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The Evolving Psychopharmacology of Major Depressive Disorder:

Narrowing the Treatment Gap

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Presented by: Rakesh Jain, MD, MPH

Position: Rakesh Jain, MD, MPH, is Associate Clinical Professor in the Department of Psychiatry at Texas Tech Health Sciences Center Medical School at Permian Basin, Midland, Texas.

Education: Dr Jain received a medical degree from the University of Calcutta in India. He then attended The University of Texas School of Public Health in Houston, and earned a Master of Public Health degree. He completed a residency in Psychiatry and a fellowship in Child and Adolescent Psychiatry at The University of Texas Medical School in Houston. In addition, Dr Jain completed a postdoctoral fellowship in Research Psychiatry at The University of Texas Mental Sciences Institute in Houston.

Practice: Dr Jain's research focuses on the effects of medications on short- and long-term treatment of depression, anxiety, pain/mood overlap disorders, attention-deficit/ hyperactivity disorder, and psychosis in adult and child/adolescent populations.

Rakesh Jain, MD, MPH, is a paid consultant for Otsuka/Lundbeck.

Presented by: Vladimir Maletic, MD, MS

Position: Vladimir Maletic, MD, MS, is Clinical Professor of Neuropsychiatry and Behavioral Science at the University of South Carolina School of Medicine in Columbia. He is also a consulting associate in the Division of Child and Adolescent Psychiatry at Duke University Medical Center in Durham, North Carolina.

Education: Dr Maletic earned his medical degree from the University of Belgrade in Yugoslavia, where he also completed his postgraduate studies in Neuroscience at the Center for Multidisciplinary Studies. He then completed a residency in Psychiatry at the Medical College of Wisconsin in Milwaukee and a residency in Child Psychiatry at Duke University Medical Center.

Practice: Dr Maletic's research focuses on the neurobiology of psychiatric illness, including schizophrenia, mood disorders, anxiety disorders, attention-deficit/hyperactivity disorder, and the regulation of sleep and wakefulness.

Vladimir Maletic, MD, MS, is a paid consultant for Otsuka/Lundbeck.

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Objectives

Describe the imbalance of neurotransmitter systems implicated in MDD and the potential need to target multiple systems in treating MDD

Consider the potential impact of MDD and inadequate treatment response on brain structure, function, and patient outcomes

Discuss the psychopharmacology of current treatment options and the role of augmentation in treating MDD

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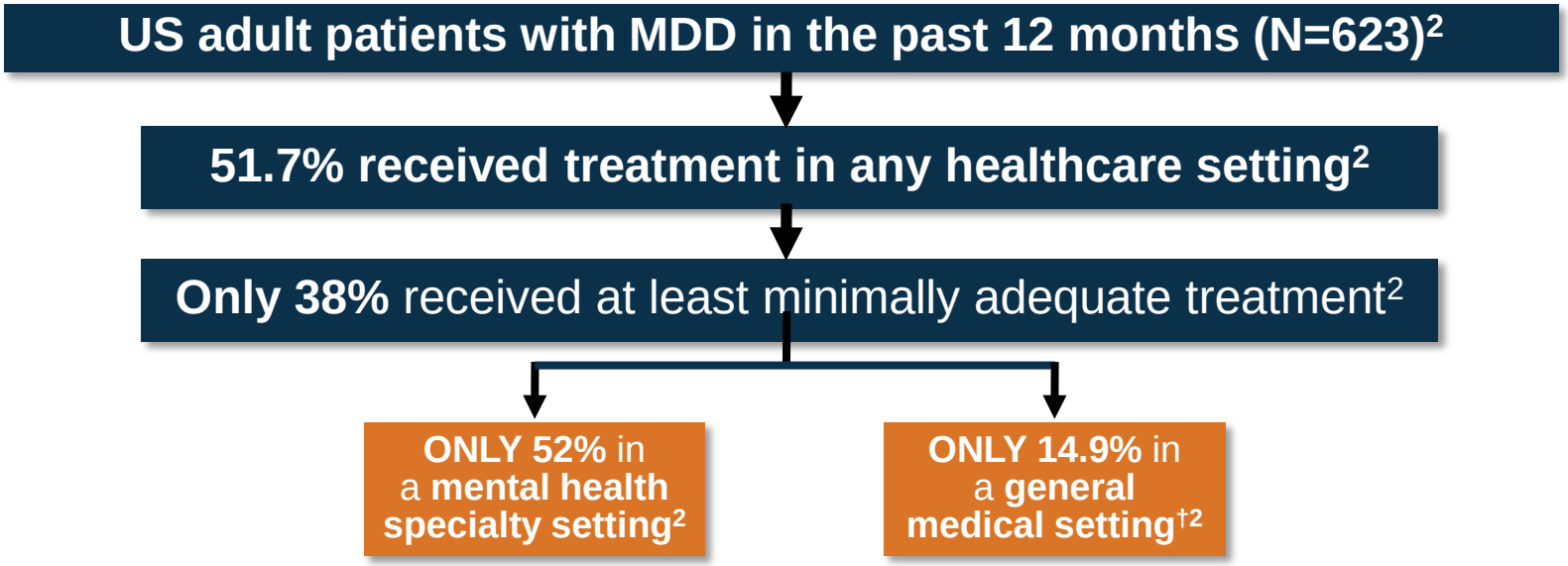
AN UNMET NEED: TREATING MDD EFFECTIVELY

Rakesh Jain, MD, MPH

MDD: The Burden of Inadequate Treatment[1-5]

In 2012, an estimated **16 million US adults** had at least one major depressive episode in the past year; representing **6.9%** of all US adults[1]

In a 2005 analysis of the National Comorbidity Survey Replication (NCS-R), **only 38% of patients** treated for MDD **received minimally adequate treatment*[2]**



