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Translating the Role of Neurotransmitter Systems into Clinical Outcomes in Schizophrenia and Bipolar Disorder

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Learning Objective 1

Recognize the relationship between neurotransmitter systems and clinical outcomes in patients with schizophrenia and bipolar disorder



Norepinephrine

Serotonin

Energy
Interest

Anxiety
Irritability

Impulsivity

Mood, Emotion,
Cognitive function

Sex
Appetite
Aggression

Motivation

Drive, pleasure/reward

Dopamine



Dopamine and Depression

- Role of dopamine neurons in behavioral and physiological areas altered in depression
- High rate of comorbidity of Parkinson's disease and depression
- Pathophysiological involvement of DA systems in depression

Imaging Studies

Postmortem studies

Biological fluid studies

- Role of DA circuits in the actions of anti-depressants
 - MAOIs
 - Effects on the DA transporter



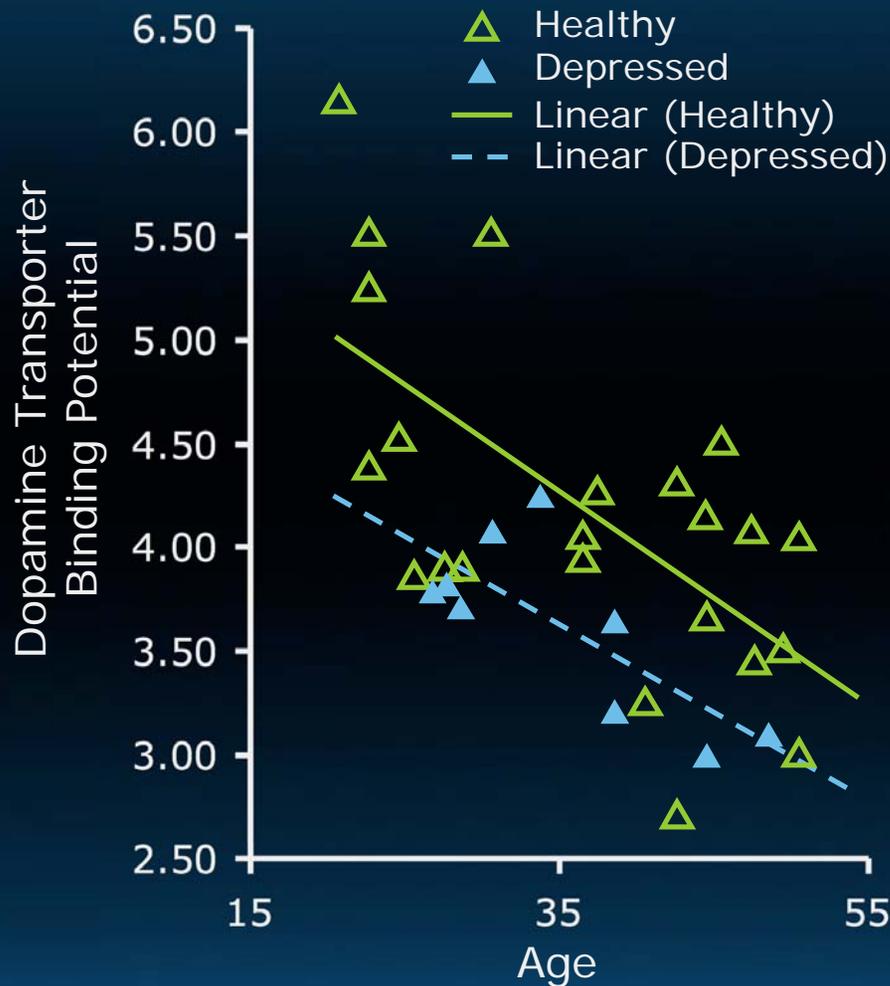
Dopaminergic Abnormalities in Amygdaloid Nuclei in Major Depression

A Postmortem Study

- **Methods:** The specific binding of [¹²⁵I]RTI 55 to the DA transporter, [³H]SCH 23390 to the D1 receptor and [¹²⁵I]epidepride to D2/D3 receptors were measured in the right amygdaloid complex in postmortem brains from 11 subjects with major depression and 11 matched control subjects.
- **Results:** The binding of [¹²⁵I]RTI 55 to DA transporter was significantly lower in the basal and central amygdaloid nuclei, whereas the binding of [¹²⁵I]epidepride to D2/D3 receptors was significantly higher in the basal, central, and lateral amygdaloid nuclei in major depression compared with control subjects. No difference in the binding of [³H]SCH 23390 to D1 receptors was observed.



Lower Dopamine Transporter Binding Potential in Striatum During Depression



- Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: $F_{1,29} = 7.1, p = .01$)

Meyer J, et al. *NeuroReport* 2001;12:4121-4125.



Decreased Presynaptic Dopamine Function in the Left Caudate of Depressed Patients with Affective Flattening and Psychomotor Retardation

