials

Agent	Incident Rates of Akathisia for Schizophrenia
Aripiprazole	10-13% monotherapy; 19-25% with lithium, divalproex, or antidepressants
Asenapine	4-11%
Brexpiprazole	4-7% (dosed 1-4 mg/day)
Cariprazine	9-14%
Clozapine	3%
Iloperidone	1-2%
Lurasidone	6-22%
Olanzapine	3%
Paliperidone	6-9%
Quetiapine	1-4%
Risperidone	5-9%
Ziprasidone	8-10%

BP: bipolar depression. MDD: major depressive disorder. SZ: schizophrenia.

Goldberg, Ernst. Managing the Side Effects of Psychotropic Medications. 2012.

Treatment Strategies for Akathisia

- Dosage reduction
- Change to lower-risk agents if feasible
  - Withdrawal akathisia can occur; allow at least 6 weeks before judging effectiveness of dose reduction/medication switch
- Adjunctive medications

Goldberg, Ernst. Managing the Side Effects of Psychotropic Medications. 2012.

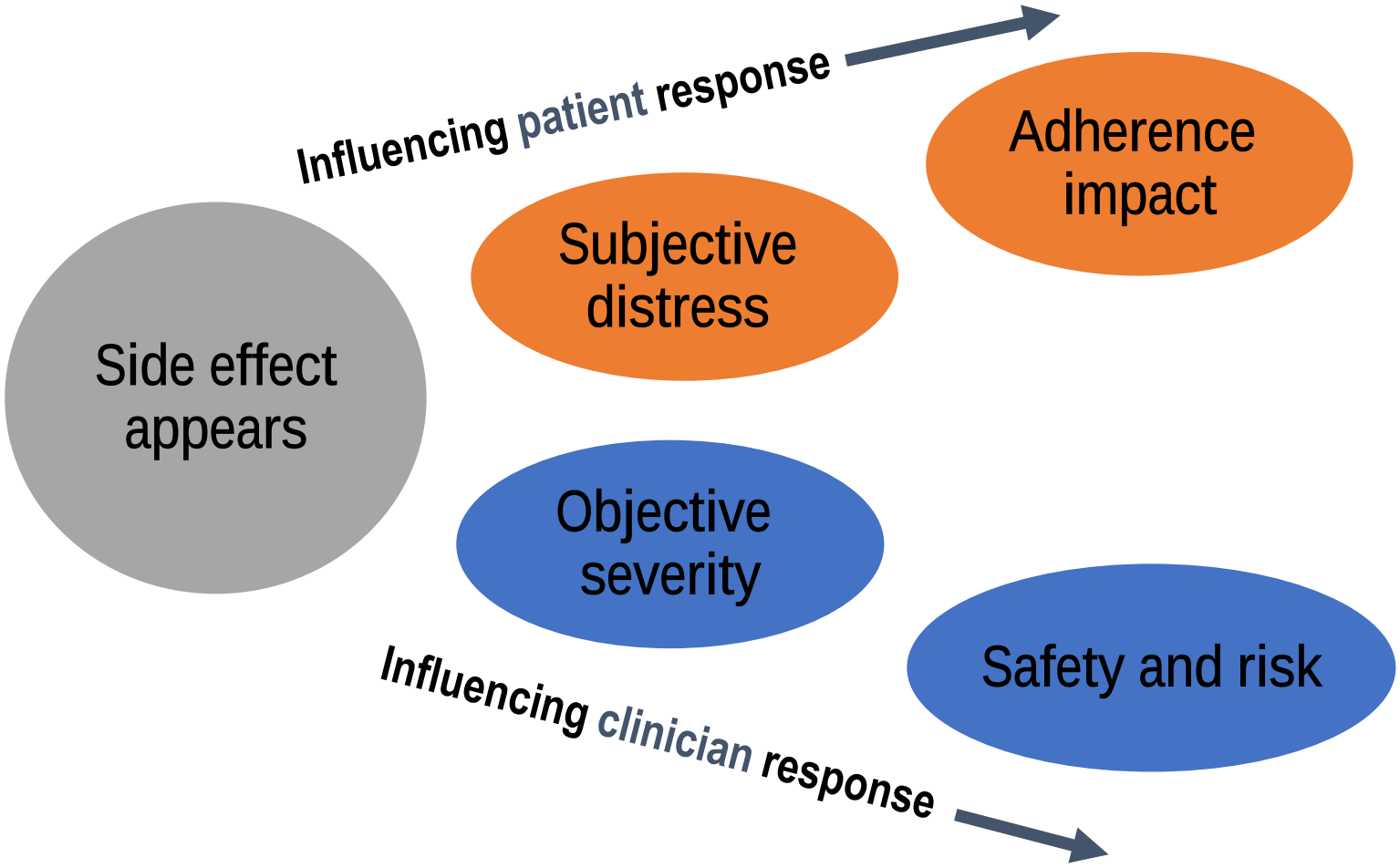
Adjunctive Treatment Strategies for Akathisia