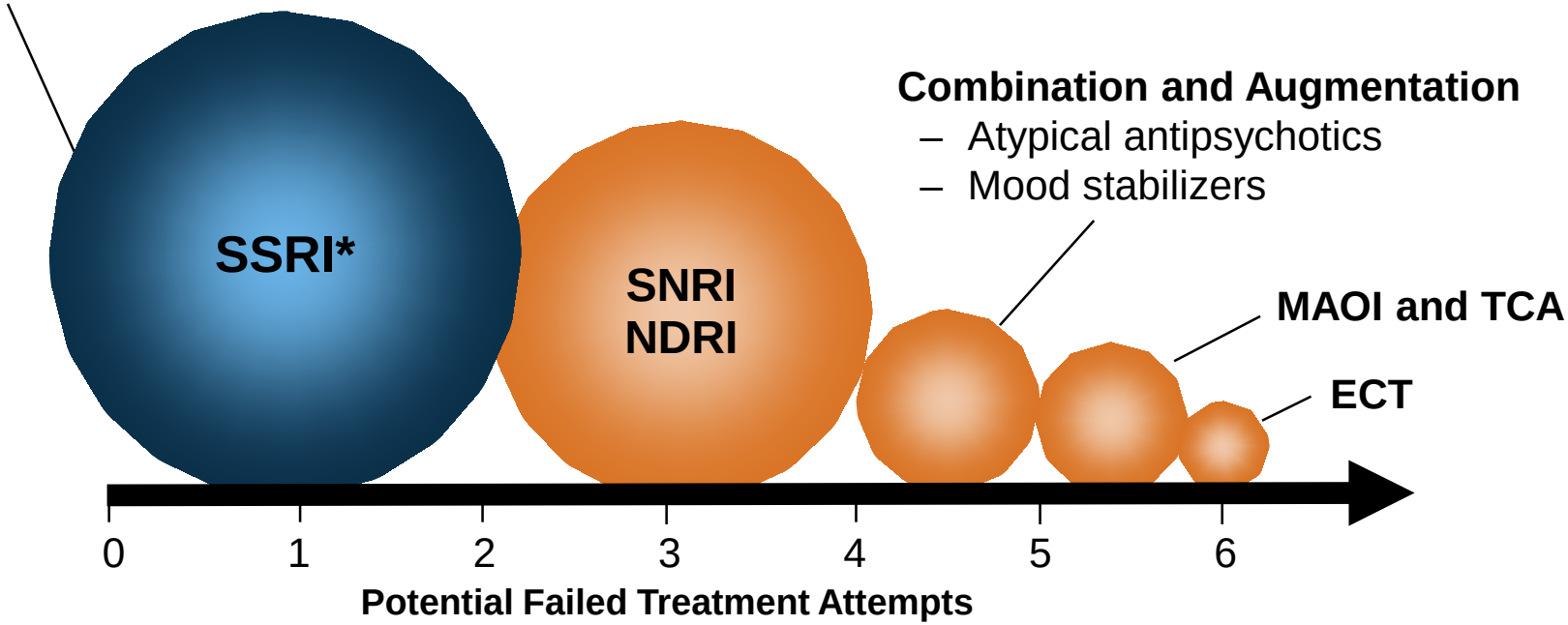
*Minimally adequate treatment was defined as receiving either pharmacotherapy (≥2 months of an appropriate medication for the focal disorder plus >4 visits to any type of physician) or psychotherapy (≥8 visits with any healthcare or human services professional lasting an average of ≥30 minutes).

†Defined as a primary care physician, other general physician, nurse, or any other health professional in non-mental health setting.

1. NIMH. Major depression among adults. Available at: http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml. Accessed April 22, 2015.
2. Wang PS, et al. *Arch Gen Psychiatry.* 2005;62(6):629-640. 3. Little A. *Am Fam Physician*. 2009;80(2):167-172. 4. Moller HJ. *Medicographia.* 2010;32:139-144.
5. Tranter R, et al. *J Psychiatry Neurosci.* 2002;27(4):241-247.

MDD: Treatment Practices

*Up to two-thirds of adult patients will not achieve remission with a selective serotonin reuptake inhibitor (SSRI); APA Guidelines recommend the first strategy when a treatment change is necessary may be to try to optimize SSRI dose



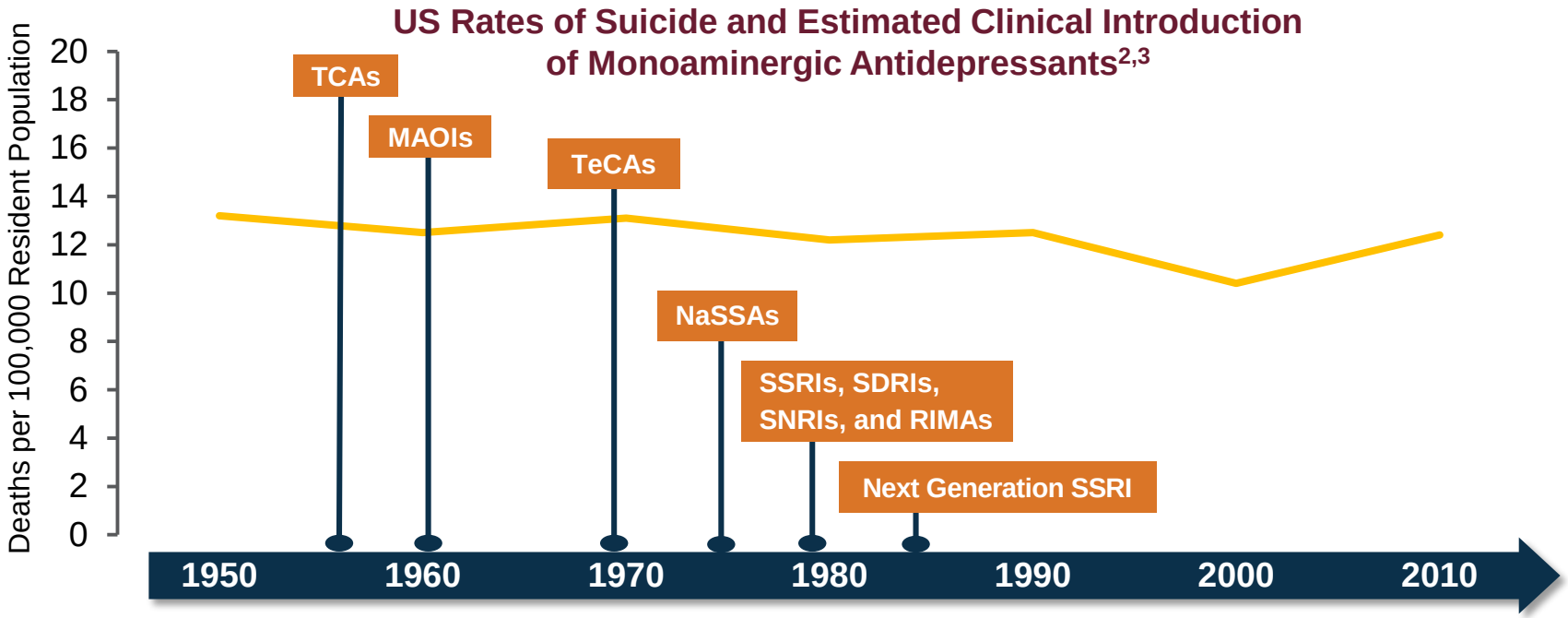
- VNS may be an additional option for individuals who have not responded to at least 4 adequate trials of antidepressant treatment, including ECT

SNRI=serotonin-norepinephrine reuptake inhibitor; NDRI=norepinephrine-dopamine reuptake inhibitor; MAOI=monoamine oxidase inhibitor; TCA=tricyclic antidepressant; ECT=electroconvulsive therapy; VNS=vagus nerve stimluations.

