I BLOCKED D2 AND ALL I GOT WAS THIS LOUSY SIDE EFFECT: WHAT TO DO WHEN D2 ISN'T ENOUGH

Learning Objectives

- Evaluate the evolving data on the neuropathology of schizophrenia
- Differentiate the mechanisms of action and corresponding clinical profiles of antipsychotics
- Evaluate the mechanisms and latest clinical data on new and emerging antipsychotics

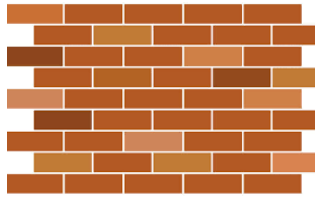
Challenges of Treating Schizophrenia

- Chronic, severe, and debilitating brain disorder resulting in positive and negative symptoms, mood/affective impairments, and cognitive dysfunction

Schizophrenia Marketplace: Drug Development Areas for Unmet Needs

Drugs that treat negative symptoms

Drugs that enhance cognition



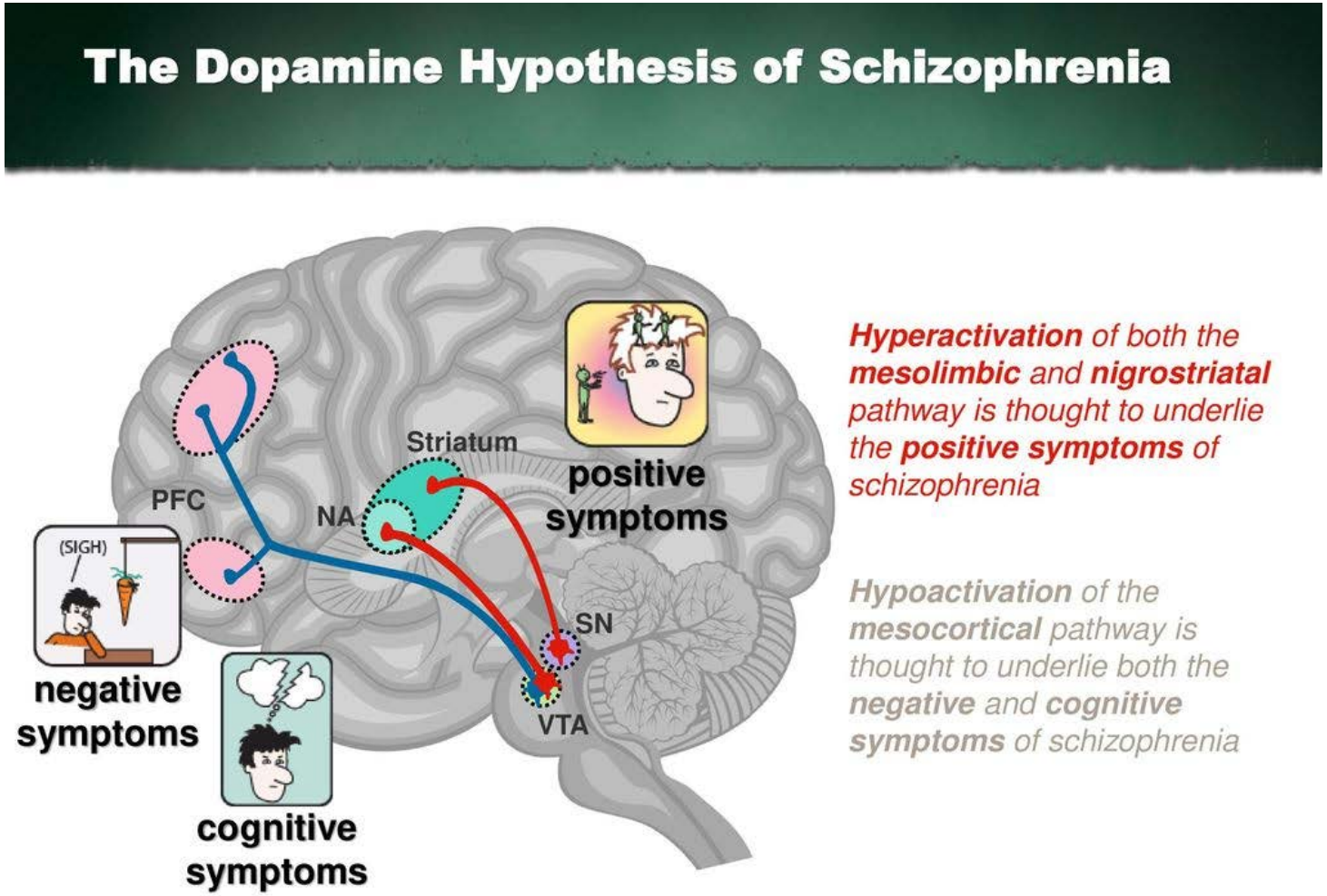
Drugs that provide improved options for treatment resistant patients

Drugs with enhanced safety profiles

Drugs that increase compliance

Fellner et al. Pipeline Plus 2017;42(2):130-134.

Dopamine Pathways Relevant to Schizophrenia Symptoms



[1]Stahl SM. *Stahl's Essential Psychopharmacology*, Cambridge, Cambridge University Press. 2013.
[2]Kegeles et al. *Arch Gen Psychiatry*. 2010;67(3):231-239.

Efficacy: Beyond D2 Hypothesis

- Schizophrenia has been primarily associated with dopamine dysfunction
    - All effective treatments directly target the dopamine D2 receptor
- Core pathophysiology may also involve dysfunction of glutamatergic, serotonergic, cholinergic, and gamma-aminobutyric acid (GABA) signaling
    - Imbalance within any of these may influence the entire system
    - Novel treatment development is focusing on targets beyond dopamine, including glutamate, serotonin, acetylcholine, GABA, and inflammatory cytokines

Yang et al. International Journal of Molecular Sciences. 2017;18(8):1-14.

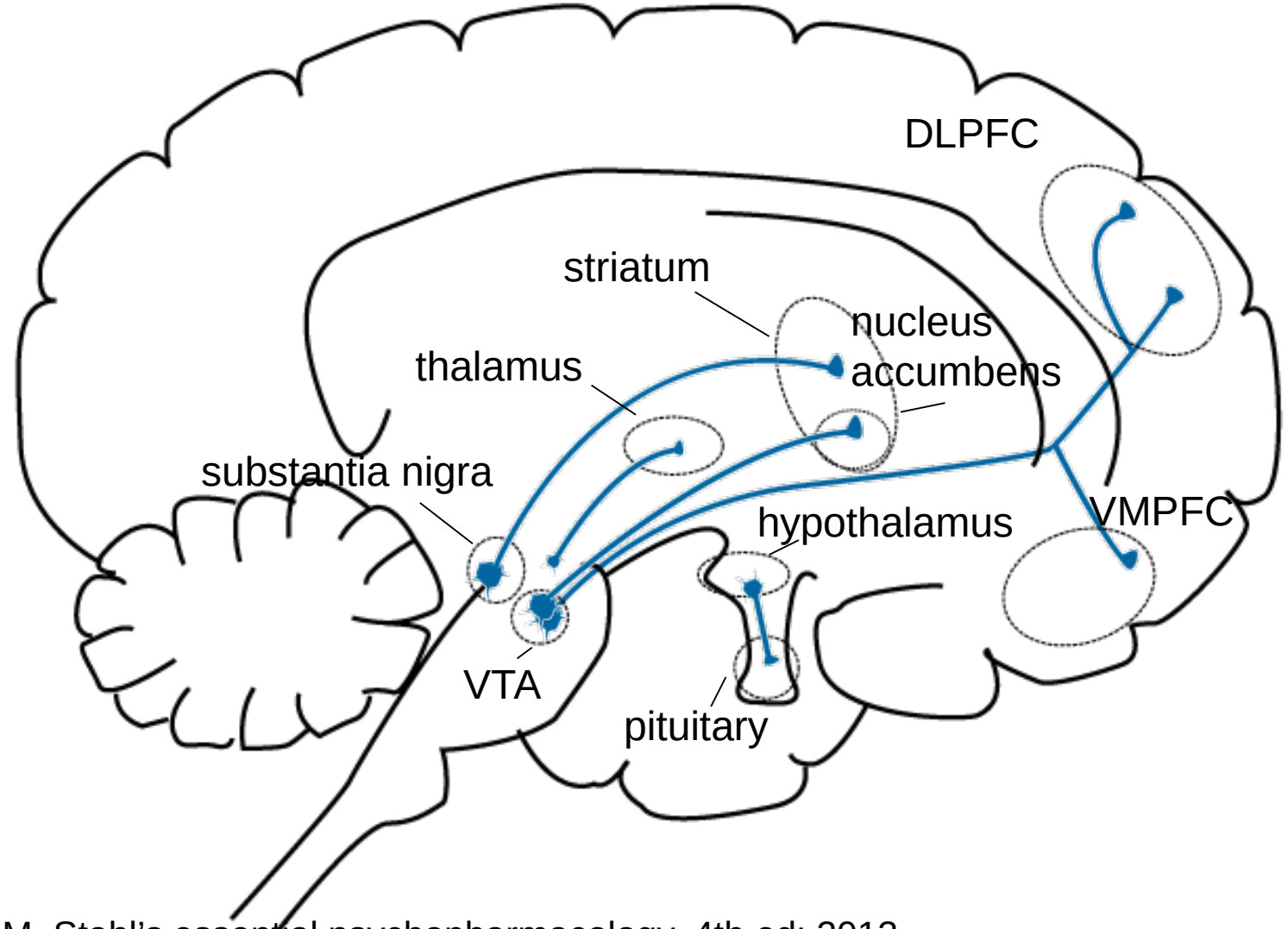
Beyond the D2 Hypothesis: Novel Treatment Targets for Schizophrenia