- **Centrally-acting beta blockers**
  - Propranolol: nonselective, lipophilic. Dose: 30-90 mg/day: start at 10 mg BID, increase by 10 mg BID increments as tolerated
  - Betaxolol: $beta_1$, selective, lipophilic 10-20 mg/day
- **Mirtazapine:** 5HT2A antagonist property helps mitigate akathisia
  - 15 mg/day is the most common mirtazapine dose studied; unclear if higher doses are more effective. Avoid if h/o mania
- **Clonazepam**
- Anticholinergics (e.g., benztropine): appear less effective than other agents, and carry the anticholinergic burden. Generally avoided

Rathbone and Soares-Weiser, 2006 (PMID: 17054182);
Laoutidis and Luckhaus, 2014 (PMID: 24286228); Poyurovsky et al., 2006 (PMID: 16497273).

Reverberations From Side Effects

How patient and clinician responses may differ



- Weiden PJ, Buckley PF. J Clin Psychiatry 2007;68(suppl 6):14-23.

Considering the Side Effect Profile When Choosing a Treatment

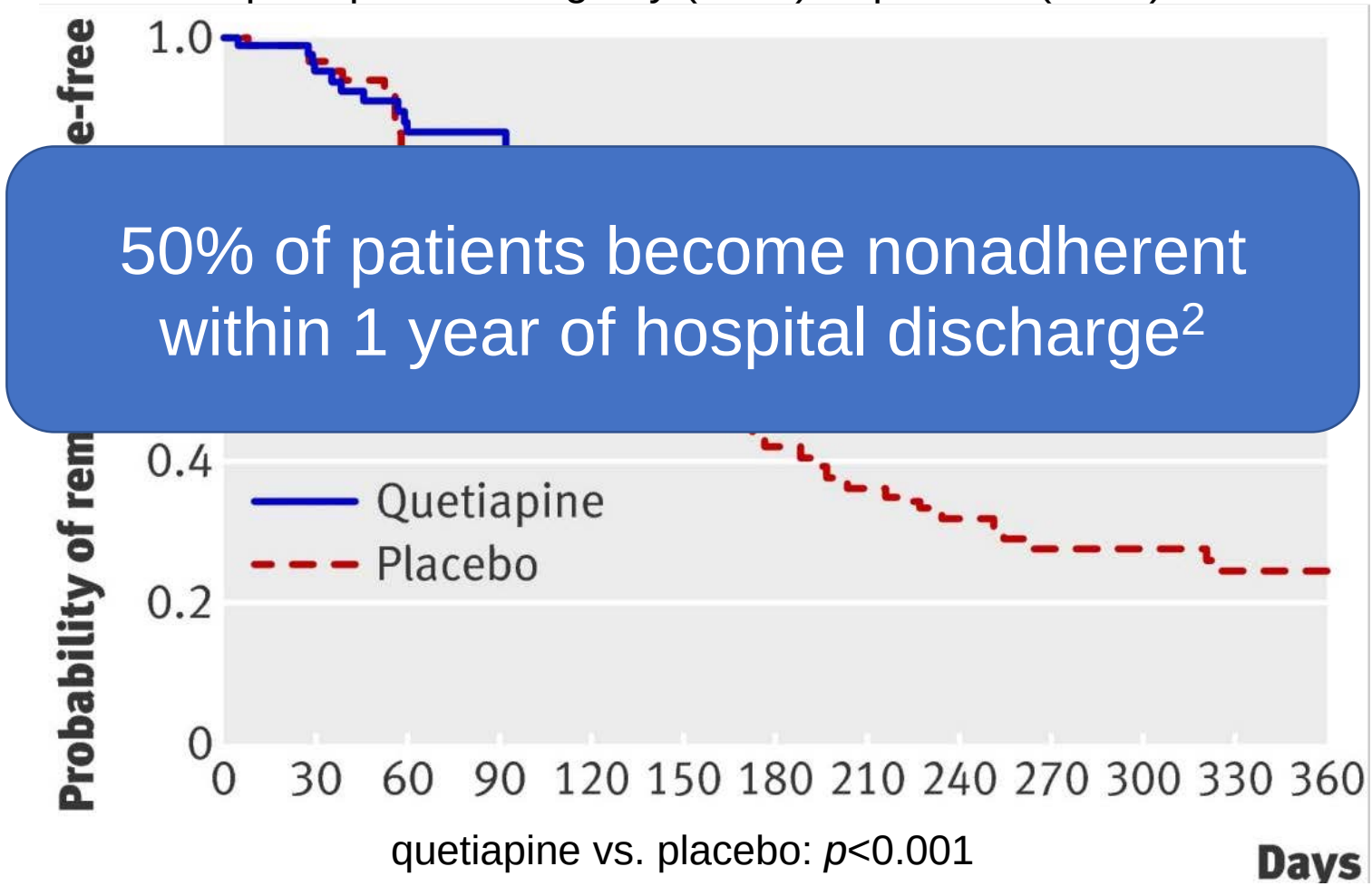
- Important because side effects may:
  - Contribute to treatment nonadherence
  - Limit return to maximal levels of social functioning
  - Potentially contribute to long-term morbidity
- Atypical antipsychotics are better tolerated than typical antipsychotics (mainly due to decreased EPS)
- Differences in drug-specific adverse effect profiles, including metabolic effects, may impact treatment adherence and long-term outcomes