1. Gelenberg AJ, et al; on behalf of the Work Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder.* Third Edition. 2010 2. Al-Harbi KS. *Patient Prefer Adherence.* 2012;6:369-388. 3. Nemeroff CB. *J Clin Psychiatry.* 2007;68 Suppl 8:17-25.
4. Mojtabai R, Olfson M. *J Clin Psychiatry.* 2008;69(7):1064-1074.

Suicide Rates and Antidepressants: Increased Availability Has Had Limited Effect

- Use of antidepressants among adults 18–64 years of age has increased in the United States from 2.2% (1988–1994) to 10.6% (2007–2010)[1]
- Depression is present in at least 50% of all suicides; 15% of patients with treated depression eventually die by suicide[2]



NaSSAs=noradrenergic and specific serotonergic antidepressants; RIMAs=reversible and selective inhibitors of MAO; SDRIs=selective dopamine reuptake inhibitors; TeCAs=tetracyclic antidepressants.

1. NCHS. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD; 2014. 2. American Association of Suicidology. Depression and Suicide Risk (2014). Available at: http://www.suicidology.org/Portals/14/docs /Resources/FactSheets/2011/DepressionSuicide2014.pdf. Accessed December 26, 2014. 3. Lopez-Munoz F, Alamo C. *Curr Pharm Des.* 2009;15(14):1563-1586. 4. Murphy SL, et al. *National Vital Statistics Reports*. 2013;61(4):1-117.

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MDD: MANY THEORIES OF PATHOLOGY

Vladimir Maletic, MD, MS

MDD Pathophysiology: Several Evolving Theories

Figure adapted from: Racagni G and Popoli M. *Dialogues Clin Neurosci.* 2008;10:385-400.[9]

Monoamine depletion studies have demonstrated the importance of competent monoaminergic pathways in combating depression[1,2]

GABA=gamma-aminobutyric acid.

1. Millan MJ. *Eur J Pharmacol.* 2004;500(1-3):371-384. 2. Delgado PL. *Primary Psychiatry*. 2004;11:28-30. 3. Lee TS, et al. *AJNR Am J Neuroradiol.* 2014;35(6 Suppl):S44-54.
4. Miller AH, et al. *Depress Anxiety.* 2013;30(4):297-306. 5. Sanacora G, et al. *Neuropharmacology.* 2012;62(1):63-77. 6. Perovic B, et al. *Neuropsychiatr Dis Treat.* 2010;6:343-364.
7. Goswami DB, et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;43:126-133.8. Feyissa AM, et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009;33(1):70-75.
9. Racagni G and Popoli M. *Dialogues Clin Neurosci.* 2008;10:385-400.

Monoamine Imbalance Theory of MDD

- One theory of depression is that it may arise from a deficit or underactivity in the brain of monoamine signaling (dopamine [DA], serotonin [5HT], and norepinephrine [NE])[1]
- Deficiency in monoaminergic neurotransmission may be in the monoamine levels themselves,or through disrupted receptor signaling[2,3]
- Evidence that supports the monoamine imbalance hypothesis is that antidepressants can, selectively or in concert, raise monoamine neurotransmission tone (5HT, NE, and/or DA) and reduce depressive symptoms[2,4]