Marie-Laure Paillère Martinot, MD, PhD

Véronique Bragulat, MB

Eric Artiges, MD

Frédéric Dollé, PhD

Françoise Hinnen

Roland Jouvent, MD, PhD

Jean-Luc Martinot, MD, PhD

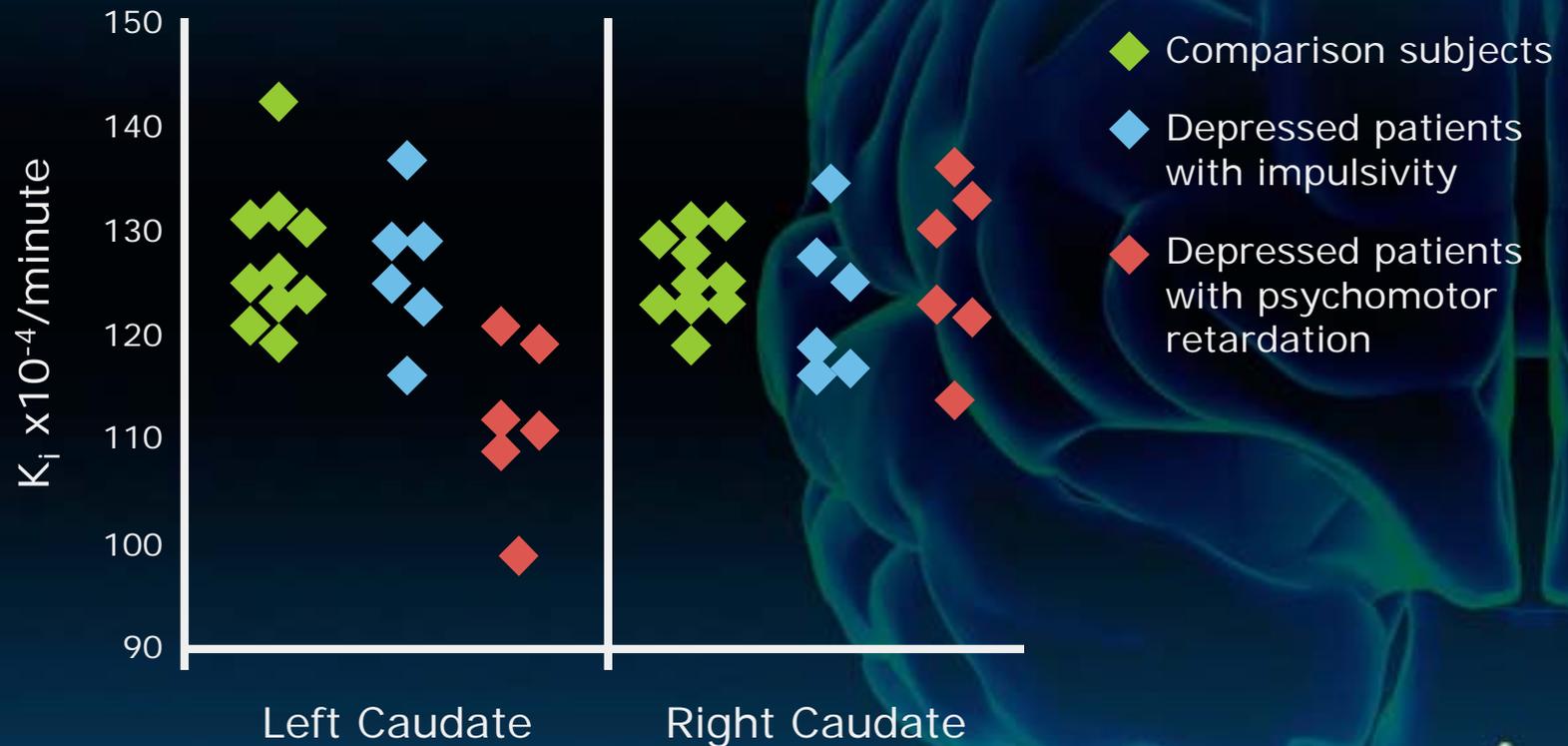


Objective, Method, Results

- **Objective:** The study assessed striatal presynaptic dopamine function in patients with different subtypes of depression.
- **Method:** Magnetic resonance imaging and positron emission tomography with [^{18}F]fluorodopa ([^{18}F]DOPA) were used to compare six depressed patients with marked affective flattening and psychomotor retardation, six depressed patients with marked impulsivity and anxiety, and 10 healthy comparison subjects. Depressed patient groups were matched for severity of depression.
- **Results:** [^{18}F]DOPA uptake K_i values in the left caudate were significantly lower in patients with psychomotor retardation than in patients with high impulsivity and in comparison subjects.
- **Conclusions:** These results suggest that left caudate dopamine function differs between depressed patients with psychomotor retardation and those with impulsivity and provide direct evidence of a link between dopamine hypofunction and psychomotor retardation in depression.



[¹⁸F]Fluorodopa Uptake Ki Values in the Left and Right Caudate of Healthy Subjects (n = 10), Depressed Patients with Impulsivity (n = 6), and Depressed Patients with Psychomotor Retardation (n = 6)



Martinot M, et al. *Am J Psychiatry* 2001;158:314-316.

Symptom Overlap Between Schizophrenia and Bipolar Disorder

Bipolar Disorder

Schizophrenia

Mania:
Irritability
Grandiosity
Euphoria

Aggression
Agitation
Anxiety
Mood swings
Psychotic thinking
Hostility
Impulsivity
Depression
Suicidal thoughts

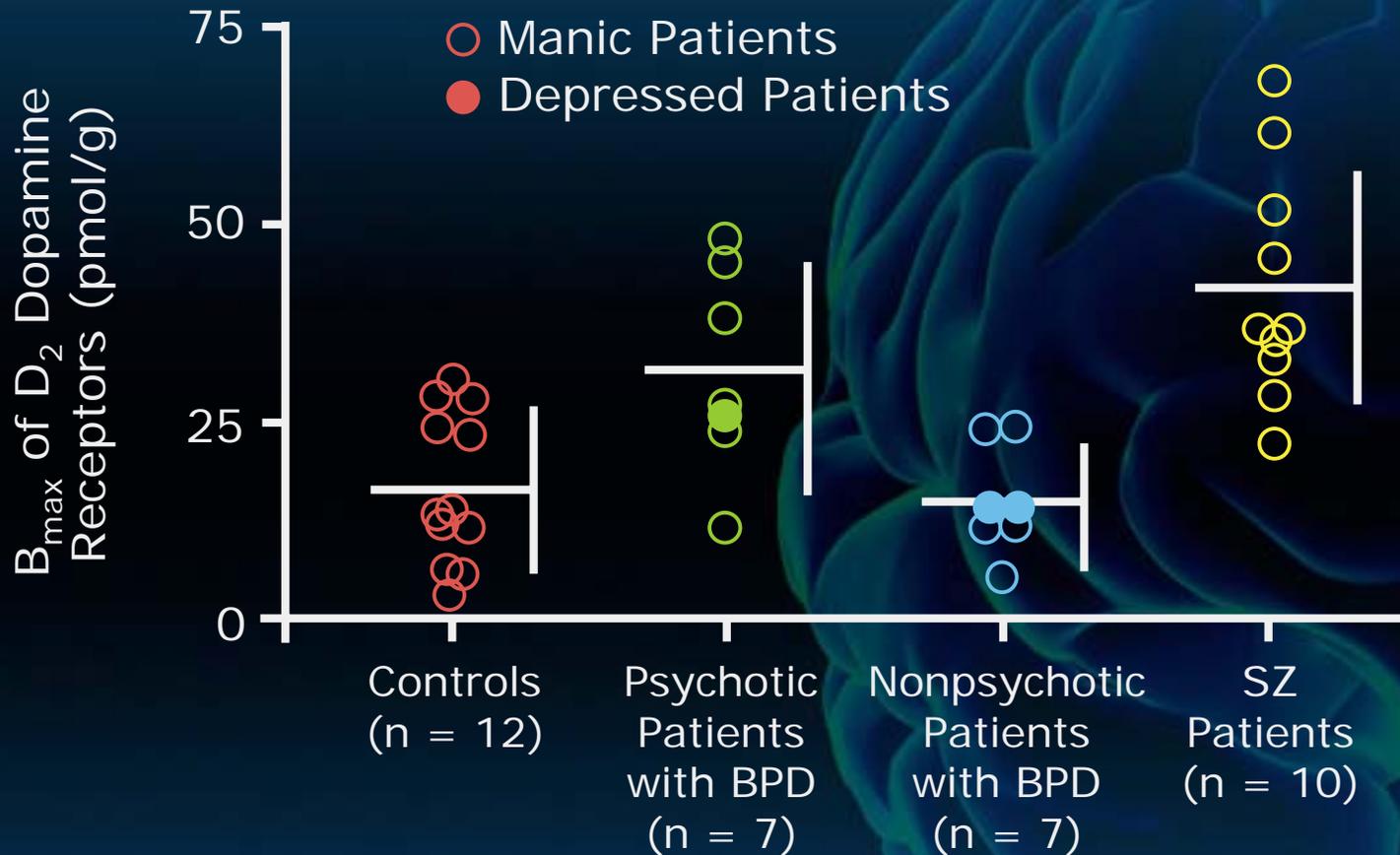
Negative Symptoms:
Affective flattening
Apathy

Positive Symptoms:
Delusions
Hallucinations

Keck PE, et al. *Med Clin North Am* 2001;85:645-661.
Escamilla MA. *Psychiatr Serv* 2001;52:911-919.



Increased D₂ Receptor Density in SZ and Psychotic Patients with BPD



Scatterplot of caudate and putamen D₂ dopamine receptor density (B_{max}) values in SZ, psychosis with BPD, non-psychosis with BPD, and normal controls

Pearlson GD, et al. *Arch Gen Psychiatry* 1995;52:471-477.



Clinical Case Challenge

- 51-year-old male presents with complaint of low mood, “I just want to lie in bed all day”
- Friends inviting him to do things but he isn't motivated to do so
- Past history of bipolar II disorder
- Currently treated with lithium
- Treatment plan - augment or not?



Pramipexole for Bipolar II Depression

A Placebo-Controlled Proof of Concept Study

Carlos A. Zarate, Jr., Jennifer L. Payne,
Jaskaran Singh, Jorge A. Quiroz,
David A. Luckenbaugh, Kirk D. Denicoff,
Dennis S. Charney, and Husseini K. Manji

Zarate C, et al. *Biol Psychiatry* 2004;56:54-60.