Velligan DI et al. J Clin Psychiatry 2009;70(suppl 4):1-46; Tandon R. Psychiatr Q 2002;73(4):297-311.

NONADHERENCE AND PLASMA LEVELS

Rates of Relapse With Continued vs. Discontinued Treatment

178 asymptomatic patients treated for ≥1 year with AP and randomized to quetiapine 400 mg/day (n=89) or placebo (n=89).[1]



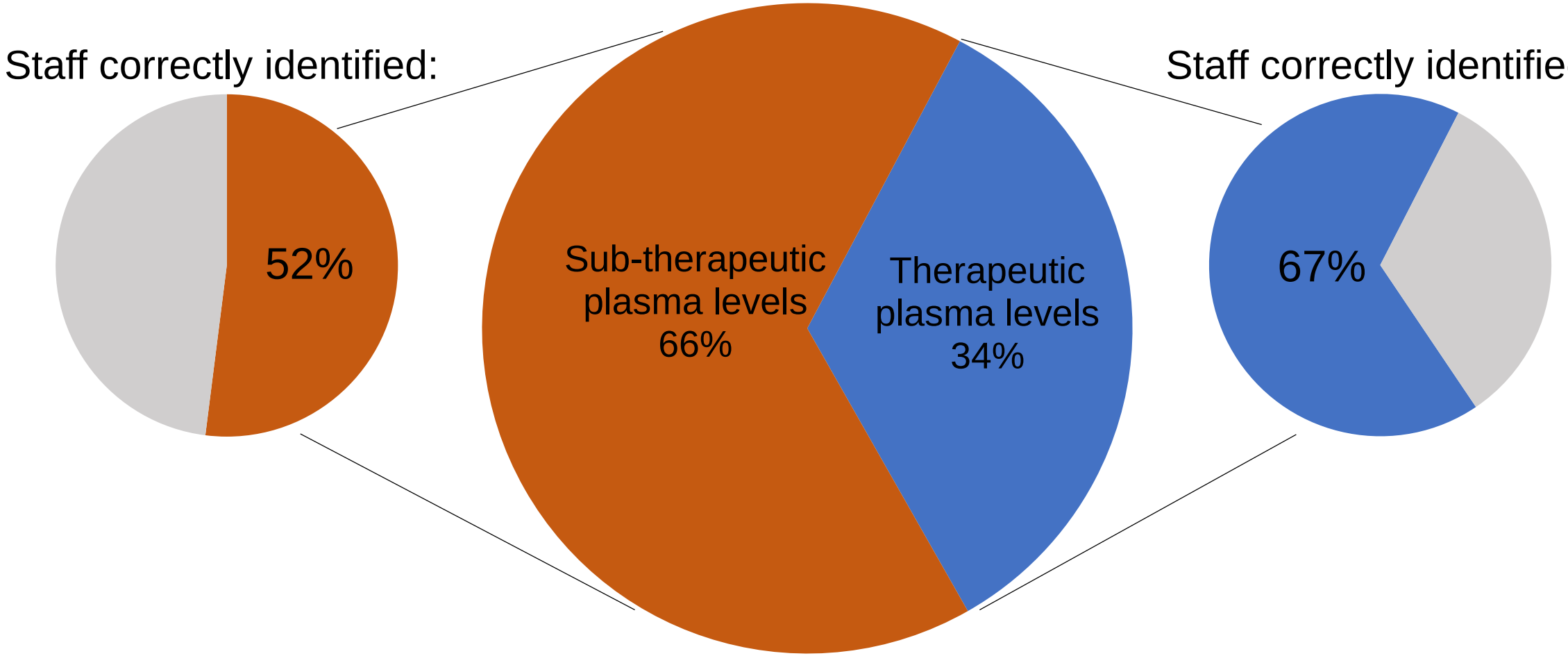
50% of patients become nonadherent within 1 year of hospital discharge[2]