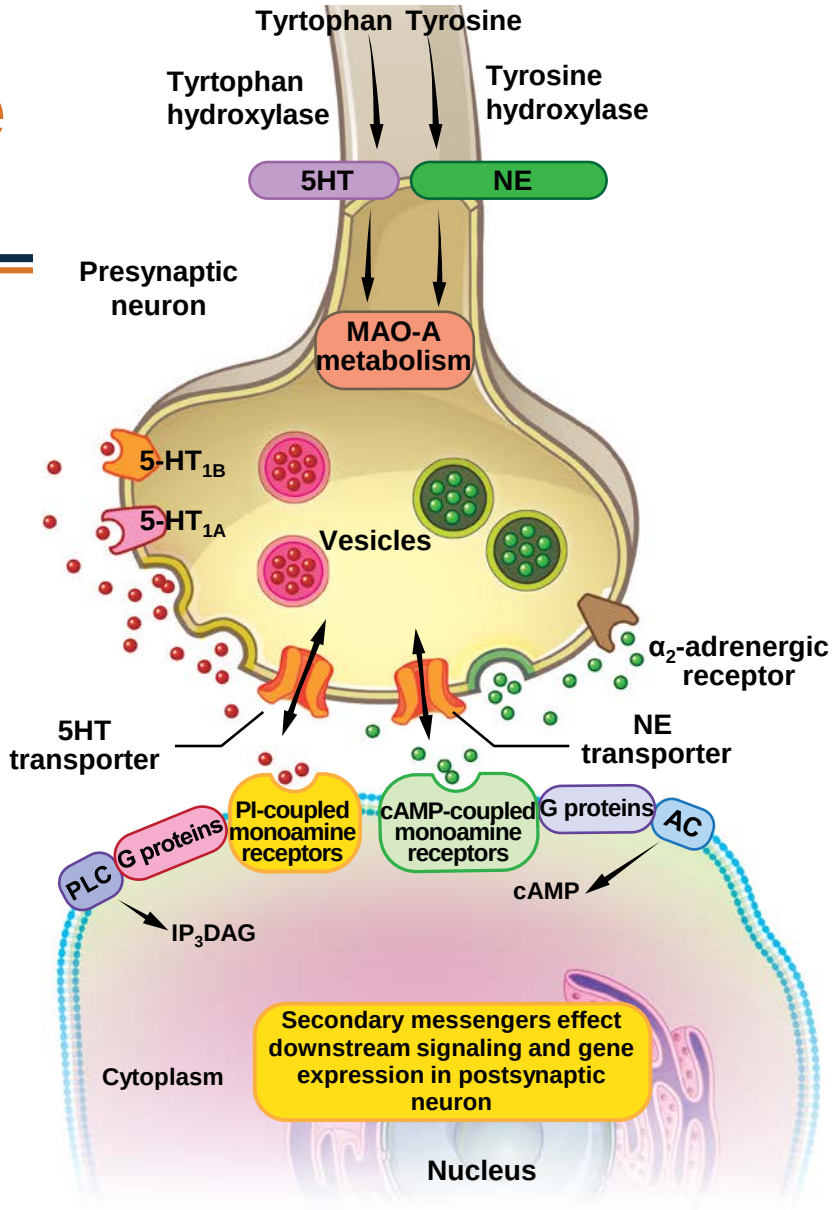


Figure adapted from Perovic et al. *Neuropsychr. Dis. Treat*. 2010;6:343-364[5]

MAO-A=monoamine oxidase A; PLC=phospholipase-C; PI=phosphoinositide; cAMP=cyclic adenosine monophosphate; AC=adenylate cyclase; IP_3DAG=ionsitol triphosphate diacylglycerol.

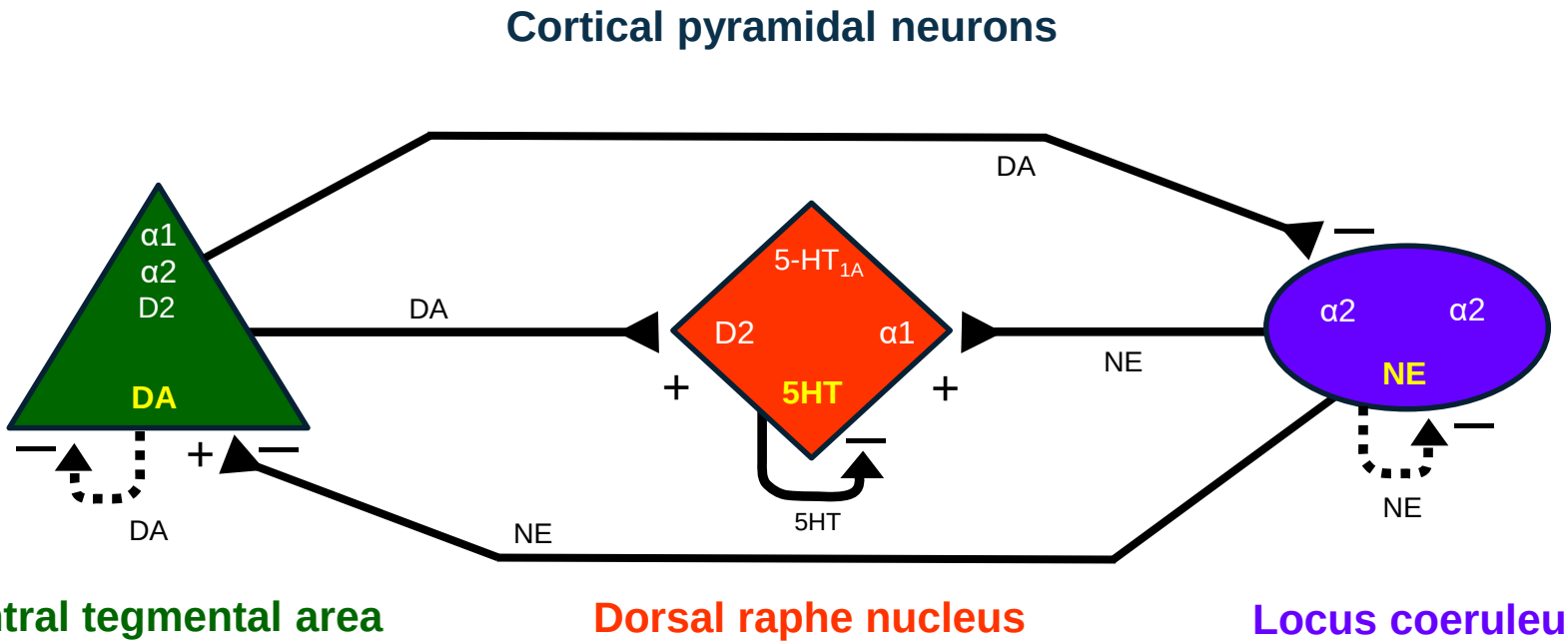
1. Delgado PL. *Primary Psychiatry*. 2004;11:28-30. 2. Svenningsson P, et al. *Science.* 2006;311(5757):77-80. 3. Savitz JB, Drevets WC. *Neurobiol Dis.* 2013;52:49-65. 4. Tran P, et al. *J of Psychiatric Research*. 2012;46:64-71. 5. Perovic B, et al. *Neuropsychiatr Dis Treat.* 2010;6:343-364.

Monoamine Pathways Overlap in Several Areas of the Brain

- Norepinephrine fibers: originate from locus coeruleus of the brain stem
- Dopamine fibers: originate from ventral tegmental area and substantia nigra
- Serotonin fibers: originate from the brain stem

Stahl SM, ed. Stahl's Essential Psychopharmacology: *Neuroscientific Basis and Practical Application*. 4th ed; 2013.

The Neural Circuitry of Monoamines Also Overlap



Hypothetical model of brain neural circuitry, primarily supported through animal models*[1]

*Although the exact cellular taxonomy and neural circuitry of the human brain is still being determined, animal models have been, and continue to be, an important contributing factor to this effort, as discussed by members of the human BRAIN Initiative[2]

+ indicates stimulatory effect
— indicates inhibitory effect

1. El Mansari M, et al. *CNS Neurosci Ther*. 2010;16(3):e1-17; 2. Jorgenson LA, et al. *Philos Trans R Soc Lond B Biol Sci*. 2015;370(1668):1-12.