Hypothesis	Target	Strategy
Dopamine	Dopamine stabilizers	Improve medication adherence
Glutamate	NMDA, AMPA, or metabotropic receptors	Improve negative symptoms and cognitive impairments
Serotonin	5HT1A agonists, 5HT2C antagonists and agonists, 5HT3 antagonists, 5HT6 and 5HT7 antagonists, 5HT reuptake inhibitors	Reduce EPS; Improve negative symptoms, mood and cognitive impairments; Potential treatment for different phases of the illness
Acetylcholine	α-7 nicotinic and M1 muscarinic agonists and positive allosteric modulators	Nicotinic agonists for cognitive symptoms; Muscarinic agonists for positive symptoms
GABA	Selective GABA-A agonists, GABA-B antagonists, and allosteric modulators at GABA-A receptor subtypes	Augmentation of psychosis treatment
Inflammation	Cytokines	Possibly the early period of psychosis
Phosphodiesteras		Activates cAMP/PKA signaling, leading to

NMDA: N-methyl-D-aspartate; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; 5-HT: 5-hydroxytryptamine (serotonin); GABA: gamma-aminobutyric acid

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

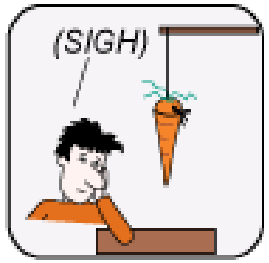
mesolimbic



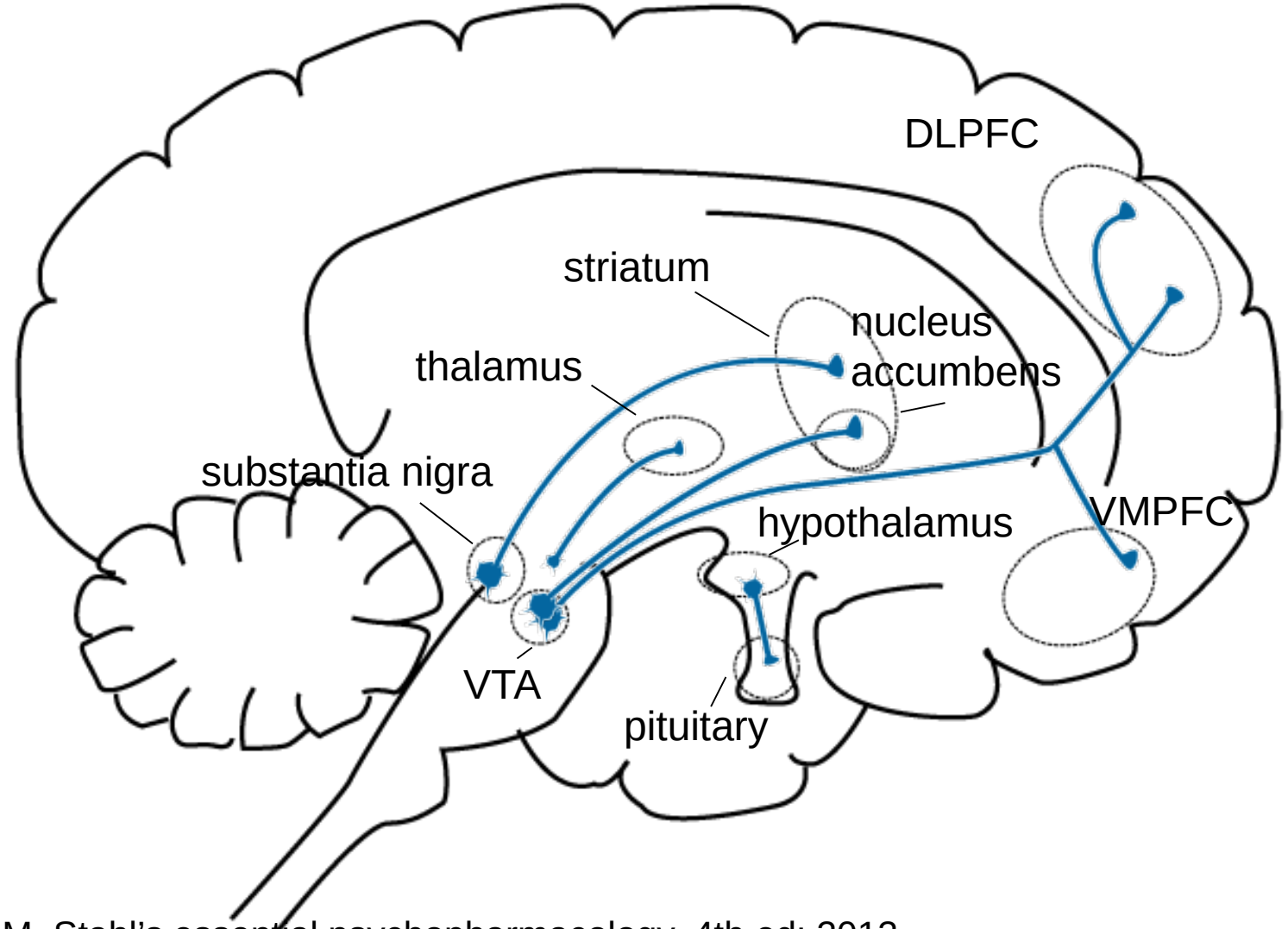
Stahl SM. Stahl's essential psychopharmacology. 4th ed; 2013.