quetiapine vs. placebo: $p<0.001$

Chen EYH et al. BMJ 2010;310:c4024. Farooq et al. Br J Psychiatry 2011;199:467-72.

We Are Not Good at Estimating Adherence: Clinician Assessment vs. Plasma Levels

Among 105 patients admitted to a US psychiatric hospital previously on antipsychotics:



Antipsychotic: risperidone, olanzapine, quetiapine, paliperidone, aripiprazole

Lopez LV et al. J Clin Psychopharmacology 2017;37:310-14.

Many treatment-resistant patients have subtherapeutic plasma levels.

Study 1: Antipsychotic plasma levels were measured in 36 outpatients identified as having treatment-resistant schizophrenia by their treating clinicians in the UK. **44% of patients showed subtherapeutic levels, 43% of which were undetectable. 56% of patients had levels in the therapeutic range.**

Study 2: Antipsychotic plasma levels were measured in 99 outpatients identified as having treatment-resistant schizophrenia by their treating clinicians in the UK. **35% of patients showed subtherapeutic levels, 34% of which were undetectable. 65% of patients had levels in the therapeutic range.**

McCutcheon R., et al. Journal of Psychopharmacology 2015; 29(8) 892–897; McCutcheon R, et al. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. Acta Psychiatr Scand 2018; 137(1): 39-46.

Which antipsychotics are recommended for plasma level monitoring?

Usual Doses to Achieve 60–80% D2 Receptor Occupancy		
	Usual dose range (mg/d)*	**Rec plasma levels (ng/mL)[1]**
Aripiprazole	15–30	150–500
Clozapine	300–450	350–700
Fluphenazine	0.5–10	0.8–2.0
Haloperidol	1–40	3–20
Olanzapine	10–20	20–80
Paliperidone	3–6	20–60
Perphenazine	2–8	20–60
Risperidone	2–8	20–60
Ziprasidone	40–200	50–200

*In schizophrenia

Hiemki C et al. Pharmacopsychiatry 2011;44(6):195-235;
Potkin SG et al. CNS Spectrums 2014;19(2):176-81.

Dosing/Plasma Levels for Newer Antipsychotics

Usual Doses to Achieve 60–80% D2 Receptor Occupancy		
	Usual dose range (mg/d)*	**Rec plasma levels (ng/mL)[1]**
Asenapine	10–20	2–5
Brexpiprazole	2–4	?
Cariprazine	1.5–6	?
Iloperidone	12–24	5–10
Lurasidone	40–160	>70[2]
Quetiapine	400–800	Not reliable or used

*In schizophrenia

Hiemki C et al. Pharmacopsychiatry 2011;44(6):195-235;
Potkin SG et al. CNS Spectrums 2014;19(2):176-81.

Obtaining Plasma Levels

- 12-hour trough
- For patients on twice/day dosing, make sure they hold the morning dose until the AM trough is obtained
- Levels may fluctuate up to 30% in adherent patients
- Greater fluctuations likely reflect nonadherence or kinetic issues

Technology-Based Services

- Text reminders
  - Two studies found that 3–4 texts/day (about adherence, socialization, and hallucinations) significantly improved adherence in patients living independently for up to 6 months
- Phone calls
  - Weekly calls led to significantly higher adherence
- Electronic pill counters
  - Adherence rate of 67% at 6 weeks
- Tracking devices?

Haddad et al. Patient Related Outcome Measures. 2014; 5(43): 43-62.

Summary

- D3 antagonism is a potential mechanism for reducing negative symptoms
- Other pharmacological mechanisms are being investigated, but so far nothing shows robust efficacy
- Established psychosocial methods may effectively treat cognitive symptoms of schizophrenia
- Nonpharmacological methods are on the horizon (e.g., TMS) for treating cognitive symptoms of schizophrenia
- There are many medications available to effectively manage adverse effects associated with antipsychotics
- Adherence can be optimized with careful monitoring