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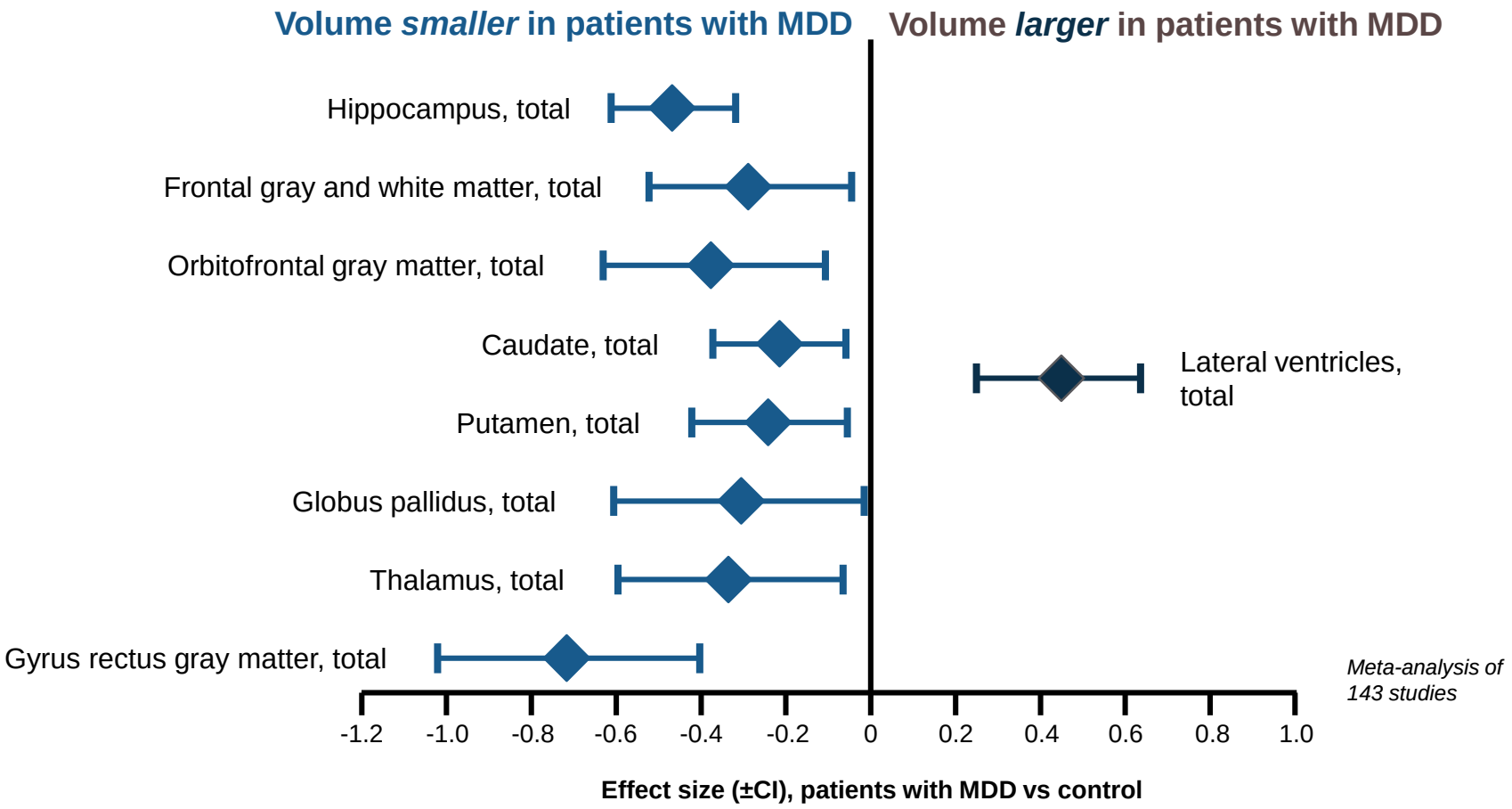
WHAT ARE SOME OF THE BRAIN STRUCTURES ALTERED IN PATIENTS WITH MDD?