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

mesolimbic



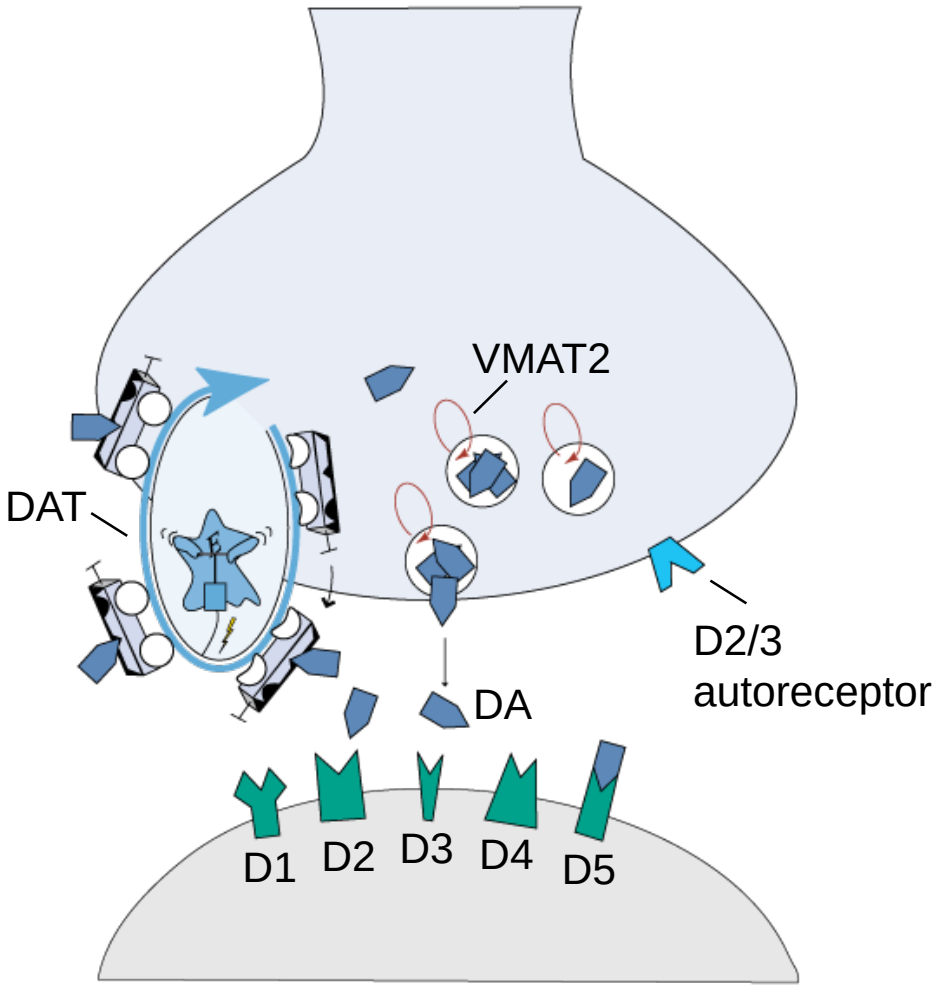
mesocortical reward circuits



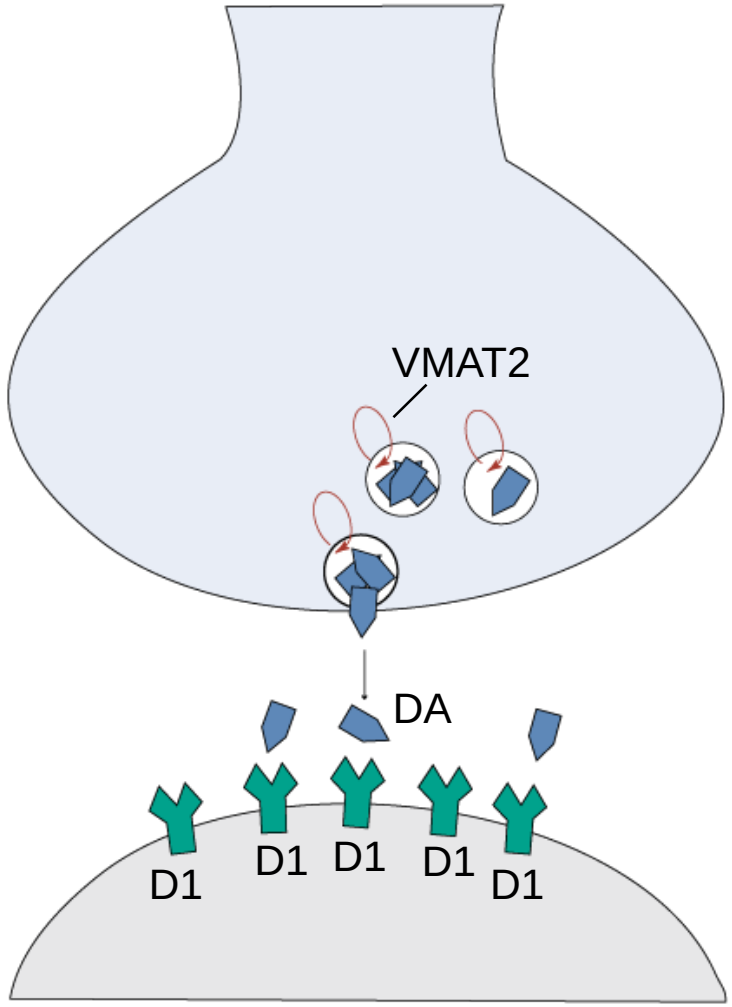
Stahl SM. Stahl's essential psychopharmacology. 4th ed; 2013.

Overview of the Dopamine Synapse

In the striatum

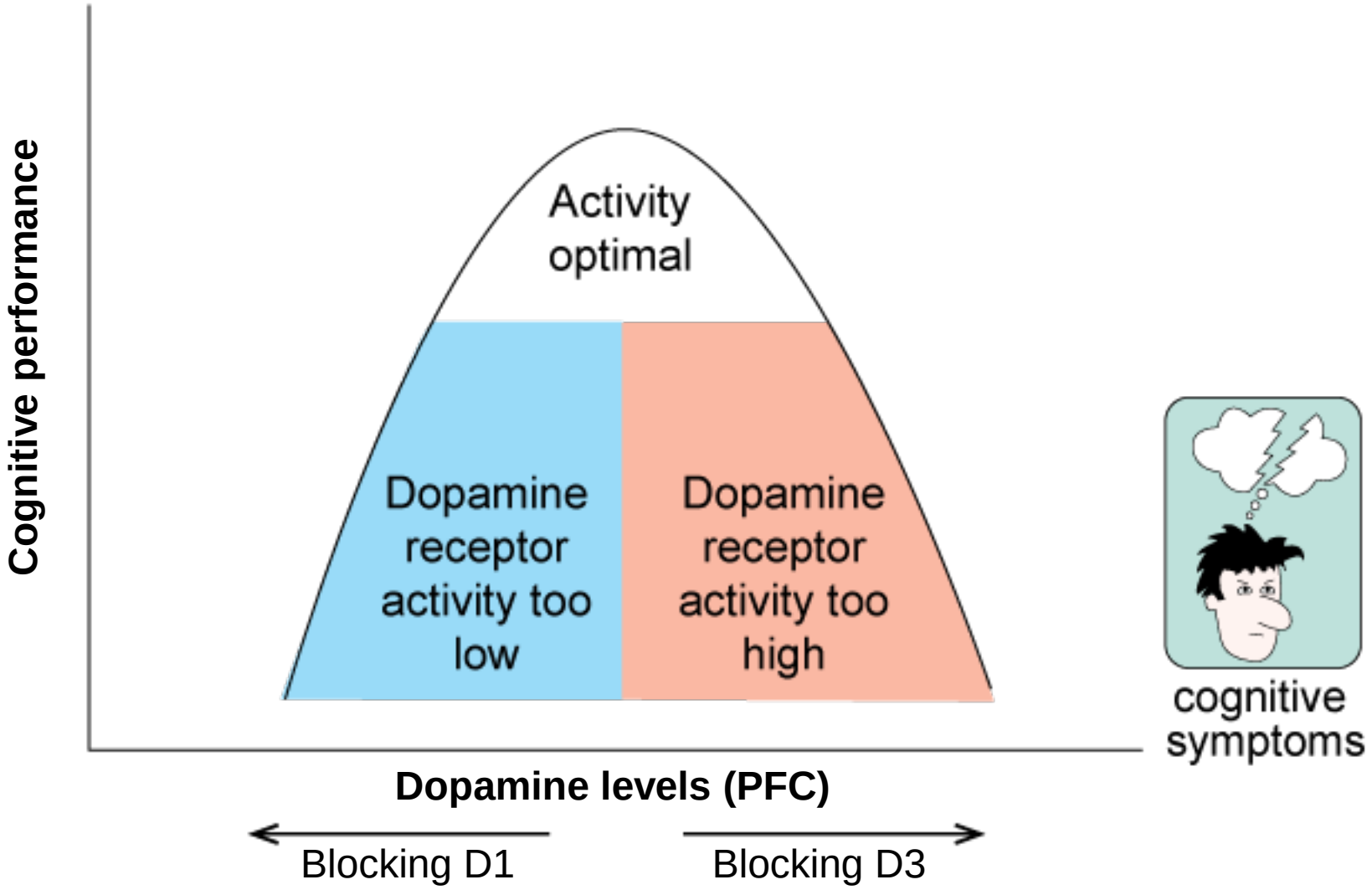


In the prefrontal cortex



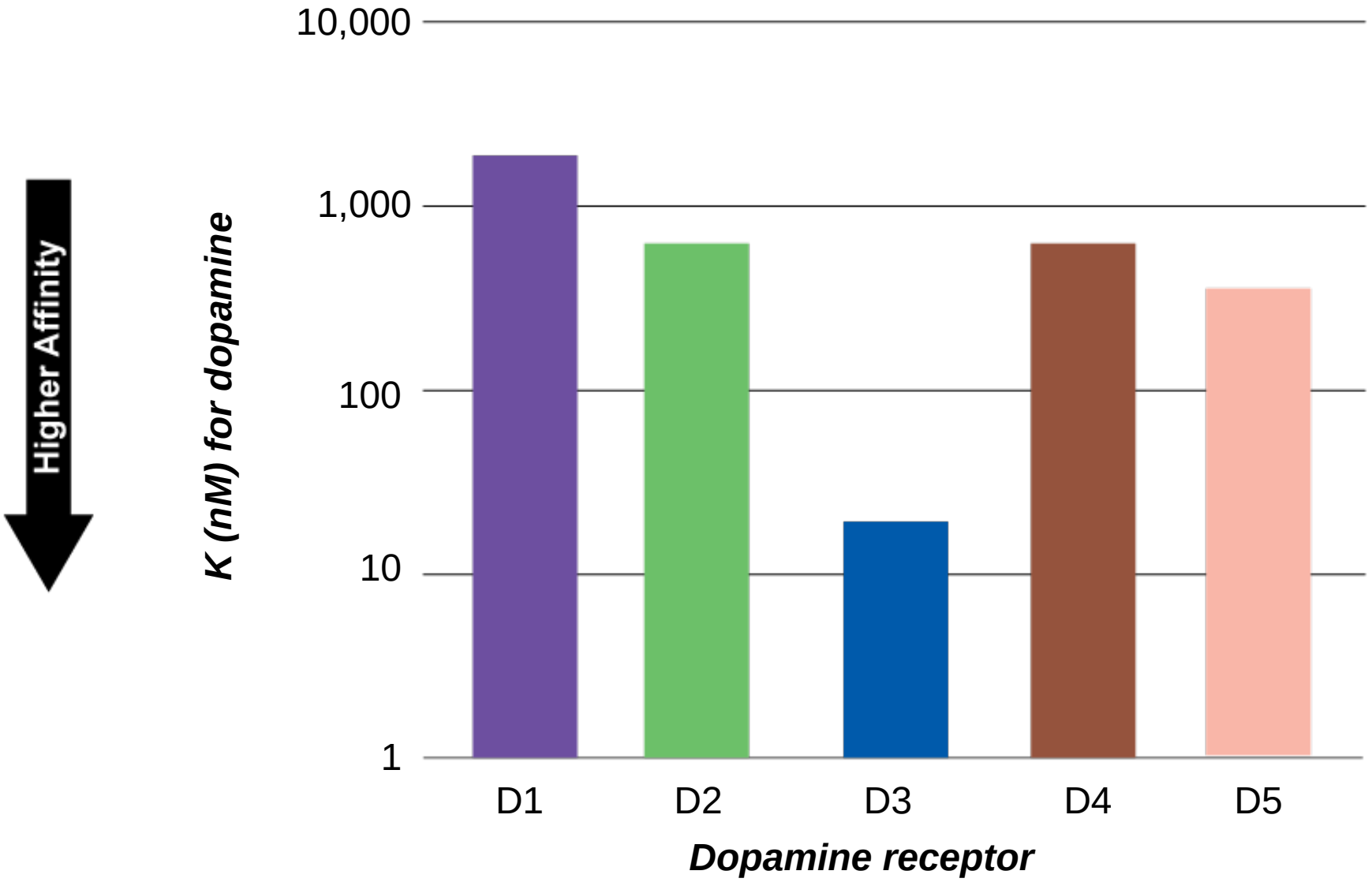
Stahl SM. CNS Spectrums 2017;22:305-11.