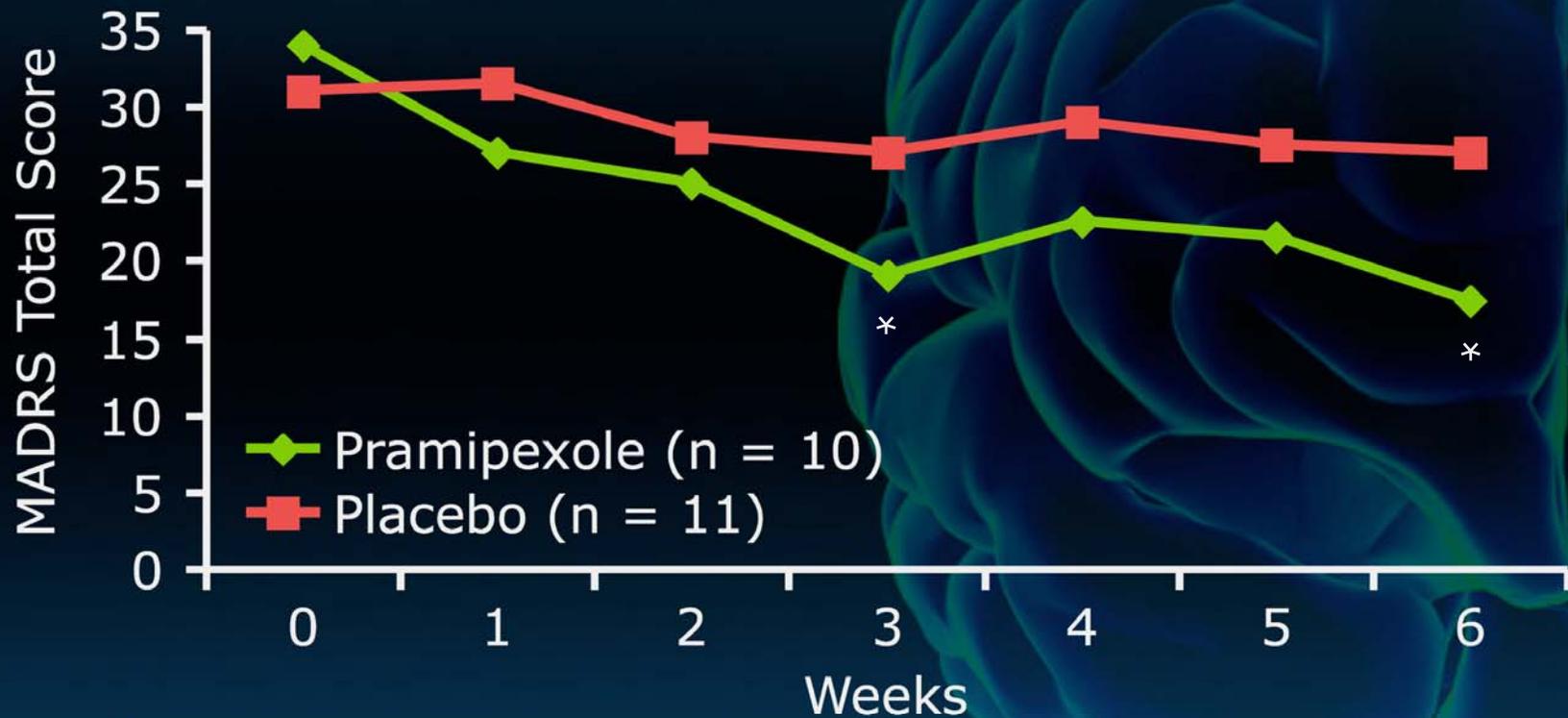


Background, Methods, Results

- **Background:** The original serotonergic and noradrenergic hypotheses do not fully account for the neurobiology of depression or mechanism of action of effective antidepressants. Research implicates a potential role of the dopaminergic system in the pathophysiology of bipolar disorder. The current study was undertaken as a proof of the concept that dopamine agonists will be effective in patients with bipolar II depression.
- **Methods:** In a double-blind, placebo-controlled study, 21 patients with DSM-IV bipolar II disorder, depressive phase on therapeutic levels of lithium or valproate were randomly assigned to treatment with pramipexole (n = 10) or placebo (n = 11) for 6 weeks. Primary efficacy was assessed by the Montgomery-Asberg Depression Rating Scale.
- **Results:** All subjects except for one in each group completed the study. The analysis of variance for total Montgomery-Asberg Depression Rating Scale scores showed a significant treatment effect. A therapeutic response (>50% decrease in Montgomery-Asberg Depression Rating Scale from baseline) occurred in 60% of patients taking pramipexole and 9% taking placebo ($p = .02$). One subject on pramipexole and two on placebo developed hypomanic symptoms.



Mean Change in MADRS Total Scores from Baseline in Patients with Bipolar II Depression Who Were Treated with Pramipexole or Placebo for 6 Weeks



* $p < .05$

MADRS = Montgomery-Asberg Depression Rating Scale

Zarate C, et al. *Biol Psychiatry* 2004;56:54-60.



Conclusions

The dopamine agonist pramipexole*
was found to have significant
antidepressant effects in patients
with bipolar II depression

* Not an approved FDA indication

Zarate C, et al. *Biol Psychiatry* 2004;56:54-60.



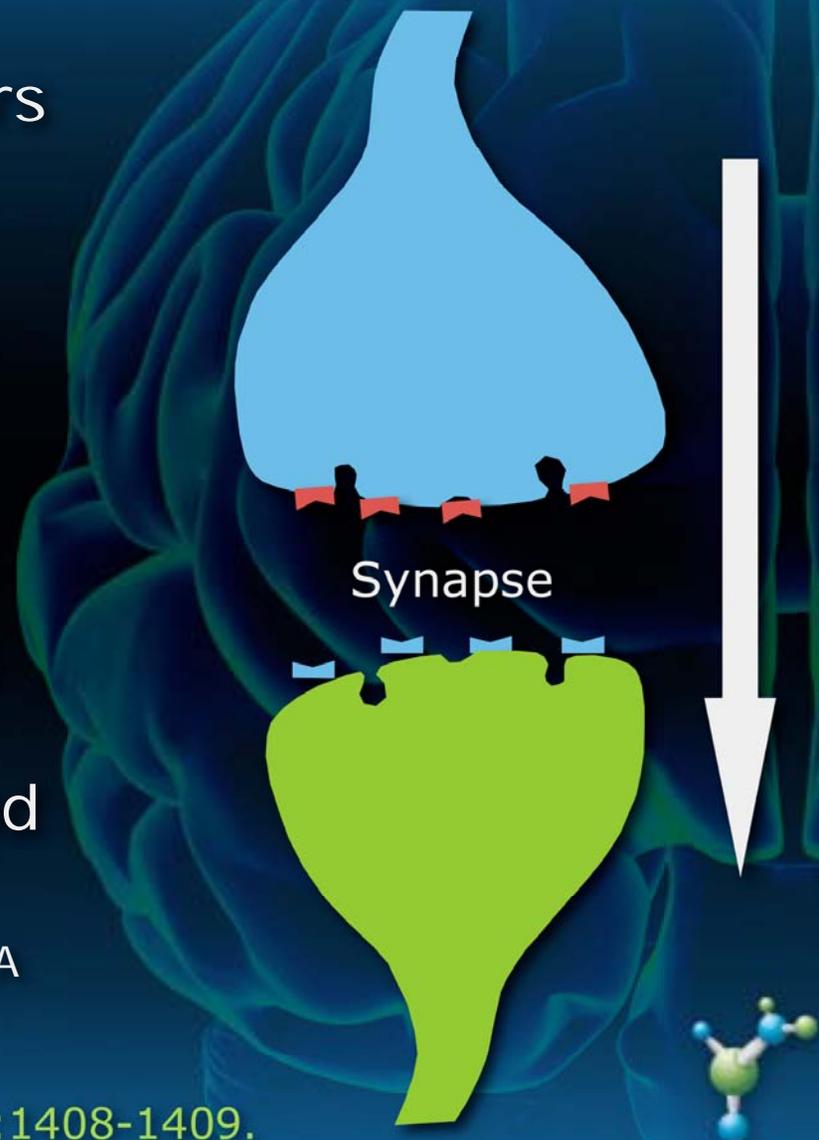
Learning Objective 2

Compare and contrast the pharmacologic properties of antipsychotics in an evidence-based model to identify the most appropriate therapy for each patient



Serotonin (5-HT) System

- 14 types of 5-HT Receptors in the human brain
- **Presynaptic** and postsynaptic
- Most important one are:
 - 5-HT_{2A}
 - 5-HT_{2C}
 - 5-HT_{1A}
- Typical antipsychotics are not active against 5-HT_{2A}
- Atypicals activity is in good part derived from their antagonism toward 5-HT_{2A} and D₂



Role of Serotonin Receptor 2A

- Serotonin controls, via its receptor 5-HT_{2A}, the release of dopamine in important pathways
- Nigrostriatal area:
 - 5-HT opposes DA release
 - Antagonism of the 5-HT_{2A} reverse dopamine blockade and maintain physiologic function of DA neurons regulating movement
- Mesolimbic area:
 - Block DA release but to a lesser degree
 - Antagonism of the 5-HT_{2A} will not reverse antipsychotic action of the dopamine
- Mesocortical area:
 - 5-HT decreases DA neurons activity
 - 5-HT_{2A} reverse suppression
 - Stimulate depressed DA neurons involved in negative and cognitive symptoms

Stahl SM, et al. *J Clin Psychiatry* 2003;64:1408-1409.