Vladimir Maletic, MD, MS

Gray Matter Volume: Changes Found in Patients With MDD

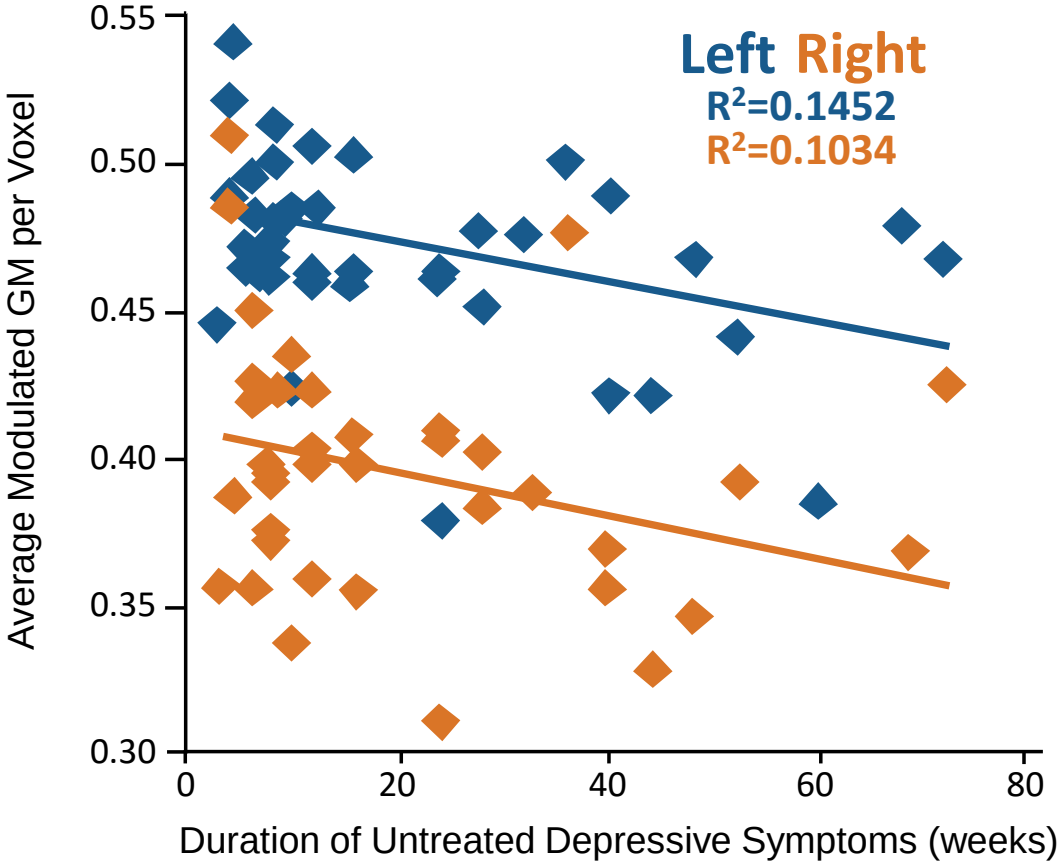


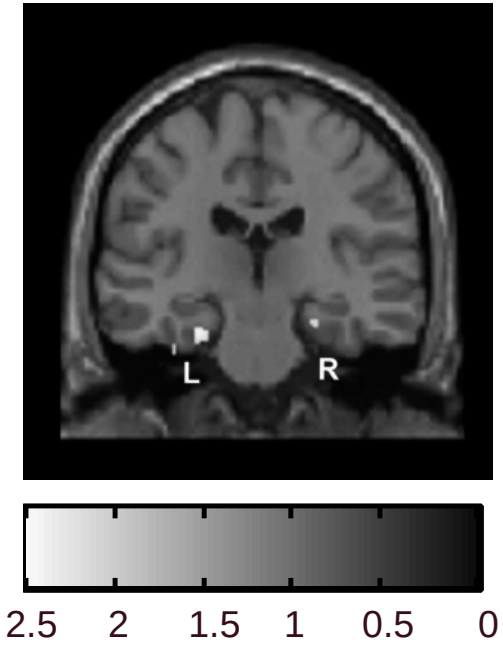
CI=confidence interval.

1. Kempton MJ, et al. *Arch Gen Psychiatry*. 2011;68(7):675-690.

Decreased Hippocampal Volume Correlates With Number of Untreated Days Depressed

- There is a negative correlation between duration of untreated depressive symptoms and gray matter (GM) volume in both the left (L) and right (R) hippocampal regions in untreated MDD



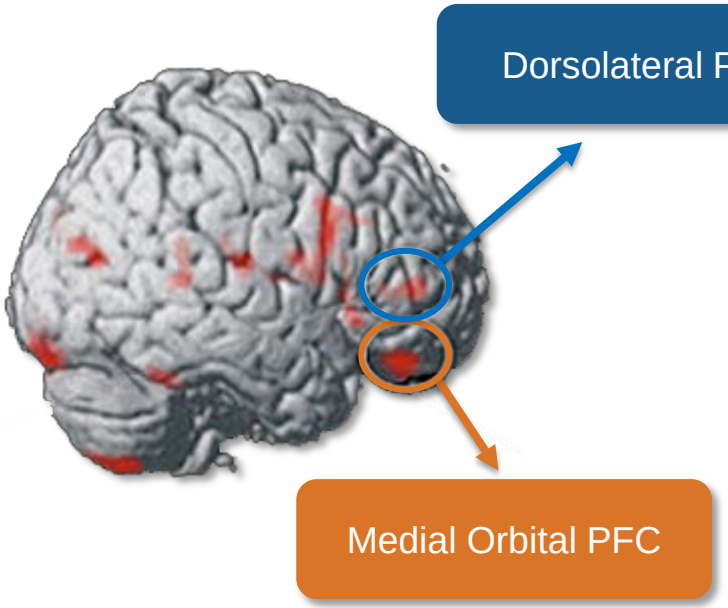


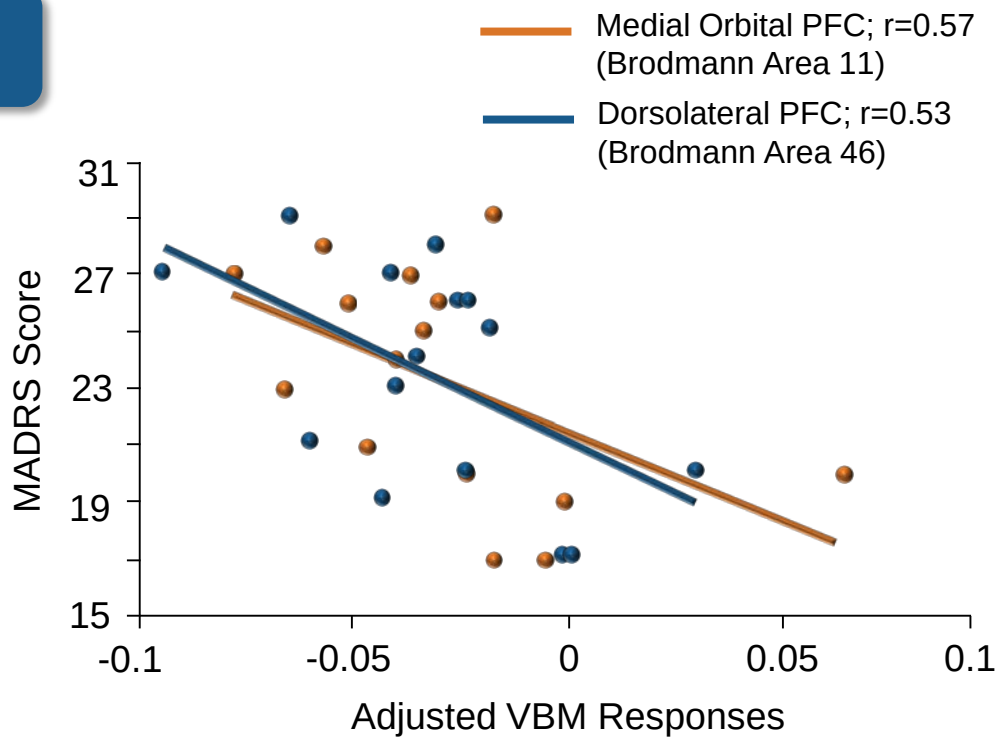
1. Arnone D, et al. *Mol Psychiatry.* 2013;18(12):1265-1272. 2. Stratmann M, et al. *PLoS One.* 2014;9(7):e102692.

Images: Arnone D, et al. Reprinted by permission from Macmillan Publishers Ltd on behalf of Cancer Research UK. *Mol Psychiatry*. © 2013.

Decreased PFC Volume and Increased Symptom Severity Observed in Patients With MDD

Comparison of 15 Subjects With MDD and 14 Healthy Controls





MADRS=Montgomery-Asberg Depression Rating Scale; VBM=voxel-based morphometry.

1. Vasic N, et al. *J Affect Disord*. 2008;109(1-2):107-116.

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IS THERE EVIDENCE TO SUGGEST THAT ACHIEVING REMISSION IN MDD CAN IMPROVE BRAIN STRUCTURE?