Functional Output of Cortical Dopamine and Cognition



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

Dopamine Receptor Affinities



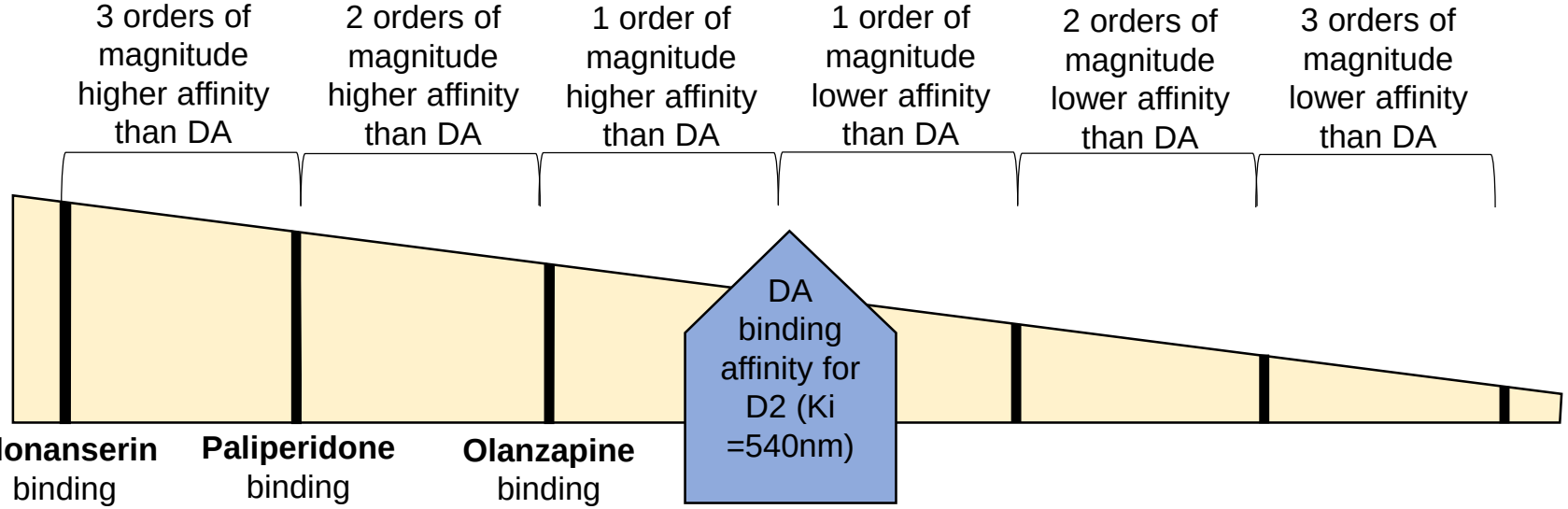
Stahl SM. CNS Spectrums 2017;22:305-11.

D1 and D3 vs. D2 Receptor Affinity

- 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)

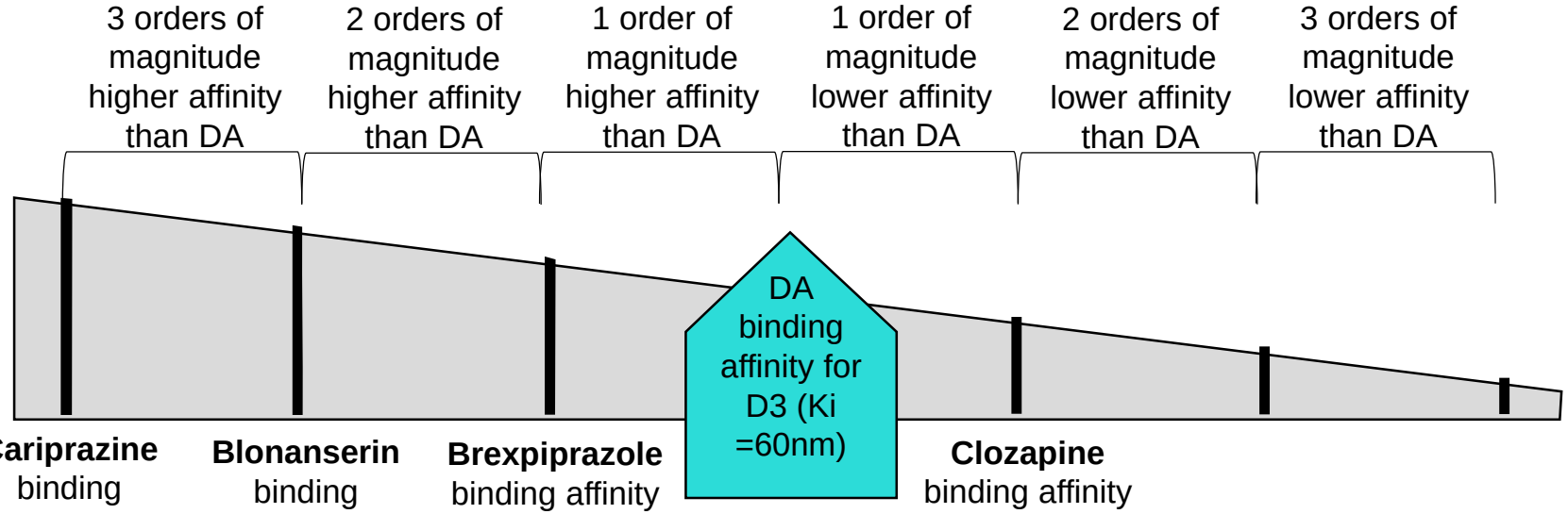
Ziprasidone binding affinity for D2 (4.75nM)

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)



Cariprazine binding affinity for D3 (0.09nM)

Blonanserin binding affinity for D3 (0.49nM)

Brexpiprazole binding affinity for D3 (1.1nM)

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)

Iloperidone binding affinity for D3 (10.5nM)

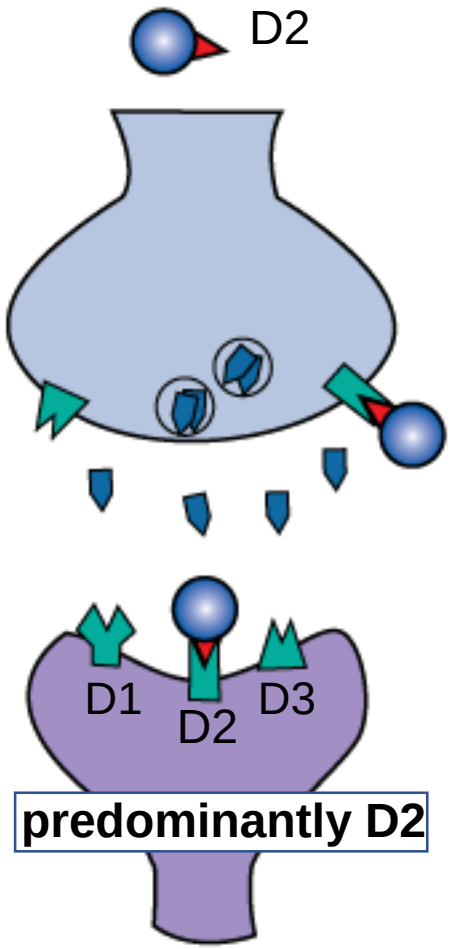
Lurasidone binding affinity for D3 (15.7nM)

Olanzapine binding affinity for D3 (38.1nM)

Clozapine binding affinity for D3 (310nM)

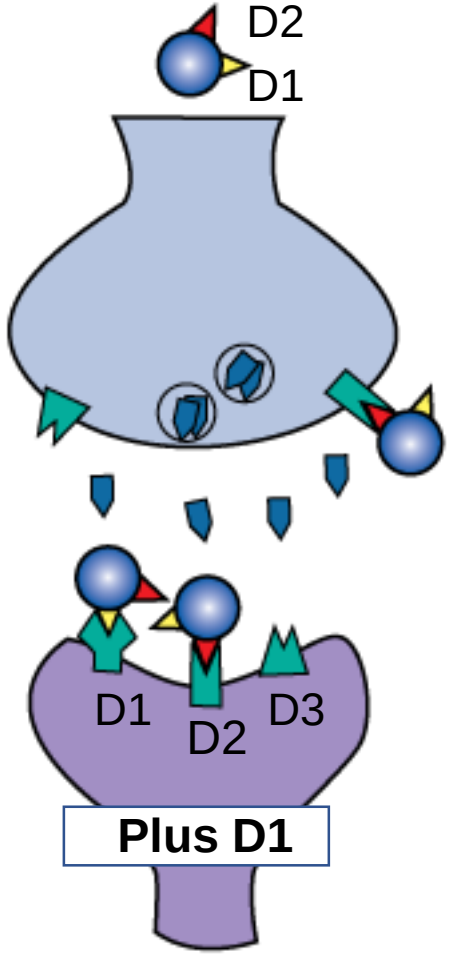
Quetiapine binding affinity for D3 (394nM)

Summary:
Antipsychotic Binding at Dopamine Receptors



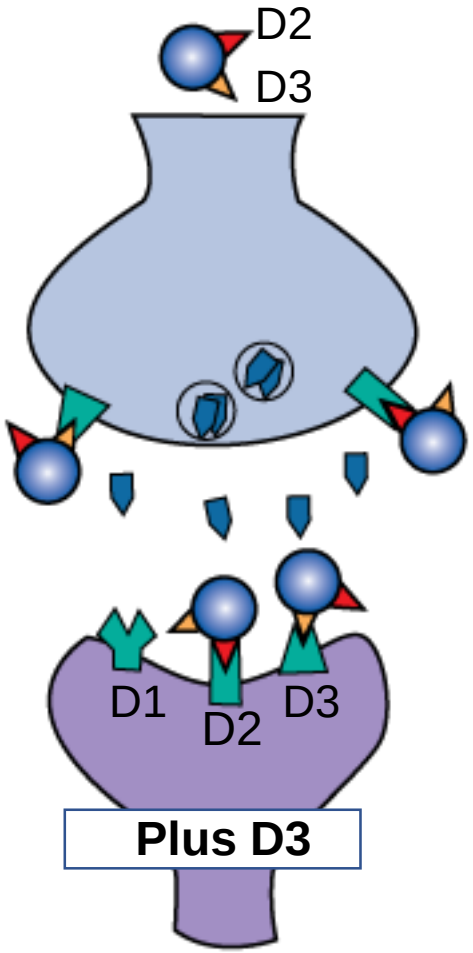
predominantly D2

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.