Role of Serotonin Receptor 2C

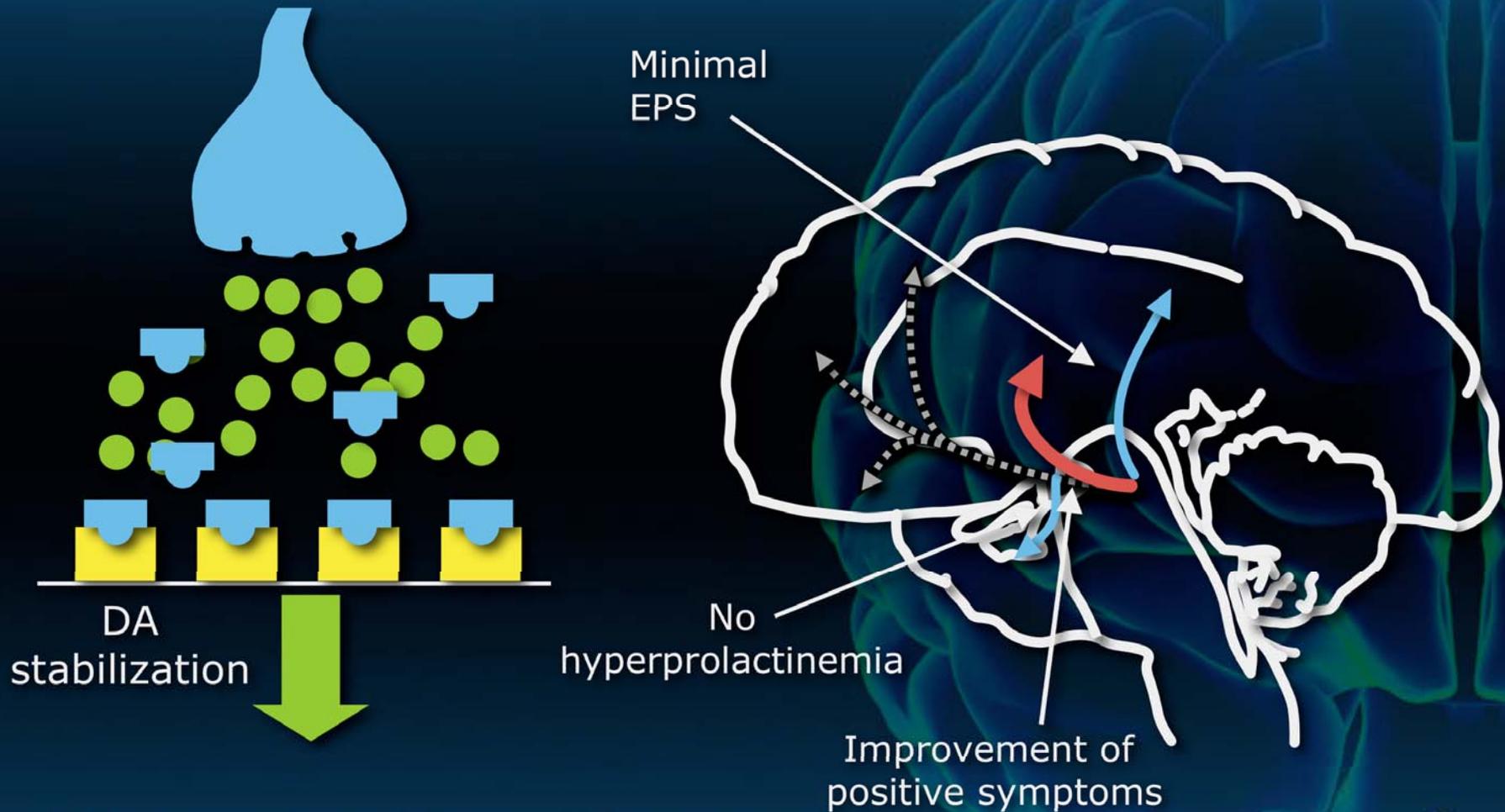
- Involved in the down-regulation of dopamine and norepinephrine in the cortex
- Partial agonism at the 5-HT_{2C} receptor disinhibits dopamine and norepinephrine circuits in the cortex

Stahl SM, et al. *J Clin Psychiatry* 2003;64:1408-1409.



Dopamine Partial Agonist

Decrease EPS, Prolactin, Positive Symptoms



EPS = extrapyramidal symptoms

Adapted from Burris K, et al. *J Pharmacol Exp Ther* 2002;302:381.

Kane J, et al. *J Clin Psychiatry* 2002;63:763.



Implications of Partial Agonist Activity at the D₂ receptor

- Allows “physiologic” activity of dopamine system¹
- Provides potent antipsychotic activity with minimal EPS^{2,3}

1. Burris K, et al. *J Pharmacol Exp Ther* 2002;302:381.

2. Kane J, et al. *J Clin Psychiatry* 2002;63:763.

3. McGavin, Goa. *CNS Drugs* 2002;16:779.



Relative Receptor Binding Affinities of Atypical Antipsychotics

	ZIP ^{1,2}	RIS ^{1,2}	OLZ ^{1,2}	QUE ²	CLO ²	ARI ³
D ₂	++++	++++	++	+	+	++++*
5HT _{2A}	++++ +	++++	++++	+	++++	++++
5HT _{2C}	++++ +	++++	++++	-	++	++
5HT _{1A}	++++*	+	-	+	+	++++*
5HT _{1D} ^A	++++	+	+	-	-	-
A ₁ - adrenergic	++	++++	++	++	++++	++
M ₁ - muscarinic	-	-	++++	++	++++	-
H ₁ - histaminergic	++	++	++++	++++	++++	++
5HT-NE reuptake ^B	++	-	-	(-5HT)(+NE)	(-5HT)(+NE)	(+5HT)

Affinity represented as: +++++ very high, ++++ high, ++ moderate, + low, - negligible
 A = bovine binding affinity; B = rat synaptosomes; all other affinities human.

* Partial agonist

1. Zorn. *Interactive Monoaminergic Brain Dis* 1999.

2. Schmidt AW. *Soc Neurosci Abstr* 1998.

3. Aripiprazole PI.



Receptor Pharmacology

Potential Clinical Implications of Second Generation Atypical (SGA) Receptor Activities

- D₂ antagonism → Positive symptom efficacy, EPS, endocrine effects
- 5-HT_{2A} antagonism → Negative symptom efficacy, reduced EPS
- High 5-HT_{2A}/D₂ affinity ratio → Antipsychotic efficacy, reduced EPS (compared with D₂ antagonism alone)
- 5-HT_{1A} agonism → Antidepressant and anxiolytic activity, improved cognition, reduced EPS
- 5-HT_{1D} antagonism → Antidepressant activity
- 5-HT_{2C} antagonism → Antidepressant activity
- Mixed 5-HT/NE neuronal reuptake inhibition → Antidepressant and anxiolytic activity
- α₁ antagonism → Postural hypotension
- H₁ antagonism → Sedation, weight gain
- M₁ antagonism → Anticholinergic side effects, weight gain (e.g., cognitive impairment)

In vitro findings may not correlate with clinical results

Zorn SH, et al. *Interactive Monoaminergic Brain Disorders* 1999:377-393.