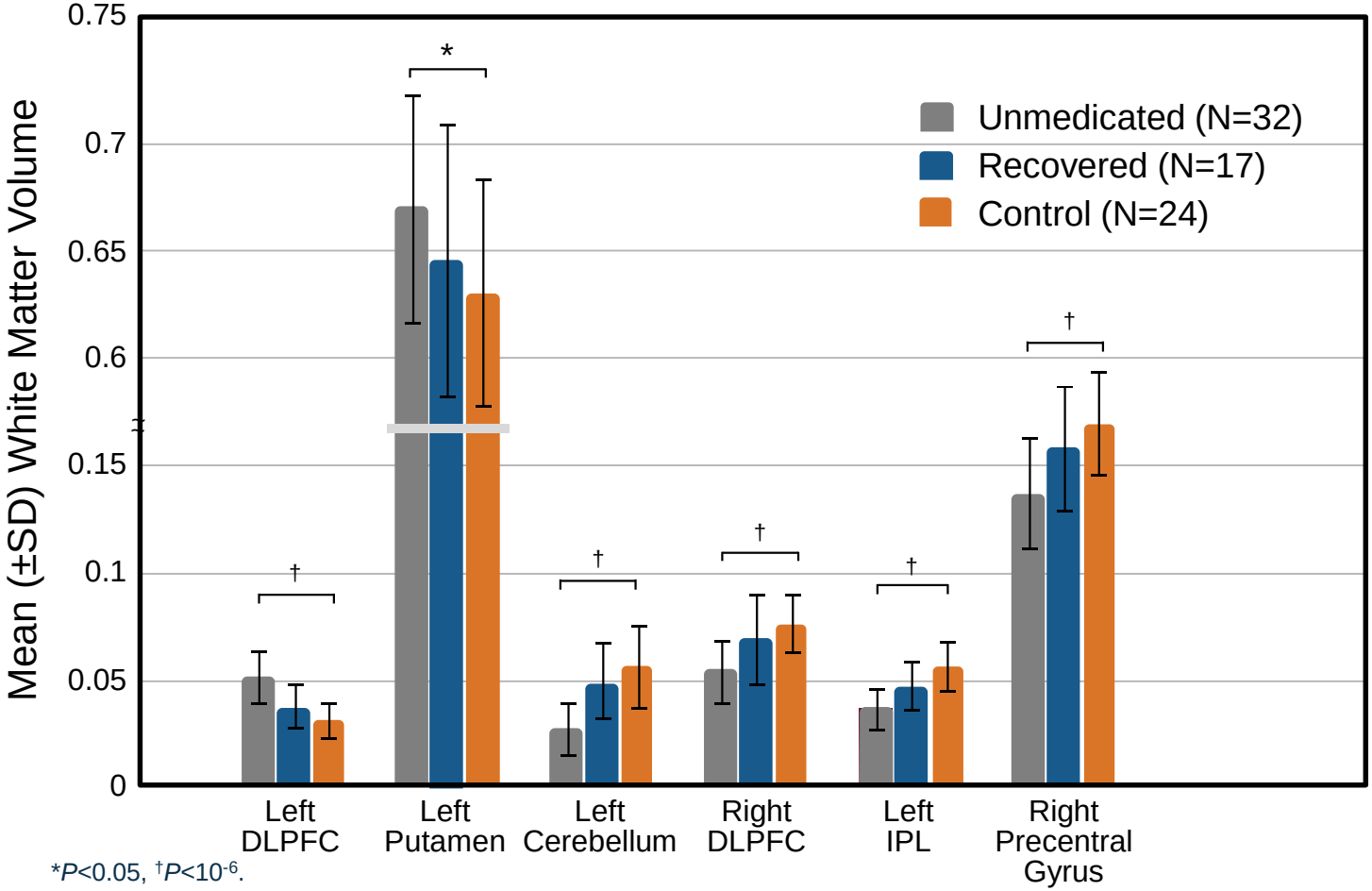
Vladimir Maletic, MD, MS

Gray Matter Volume (GMV): Comparing Patients With Unremitted and Remitted MDD

- Objective: examine brain-volume changes in patients with treatment-resistant depression, comparing those who achieved sustained remission with those who did not remit
- Prospective observational cohort study
- Compared to nonremitters (n=15), remitters (n=12) demonstrated:
  - significant mean increase in whole-brain volume during follow-up (p=0.005)
  - increased gray-matter volume in right orbitofrontal cortex (p=0.006) and the right inferior temporal gyrus (p=0.004).

Phillips JL, et al. *J Clin Psychiatry.* 2012;73(5):625-631.

Changes in White Matter Volume Observed With Remission



*P<0.05, †P<10^{-6}.

DLPFC=Dorsolateral prefrontal cortex; IPL=inferior parietal lobe.

1. Zeng LL, et al. *PLoS One.* 2012;7(8):e44248; 2. Berman MG, et al. *Soc Cogn Affect Neurosci.* 2011;6(5):548-555.

The neural circuits involved in emotional and cognitive function may be disrupted by white matter alterations

Remission resulted in white matter volumes not significantly different to healthy controls

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CURRENT MDD TREATMENT OPTIONS: PSYCHOPHARMACOLOGY AND LIMITATIONS

Rakesh Jain, MD, MPH

Proposed Mechanisms for Antidepressant Activity[1-7]

Antidepressants

- Reuptake inhibitors
  - SSRIs, SNRIs, NDRIs
  - TCAs
- MAOIs

Mood Stabilizers

- Evidence suggests some may enhance serotonergic neurotransmission

Antipsychotics

- All alter D_2 neurotransmission
- Some atypical antipsychotics also target 5HT receptors, NE receptors, and a variety of other receptor types