Dopaminergic Antipsychotics in Development

Drug	Mechanism	Status	Company	Clinical Trial
AMG579 OMS643762	PDE 10A inhibitor PDE10A inhibitor	Phase 2	Amgen	NCT01952132
DAAOI-1	DAAO catalizes D-serine and glycine	POC ongoing		NCT01390376
Eltoprazine	5-HT1A/1B agonist	POC ongoing		NCT01266174
L-DOPA	Dopamine stabilization	POC ongoing		NCT01636037
Stepholidine	D2 antagonist/D1 agonist/5HT1A agonist	POC ongoing	University of Toronto	
YKP1358	D2/D3/5HT2A antagonist	Phase 2	SK Bio-Pharmaceuticals	

Beyond D2: Drugs in Development

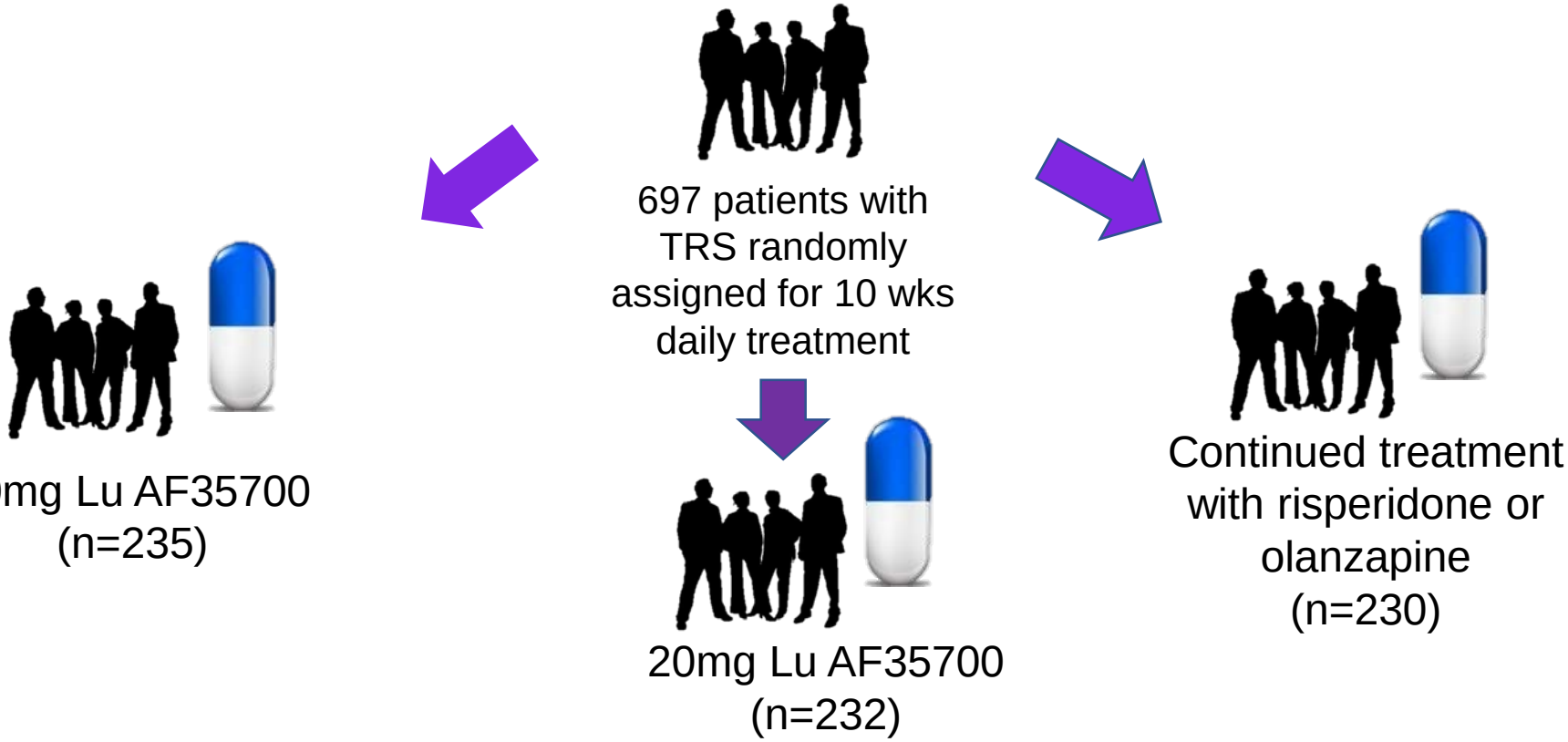
- Lu AF35700
- Lu AF11167
- Pimavanserin
- Lumateperone (ITI-007)
- Xanomeline

Beyond D2: Lu AF35700

- Lu AF35700 has a novel pharmacological profile with predominant D1 vs. D2 dopamine receptor occupancy and a high occupancy of 5-HT2A and 5-HT6 serotonin receptors
- Relatively low dopamine D2 receptor occupancy is expected to result in reduced burden of adverse events, such as EPS, prolactin elevation, dysphoria/anhedonia, and depressed mood
- In 2015, the FDA granted Fast Track designation for Lu AF35700

Fellher et at. Pipeline Plus 2017;42(2):130-134.

Lu AF35700 Results From Phase III Trial on Patients With Treatment-Resistant Schizophrenia (TRS)



October 2018: Announcement that first phase of the study did not meet the primary endpoint primary endpoint: no significant difference between Lu AF35700 and risperidone/olanzapine from baseline to week 10 in the PANSS total score

Beyond Dopamine: Pimavanserin

Patients who had not responded to clozapine (n=10)

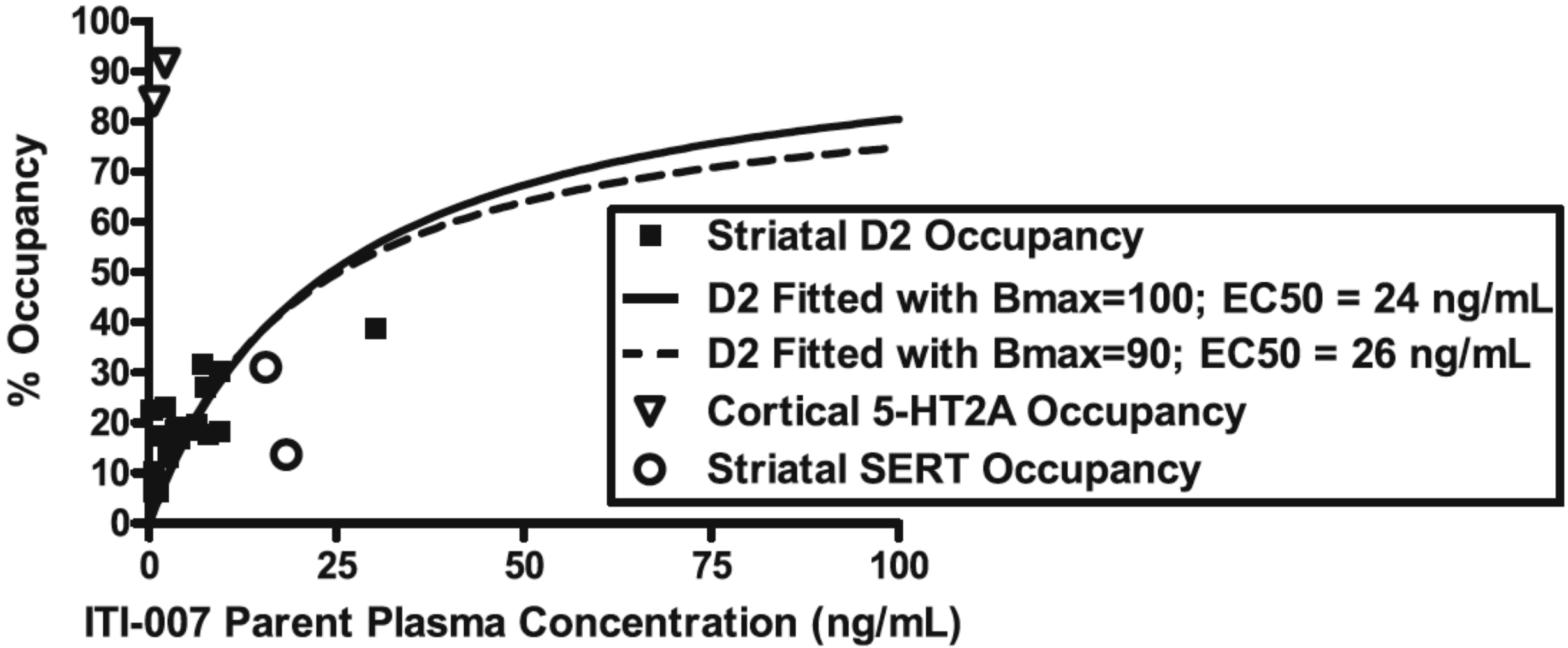
34mg/d pimavanserin for 4-8 weeks

Patients who had not responded to non-clozapine antipsychotics (n=10)

- All 10 patients with refractory hallucinations/delusions demonstrated marked response to pimavanserin, with continuation of response for several months of follow-up
- Improvements in negative symptoms and social functioning were also observed

Nasrallah et al. Schizophrenia Res. 2019;doi:10.1016.