Tandon R, et al. *J Serotonin Res* 1997;4:159-177.



Learning Objective 3

Design and implement a treatment strategy that incorporates non-pharmacologic and pharmacologic strategies to improve outcomes in patients with schizophrenia and bipolar disorder

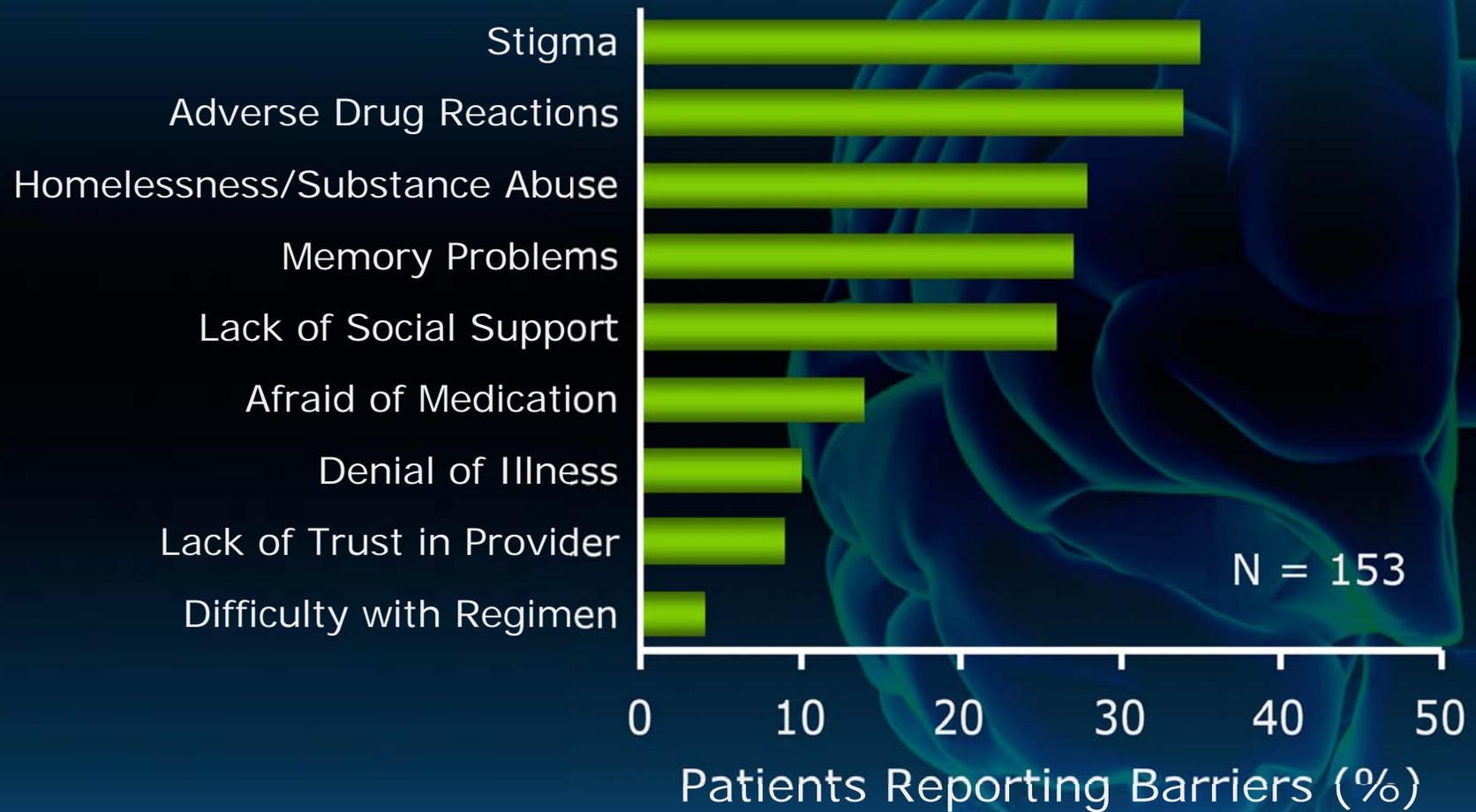


Clinical Case Challenge

- 31-year-old female
- Past history of schizoaffective disorder, currently has good control of symptoms
- Gained 12 lbs on current atypical antipsychotic
- Decrease in medication compliance due to weight gain
- Treatment dilemma: *the equipoise of efficacy vs. tolerability*

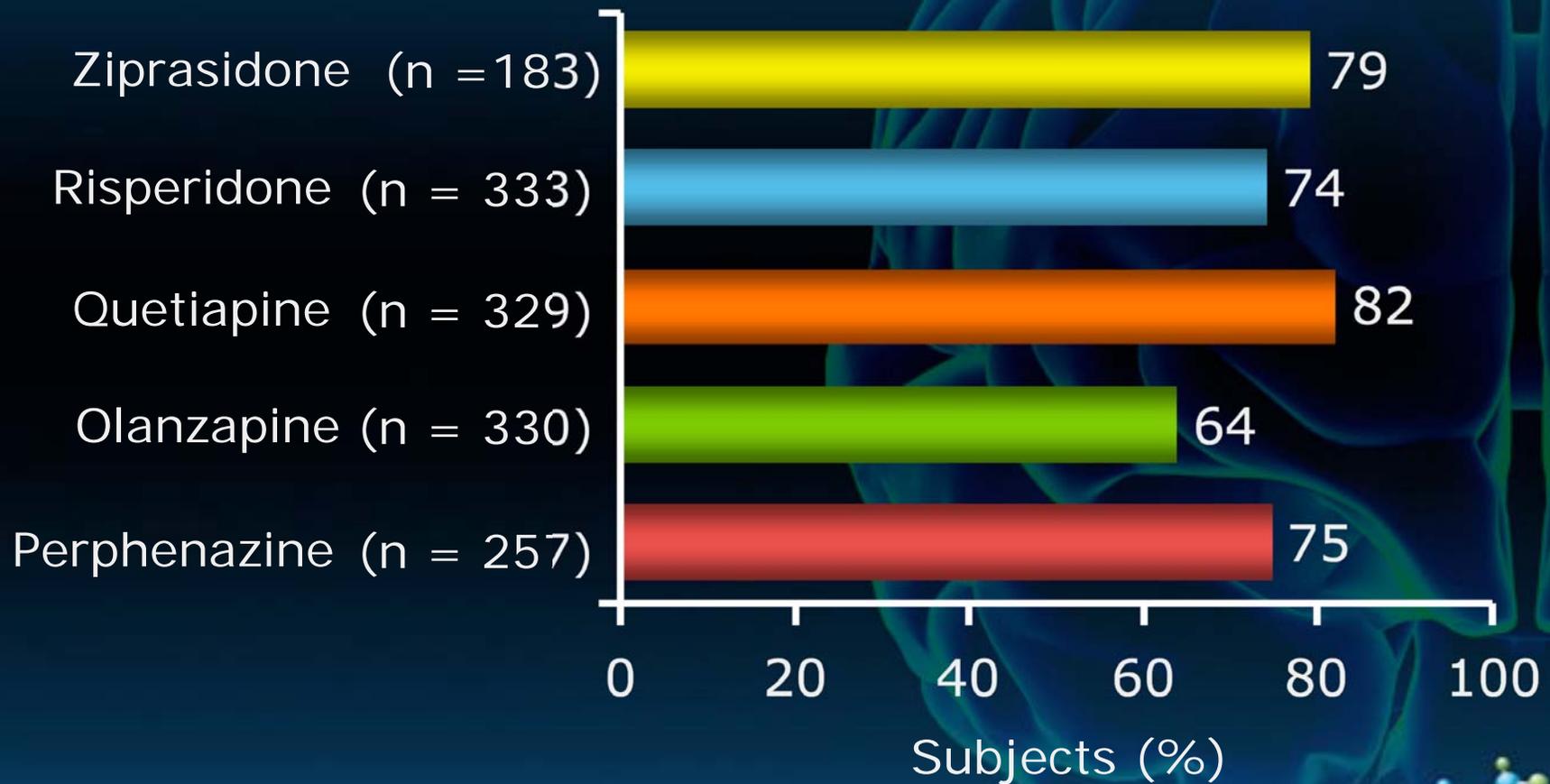


Side Effects Are a Key Reason Why Patients Stop Their Antipsychotic Medications



Hudson TJ, et al. *J Clin Psychiatry* 2004;65:211-216.

CATIE: *Treatment Discontinuation All Causes (74%)*

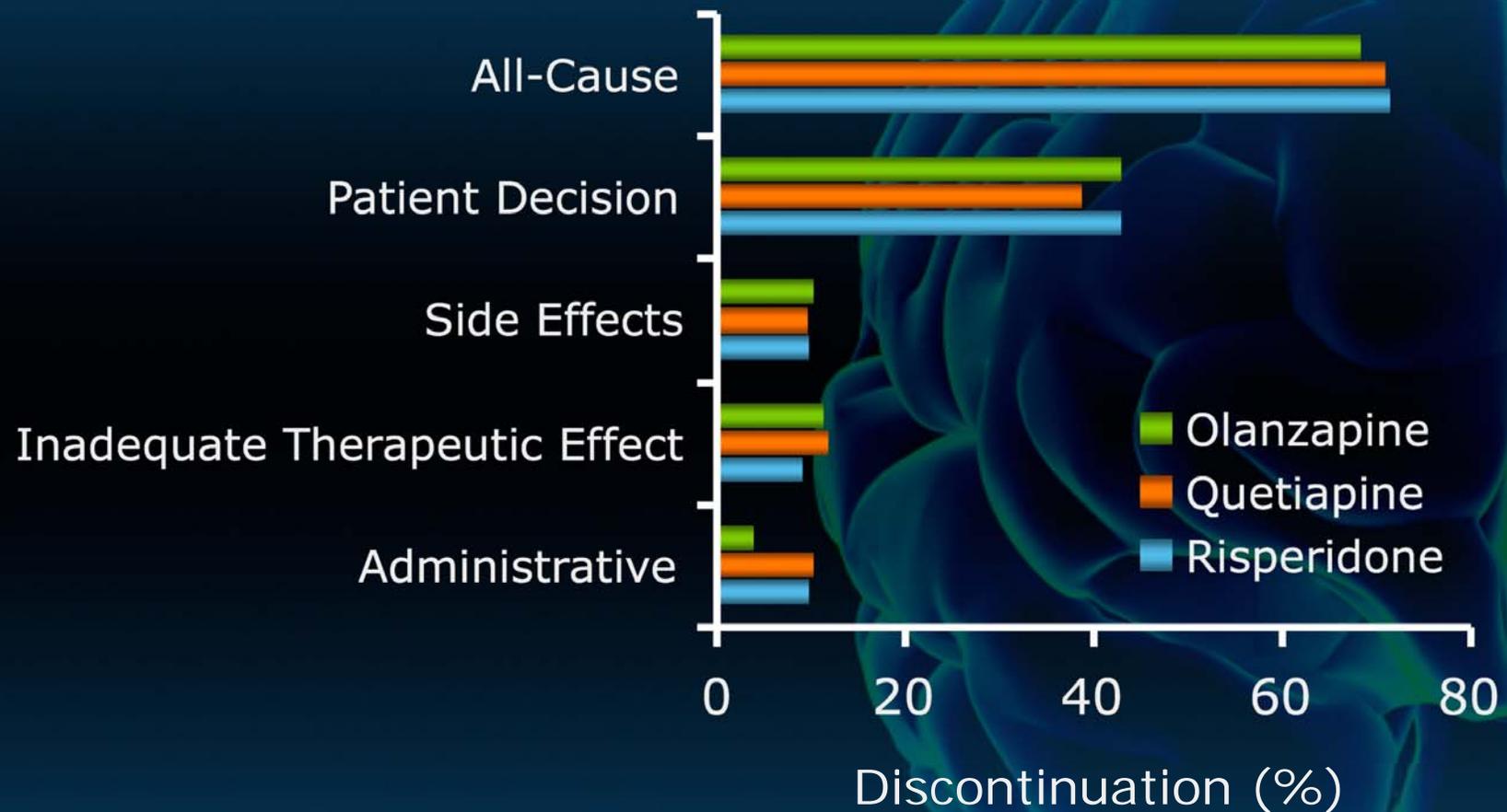


Lieberman JA, et al. *N Engl J Med* 2005;353:1209-1223.



CAFE

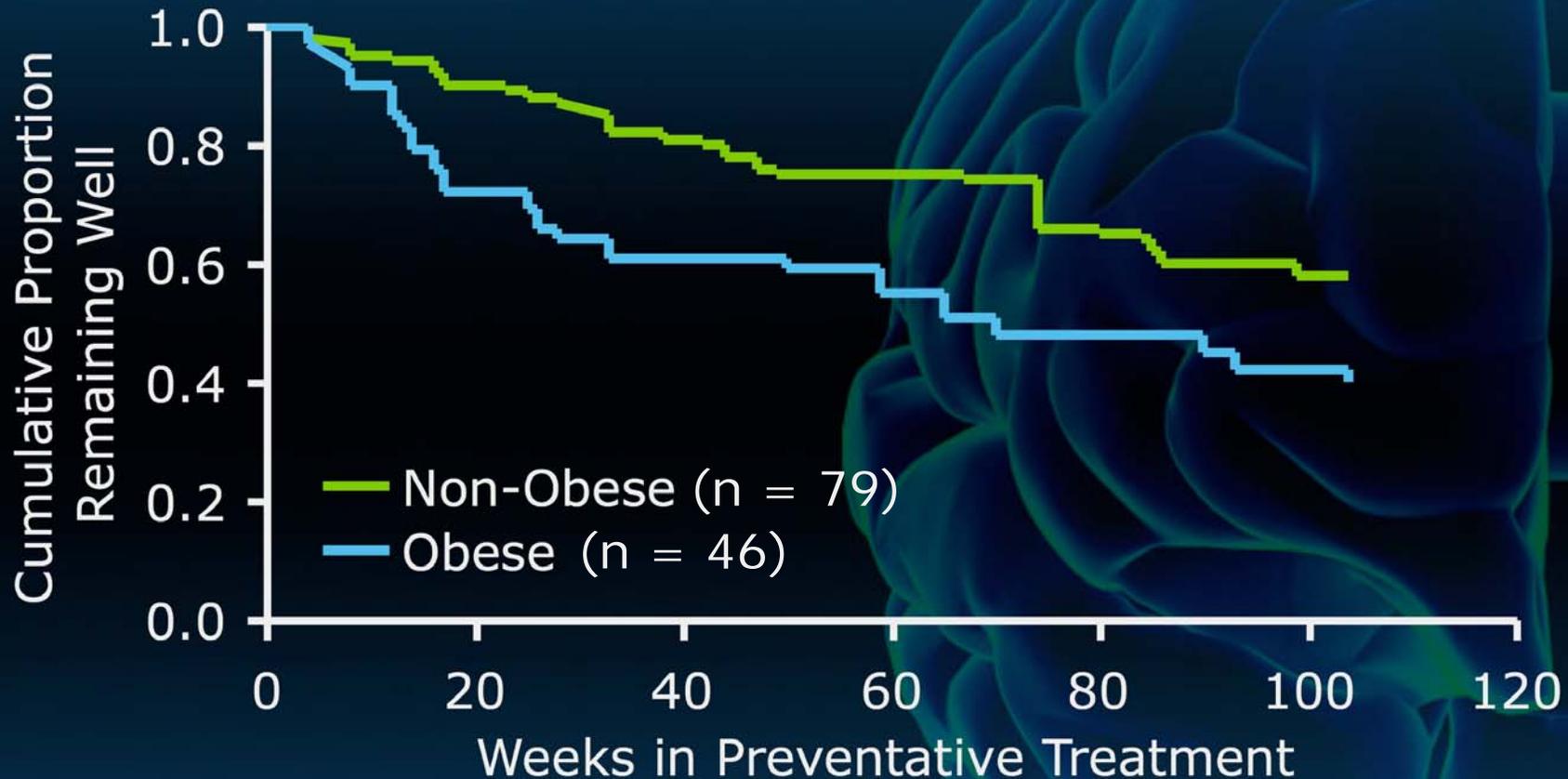
Treatment Discontinuation



For each category above, the comparison of quetiapine vs. olanzapine and quetiapine vs. risperidone met *a priori* test of non-inferiority (20%) at $p < .05$

McEvoy J, et al. *Am J Psychiatry* (in press).