Lumateperone (ITI-007)



Snyder et al. Psychopharmacology 2015;232(3):605-21; Davis RE et al. Psychopharmacol (Berl) 2015; 232(15): 2863-72.

Comparison of ITI-007 D2 Occupancy to Other Antipsychotics

60

Table 3. Mean D_2RO in Caudate & Putamen at antipsychotic oral doses as measured by displacement of [^{11}C]-raclopride

Drug	Dose range	Mean D_2RO in Caudate and Putamen	Reference
ITI-007	60 mg/day	~ 40%	Present results
Clozapine	75–900 mg/day	48–61%	Farde et al. [2]; Kapur et al. [39]; Tauscher et al. [31]
Quetiapine	150–750 mg/day	30–62%	Gefvert et al. [30]; Kapur et al. [32]; Tauscher et al. [31]; Tauscher-Wisniewski et al. [33]
Ziprasidone	40–160 mg/day	56 to >59%	Mamo et al. [43]; Vernaleken et al. [44]
Risperidone	4 mg/day	72–81%	Kapur et al. [38, 39]; Nyberg et al. [3]; Tauscher et al. [31]
Olanzapine	5–60 mg/day	61–80%	Nyberg et al. [45]; Kapur et al. [39, 46]; Tauscher et al. [31]
Lurasidone	40–80 mg	>65%	Wong et al. [5]
Cariprazine	1.5–3 mg/day	69 to >90%	Reviewed by Citrome [42]
Aripiprazole	10–30 mg	88–90%	Yokoi et al. [6]; Mamo et al. [7]

Vanover et al. Neuropsychopharmacology 2019;44:598-605.

Lumateperone (ITI-007) Efficacy and Tolerability

Properties	Risperidone	ITI-007
Receptor binding	12-fold difference in affinities for 5-HT2A and D2 receptors	60-fold difference in affinities for 5-HT2A and D2 receptors
Negative symptom efficacy	Reduces negative symptoms	Superior to risperidone at reducing negative symptoms, including social function, and depressive symptoms in patients with comorbid schizophrenia/depression
Neurological and endocrine adverse effects	Side effects include weight gain, extrapyramidal symptoms (EPS), increased prolactin levels	Produces little to no weight gain, does not negatively affect metabolic parameters, does not increase prolactin levels, and reduces akathisia
Metabolic adverse effects	QTc prolongation and other cardiometabolic side effects	Does not produce alterations in cardiovascular function QTc prolongation; does not increase heart rate
Suicidal ideation	Suicidal ideation reported	No evidence of suicidal ideation/behavior

Vanover et al. Abstracts for the Sixth Biennial SIRS Conference. 2018 Poster Session S341.

Lumateperone: Placebo-Controlled Clinical Trials

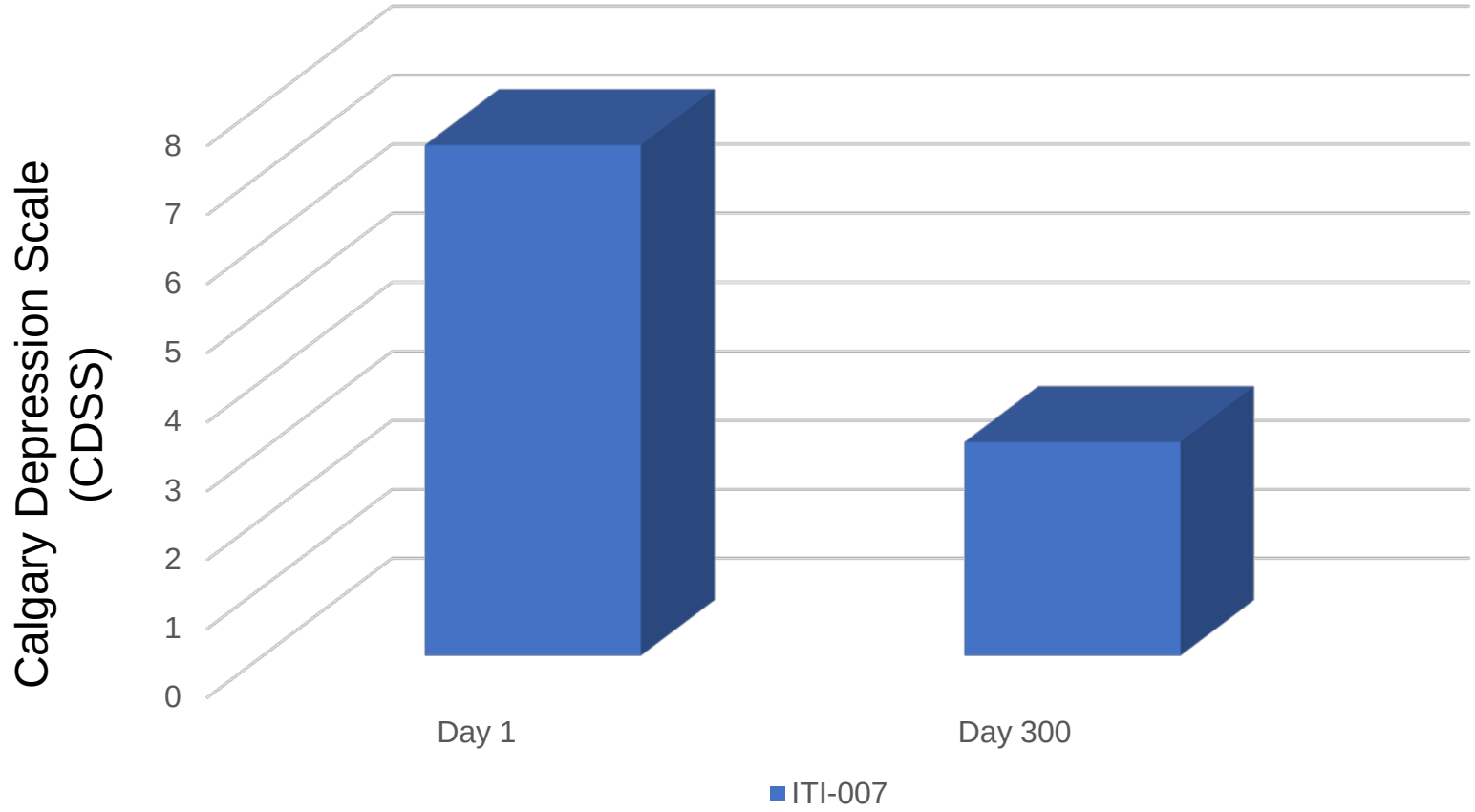
Study Title/Type	Sample Size	Protocol	Results
005, Randomized Controlled Trial (RCT)	n=335	60mg ITI-007, 120mg ITI-007, 4mg risperidone, or placebo for 4 weeks	60 mg dose: significant improvement over placebo at Day 28 on PANSS total score; ITI-007 significantly better than risperidone
301, RCT	n=450	60mg ITI-007, 40mg ITI-007, or placebo for 4 weeks	60 mg dose: significant improvement over placebo at Day 28 on PANSS total score
302	n= 696	60mg ITI-007, 20mg ITI-007, 4mg risperidone, or placebo for 4 weeks	60 mg dose: significant improvement over placebo at Day 28 on PANSS total score; ITI-007 significantly better than risperidone

In a 6-week open-label study, patients were switched from standard of care (SOC) antipsychotics to daily lumateperone, and then switched back to SOC for 2 weeks.

Statistically significant improvements from SOC were observed in body weight, cardiometabolic and endocrine parameters, which worsened when switched back to SOC

Vanover et al. CNS Spectr. 2019;24(1):190-191.

Results From Long-term Open Label Safety Study of Lumateperone (Study 303)



In patients with moderate to severe depression symptoms at baseline (CDSS≥6; N=55), lumateperone treatment was associated with marked improvement in CDSS scores. Specifically, mean CDSS scores decreased by approximately 60% from 7.4 (baseline) to 3.1 (Day 300).