Relapse in BD in Obese vs. Non-Obese Patients



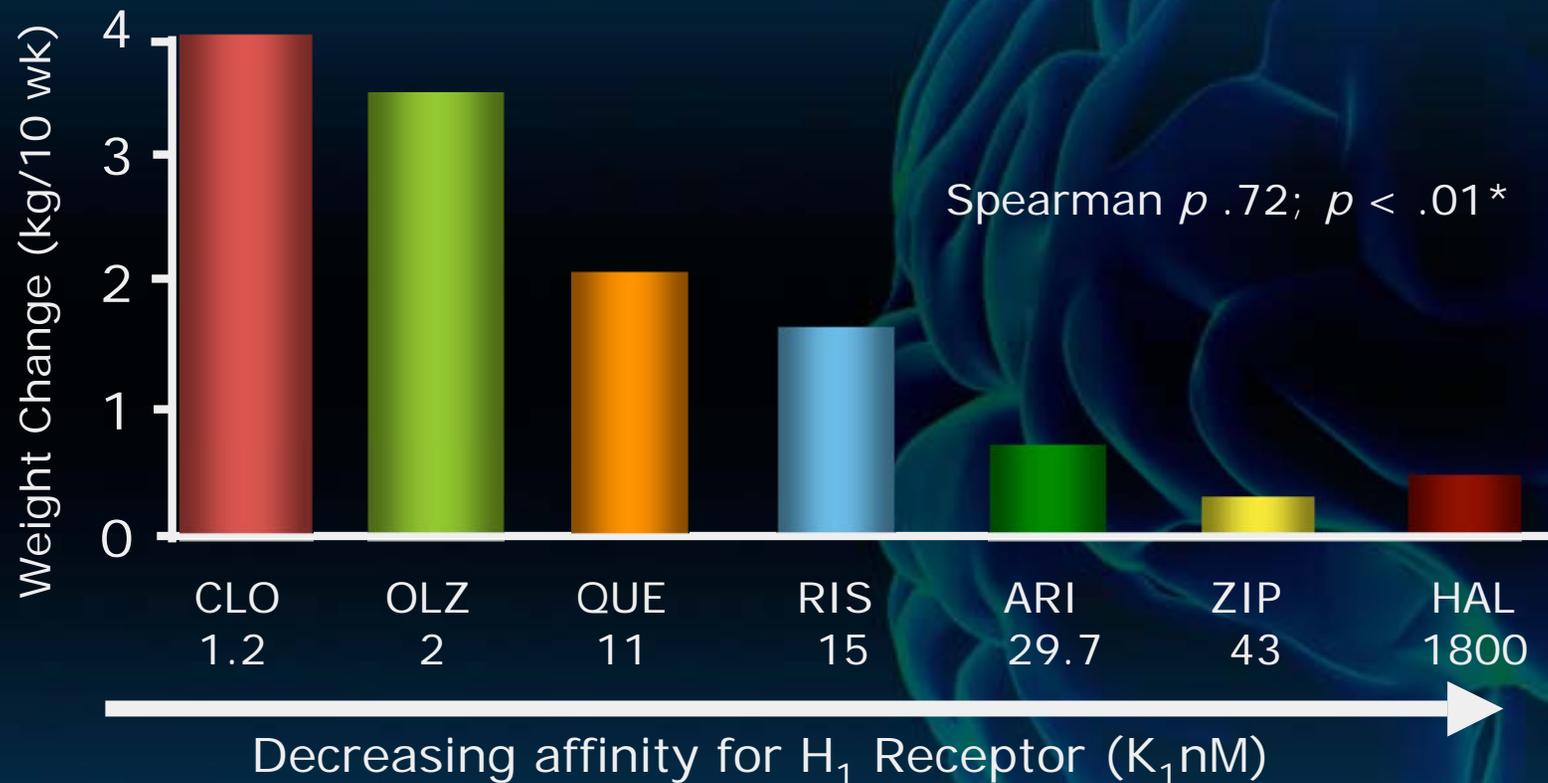
$p < .007$

Obese patients had shorter time to recurrence of depression than non-obese patients

Fagiolini A, et al. *Am J Psychiatry* 2003;160:112-117.



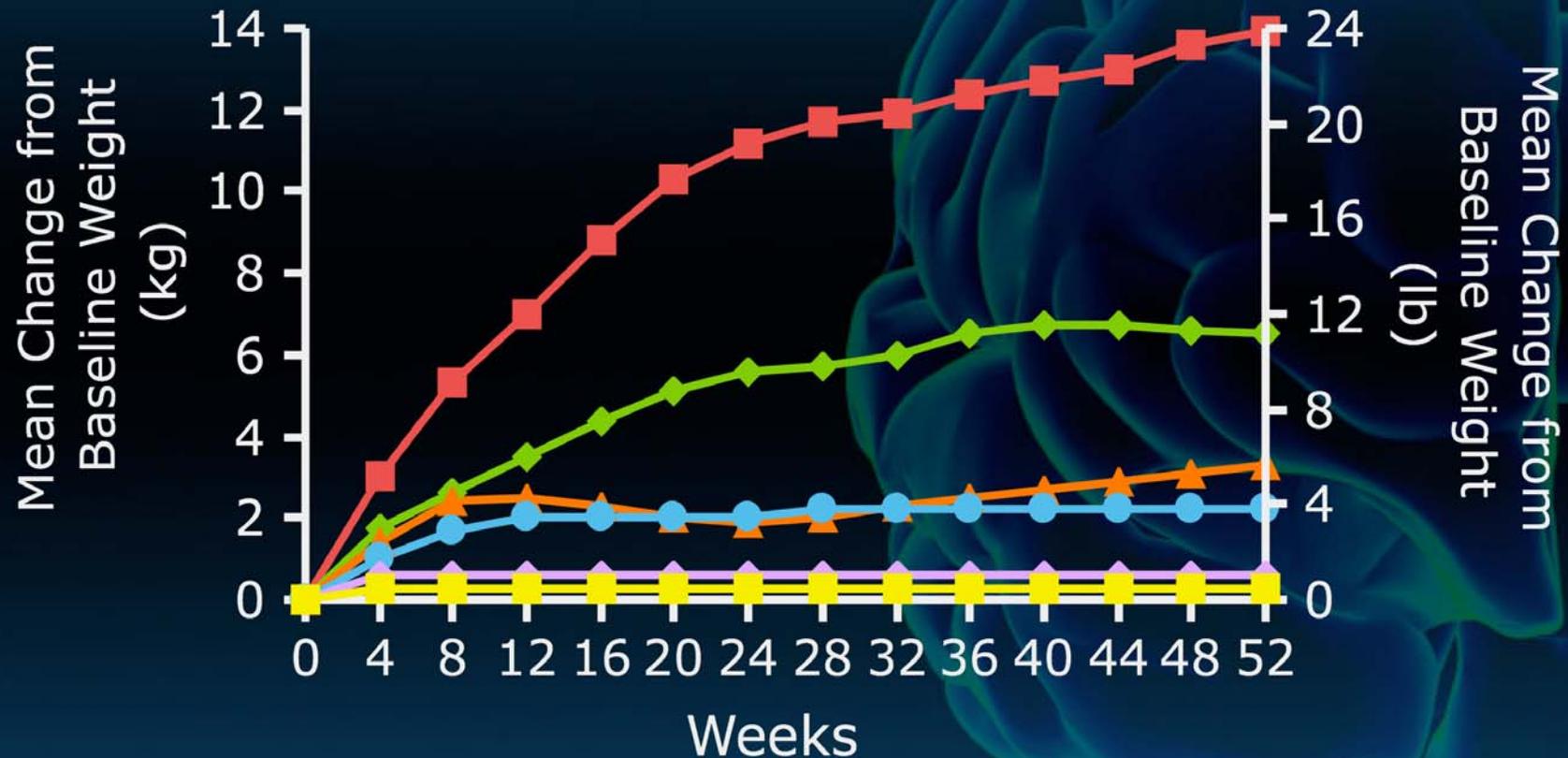
Histamine H₁ Receptor Affinity Might Predict Weight Gain



* Correlation of 17 agents to induce weight gain and affinity for 12 receptors
Adapted from Kroeze WK, et al. *Neuropsychopharmacology*. 2003;28:519-526.

1-Year Weight Change with Atypical Antipsychotic Agents

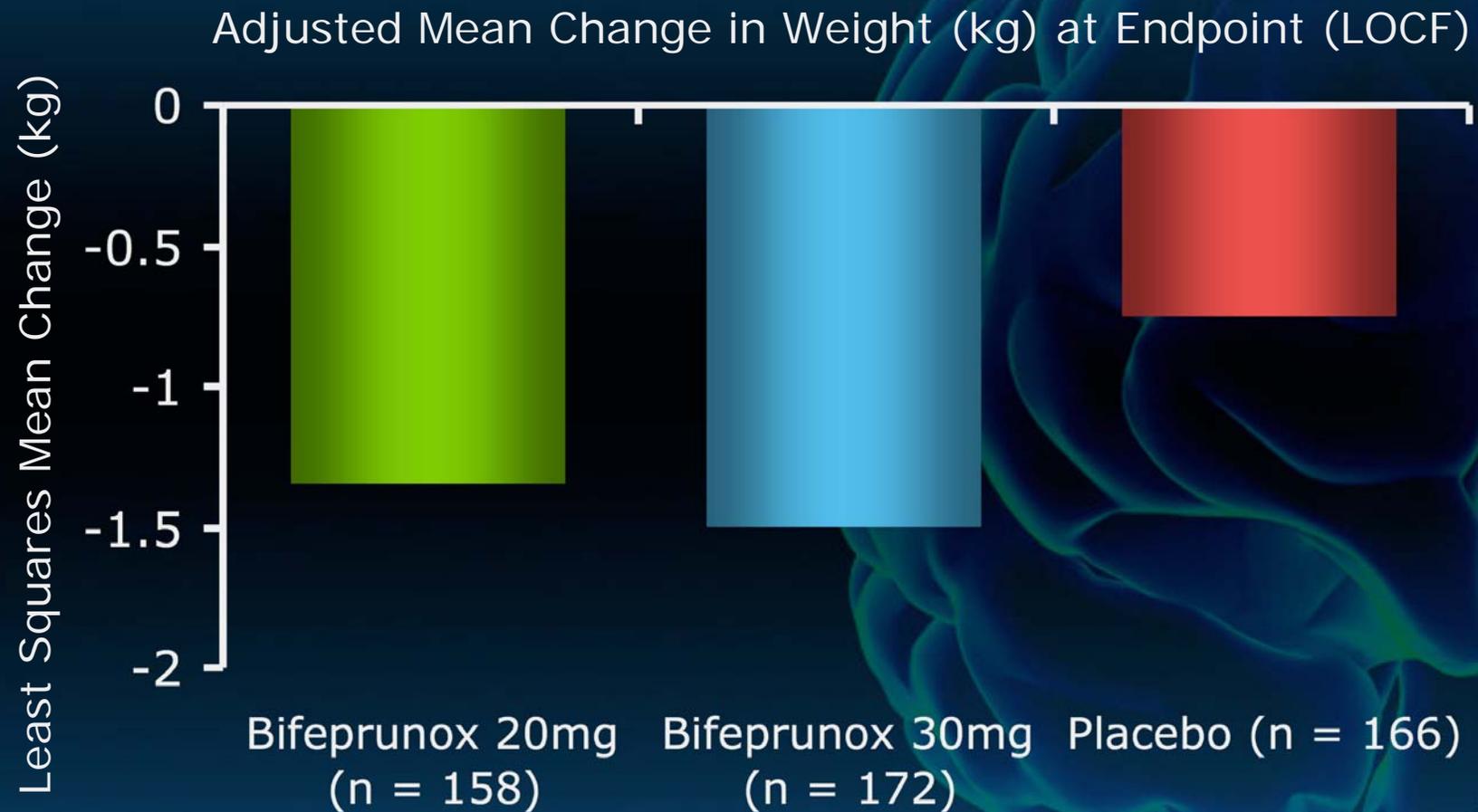
■ OLZ 15mg ◆ OLZ all doses ▲ QUE ● RIS ◆ ARI ■ ZIP



Nemeroff CB. *J Clin Psychiatry* 1997;58(suppl 10):45-49.
Kinson BJ. *J Clin Psychiatry* 1998;59(suppl 19):18-22.
Brecher, et al. *Neuropsychopharmacology* 29(Suppl 1):S109.



Mean Weight Change from Baseline with Bifeprunox 6-Month Data



Bourin M, et al. Presented at ACNP 2007.

Formulating a Treatment Plan

Nonpharmacologic Interventions

Rehabilitation

Family intervention	<ul style="list-style-type: none">● Education about the illness and treatment options● Training that includes coping and management strategies, identification of prodromal symptoms, and problem-solving skills● Support for family and caregivers● Education and training for nonfamily members who may be involved in care of patients
Social skills training	<ul style="list-style-type: none">● Behavioral techniques or learning activities that improve social interaction skills

McEvoy JP, et al. *J Clin Psychiatry* 1999;60(suppl 11):1-80.
Lehman AF, et al. *Am J Psychiatry* 2004;161(suppl):1-56.



Formulating a Treatment Plan

Nonpharmacologic Interventions

Rehabilitation	
Vocational rehabilitation	<ul style="list-style-type: none">● Ongoing job support is necessary for long-term employment● Support may include instruction on personal hygiene, provision of transportation, and on-the-job support or training with the goal of facilitating competitive employment
Cognitive remediation	<ul style="list-style-type: none">● Therapy to improve or cope with the cognitive deficits of schizophrenia
Cognitive therapy	<ul style="list-style-type: none">● Therapy to encourage patients to examine evidence for and against their belief so as to develop acceptable alternatives
Peer support/ self-help group	<ul style="list-style-type: none">● Support groups for patients and families that meet regularly to share experiences, provide advice, and offer emotional support

McEvoy JP, et al. *J Clin Psychiatry* 1999;60(suppl 11):1-80.
Lehman AF, et al. *Am J Psychiatry* 2004;161(suppl):1-56.

Formulating a Treatment Plan

Service Delivery

Service Delivery	
Case management	<ul style="list-style-type: none">● Case manager ensures that patients receive coordinated, continuous, and comprehensive services
Assertive Community Treatment (ACT)	<ul style="list-style-type: none">● Includes case management and active treatment interventions in an integrated multidisciplinary team approach with a 1:10 staff to patient ratio
Integrated treatment of dual diagnosis	<ul style="list-style-type: none">● Dual diagnosis denotes co-occurrence of mental illness and substance abuse● Combination of mental health and substance abuse interventions tailored to patient-specific needs

McEvoy JP, et al. *J Clin Psychiatry* 1999;60(suppl 11):4-72.

Lehman AF, et al. *Am J Psychiatry* 2004;161(suppl):1-56.

Clinical Connections

- Receptor pharmacology has an impact on clinical outcomes
- There is a link between side effects and medication adherence
- Minor non-adherence can have major consequences
- Design an individualized pharmacotherapy and psychotherapy plan to achieve optimal patient outcomes