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

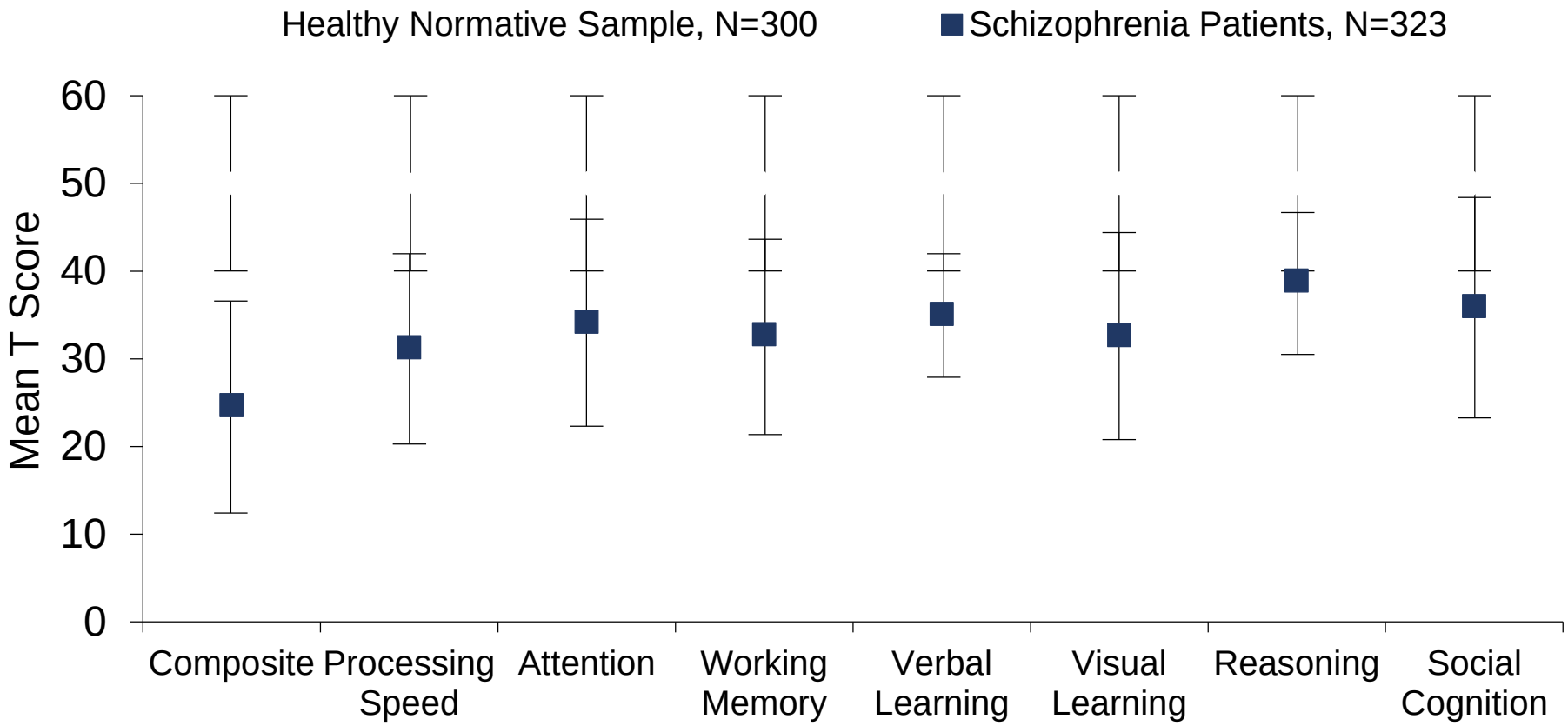
Reduced social drive

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

Phase II Study: Lu AF11167 for Negative Symptoms in Stable Patients with Schizophrenia

- Lu AF11167 inhibits the activity of the PDE10-enzyme, which alters dopamine signaling. Ideally, negative symptoms will improve while positive symptoms remain controlled
- In Jan 2019, a Phase II study was launched (3 arm, randomized) for a total of 240 patients from various European countries
- Primary objective: evaluate the efficacy of two doses of Lu AF11167 versus placebo as monotherapy on negative symptoms in stable outpatients
- Secondary objective: evaluate the efficacy of Lu AF11167 on patients' functioning, safety, and tolerability

Cognitive Impairment in Schizophrenia



Keefe RS et al. Schizophr Res 2011;125(2-3):161-8.

I Think I Can: Efficacy With Cognitive Improvement

- Novel pharmaceuticals under development have demonstrated effective improvements on cognitive measures and in neuroimaging

- New approaches to previously established non-pharmacological methods (e.g., CRT) and novel treatments (HF-rTMS) may improve cognitive dysfunction

M1/M4 Muscarinic Agonists for Treatment of Cognitive Impairment in Schizophrenia

- M2/M3 receptors are the major peripheral subtypes hypothesized to underlie dose-limiting clinical side effects (e.g., GI)
- M1 and M4 muscarinic cholinergic receptors are highly expressed in the cortex, hippocampus, and striatum and have been implicated in cognitive impairment
- First generation agonists have modest selectivity for M1/M4 receptor subtypes over M2/M3
  - More recent medicinal chemistry optimization of orthosteric agonists, allosteric agonists, and positive allosteric modulators (PAMs) has resulted in highly selective M1 and M4 agonists that may result in improved cognition

Felder et al. Neuropharmacology 2018; S0028-3908(18)30028-5.

M1 Muscarinic Agonists for Cognitive Impairment in Schizophrenia: Xanomeline (LY 593093)

Study	Number of Patients	Protocol	Results
Pilot study on xanomeline monotherapy (RCT)	n=20	Randomly assigned to placebo or titrated to 225mg xanomeline over 6 days and remained at that dose for the remainder of the 4 weeks	Significant improvements on total BPRS scores and total PANSS scores. Showed improvements in verbal learning and short-term memory function
Phase I Study on xanomeline/trospium (KarXT)	n=69	Randomly assigned to 225mg xanomeline + placebo or 225mg xanomeline + 40mg trospium	KarXT co-formulation demonstrated improved tolerability, and side effects were mild to moderate
Phase II Study on xanomeline/trospium (KarXT)	n=160	Randomly assigned to receive 120mg/20mg xanomeline/trospium with an option to increase dose to 125mg/30mg xanomeline/trospium following	Ongoing. Primary objective: change from baseline PANSS scores. Additional objectives: improvement in cognitive/negative

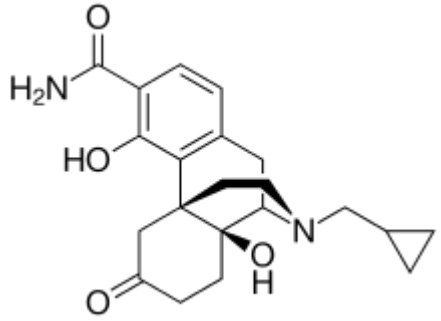
Shekhar et al. Am J Psychiatry 2008;165:1033-1039.

Novel Advancements in Minimizing Risk

Olanzapine/Samidorphan

- Samidorphan (SAM)
  - Opioid antagonist at the μ-opioid receptor, with significant activity at kappa opioid receptors
  - Investigated for addiction treatment (e.g., alcohol, cocaine)
    - By blocking opioid receptors involved in the brain reward pathway, reinforcement is reduced
    - Shows similar efficacy to naltrexone but with reduced side effects
- Research in animals suggests that naltrexone reduces food cravings but has no effect on weight gain
- Co-administration of olanzapine and SAM, but not naltrexone-mitigated olanzapine-induced weight gain, suggesting that the added K-opioid receptor properties may be clinically relevant

Receptor	Ki (nM)
μ	0.052
k	0.28
δ	2.6



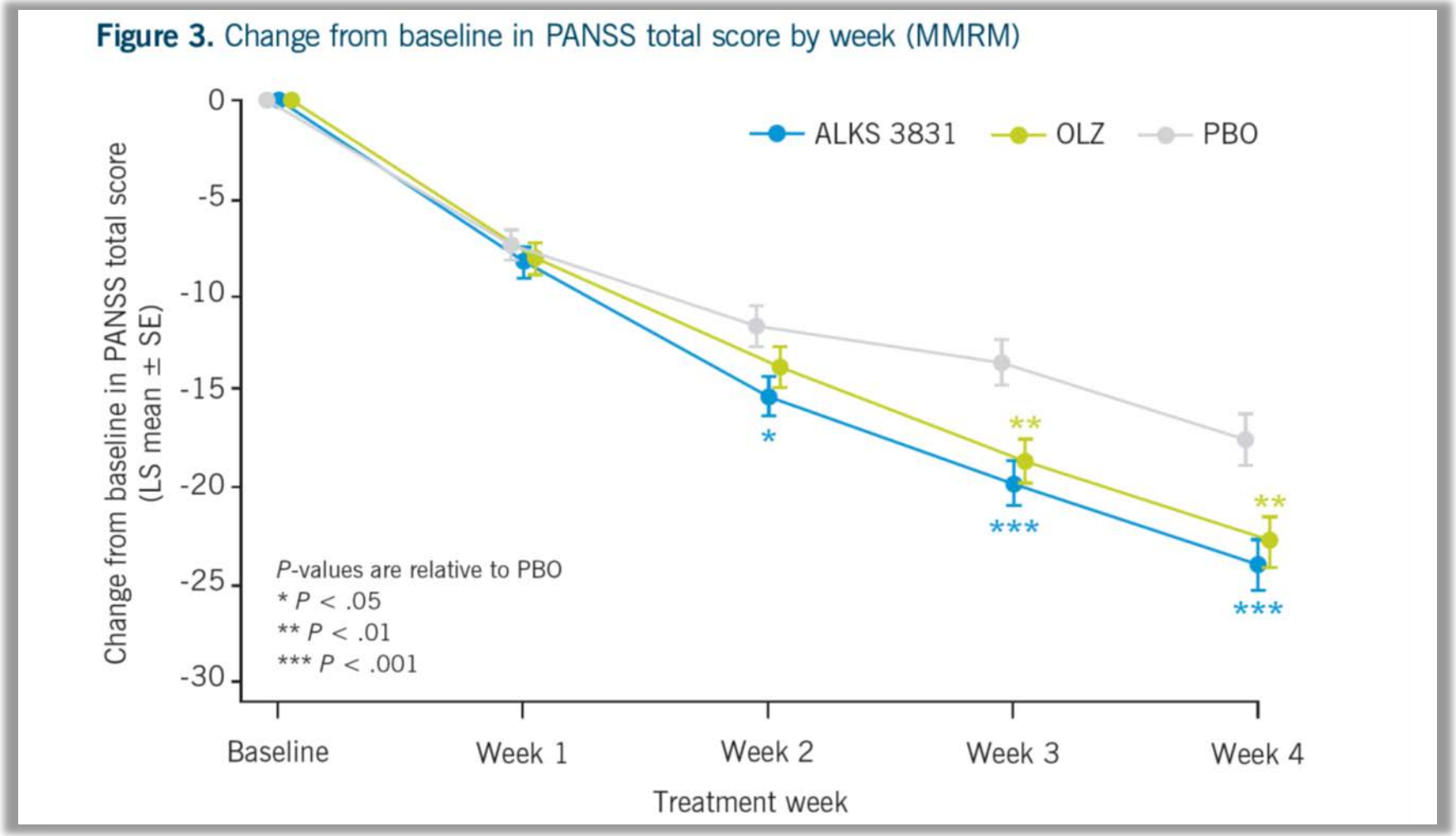
Silverman et al. Schizophr Res 2018;195:245-251.

Olanzapine/Samidorphan Study Program

- **ALKS 3831:** flexible dose of olanzapine and a fixed dose of 10 mg SAM
  - The combination has been studied in phase I trials (healthy volunteers) and phase II trials (patients with stable schizophrenia)
  - In the phase II study, co-administration of SAM mitigated OLZ-associated weight gain, and OLZ/SAM combination had similar antipsychotic efficacy to OLZ
- **Phase III (ENLIGHTEN I):** 4-week randomized, double-blind active (OLZ monotherapy) and PBO-controlled study of ALKS 3831 in acute exacerbation of schizophrenia
  - 2-week inpatient treatment (OLZ titration permitted) followed by 2-week inpatient/outpatient treatment (fixed OLZ dose)
- **Outcomes:** PANSS and Clinical Global Impression-Scale (CGI-S)

DiPetrillo et al. American Psychiatric Association (APA) Annual Meeting, May 5-9, 2018, New York, NY; Simmons et al. APA Annual Meeting, May 5-9, 2018, New York, NY; Potkin et al. APA Annual Meeting, May 5-9, 2018, New York, NY; Silverman et al. Schizophrenia Research 2017:1-7.

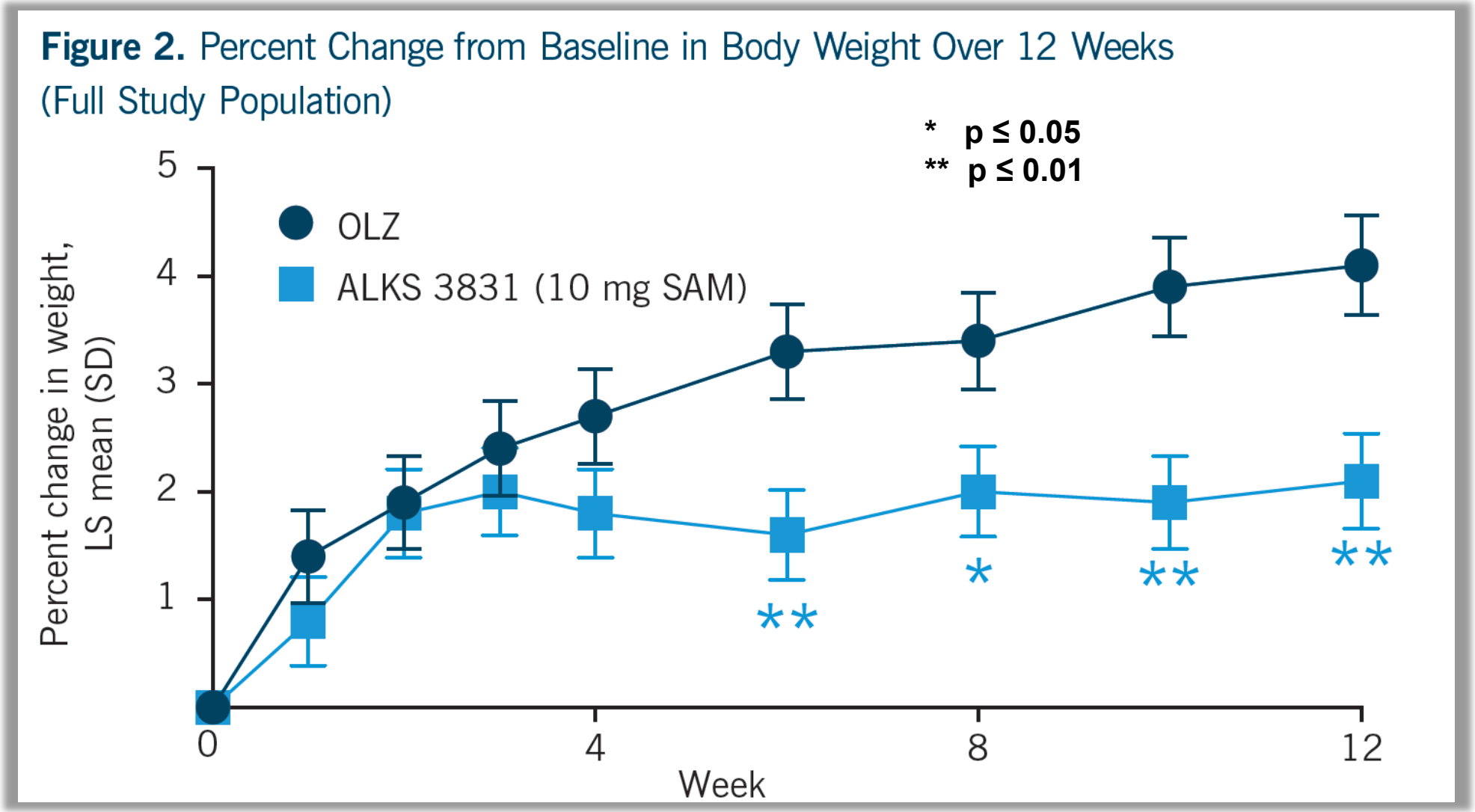
Olanzapine/Samidorphan: Phase III (ENLIGHTEN I) Efficacy Results



Mean OLZ dose: 18.4 mg/day for both active treatment arms

Potkin et al. American Psychiatric Association (APA) Annual Meeting, May 5-9, 2018, New York, NY USA.

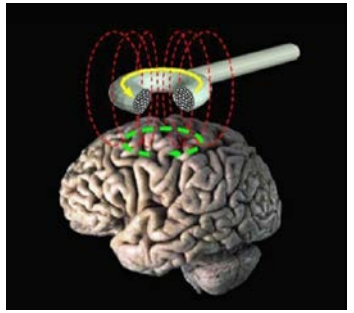
Olanzapine/Samidorphan: Phase III (ENLIGHTEN II) Weight Gain Results



DiPetrillo et al. American Psychiatric Association (APA) Annual Meeting, May 5-9, 2018, New York, NY USA.

Non-pharmacological Treatments for Positive Symptoms in Schizophrenia

TMS for Auditory Hallucinations in Psychosis



- Promising results have been reported for both high frequency (HF) and neuronavigated repetitive transcranial magnetic stimulation (rTMS)
- Recent study examined the efficacy of HF (20 Hz) rTMS applied precisely over the left temporal region using neuronavigation
  - 59 patients with schizophrenia or schizoaffective disorders were treated with rTMS or sham over 4 weeks
- The proportion of patients demonstrating ≥ 30% decrease in the Auditory Hallucinations Rating Scale (AHRS) differed significantly between conditions (p=0.016) at day 14

Dollfus et al. Schizophr Bull 2018;44(3):505-514.

Non-pharmacological Treatments for Negative and Cognitive Symptoms in Schizophrenia

Cognitive Remediation Therapy (CRT) in Schizophrenia

- CRT targets cognitive and functional difficulties. The goal is to improve attention, memory, language, executive functions
- CRT is associated with neurobiological and cognitive improvement, and affects several regions and circuits, including prefrontal, parietal, and limbic areas
  - **Changes to prefrontal areas are the most reported finding**
- **Two approaches: <u>Training or Strategy</u>**

  Training: exercises that are regularly repeated and allow for specific training in the deficient aspect of cognitive function; restoring the deficient function

  Strategy: works with preserved functions to develop strategies for processing information
- Both methods show improvements in behavior and increased cerebral activity
- Several meta-analyses suggest CRT effectiveness in schizophrenia patients, especially from early intervention

Roder et al. Schizophr Bull. 2006;32:S81-S93; McGurk et al. Am J Psychiatry 2007;164:1791-1802; Thorsen et al. Frontiers in Psychiatry 2014;5(103):1-9.

CRT and Cerebral Activity

- Recent meta-analysis included eight studies comparing cerebral activity in MRIs when the training method was used vs. the strategy method
- Several studies reported correlations between increases in cerebral activity and improvements in cognitive function (e.g., attention, working memory, verbal memory, and cognitive control)
- **Training method is capable of activating more of the targeted brain areas than the strategy method; increases in cerebral activity were observed primarily in prefrontal / temporal regions**
- **Strategy method appears to encourage more extensive activation of the cerebral networks; increased cerebral activity was concentrated in frontal regions, parietal, and occipital areas**

Bon et al. Brain and Behavior 2017;8(3):1-9.

TMS for Cognition in Schizophrenia

- A recent pilot study explored the effects of 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 treatment
- Those who received rTMS displayed improvement on a standardized cognitive test battery, both immediately following the course of study treatment and at follow-up 2 weeks later
- 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.

Summary

- Pharmacological management of schizophrenia can be challenging, especially because of the need for increased efficacy, reduced side effects, and relief from negative and cognitive symptoms

- All approved medications bind D2. There are several in development that focus on mechanisms that extend beyond the dopamine/D2 hypothesis of schizophrenia

- Exciting developments have also been made in behavioral and other non-pharmacological approaches to treat cognitive impairment in schizophrenia