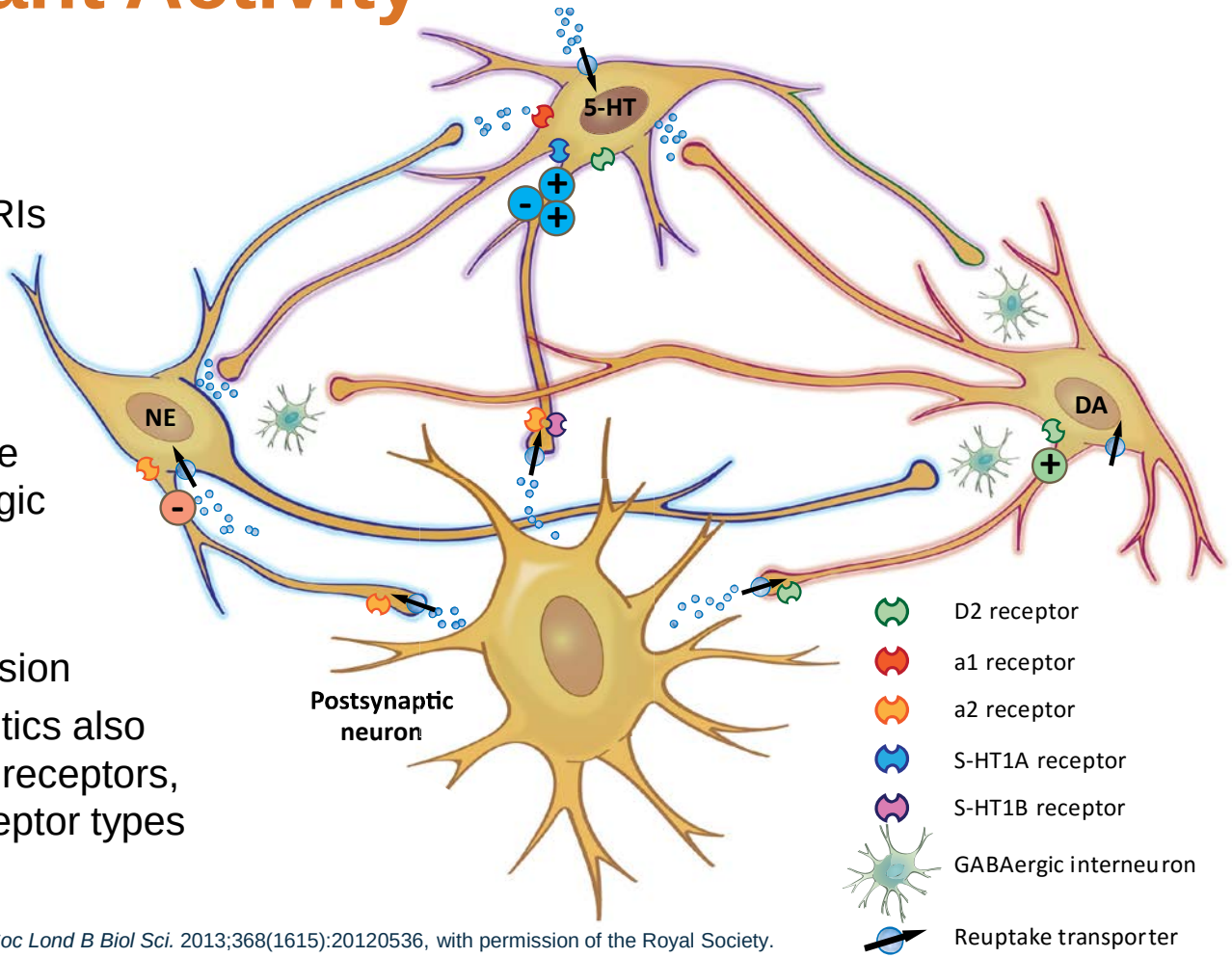
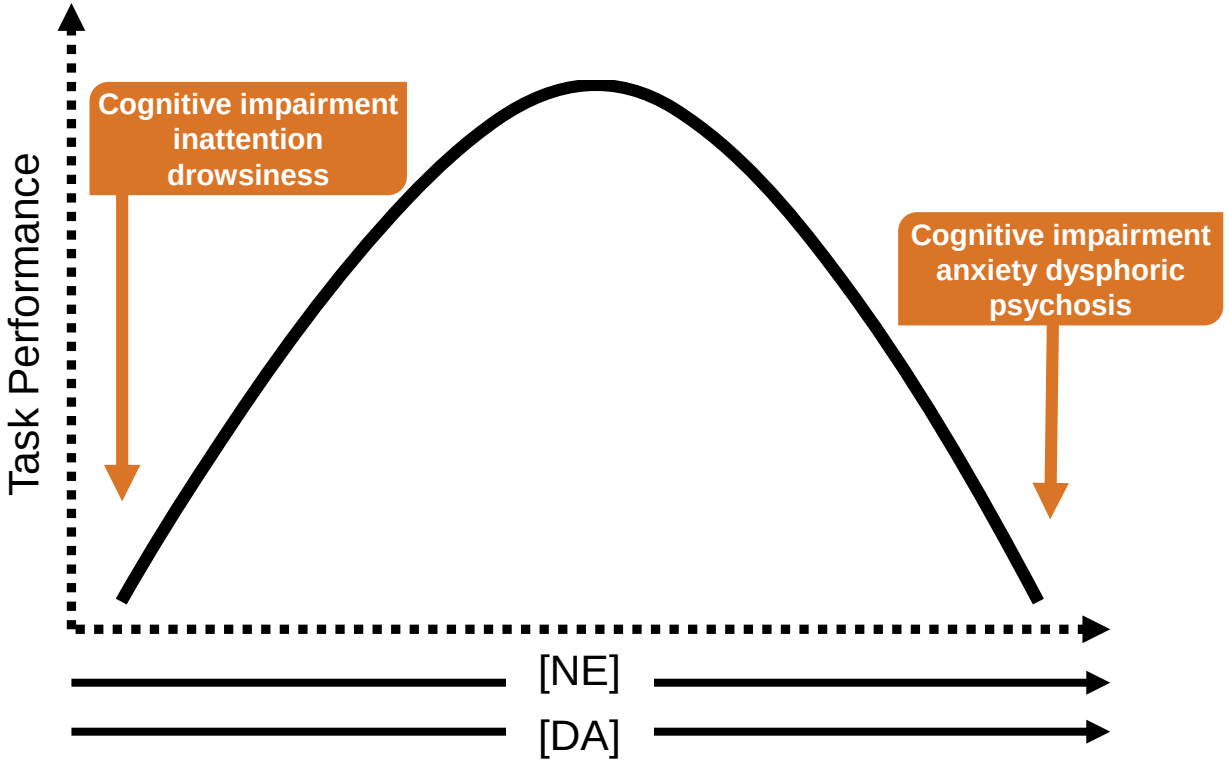


Image adapted from: Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536, with permission of the Royal Society.

1. Stahl SM. Chapter 5. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed; 2013:129-236. 2. Stahl SM. Chapter 7. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed; 2013:284-369. 3. Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536. 4. Rang HP, Dale MM. In. *Rang and Dale's Pharmacology*. 7th ed; 2012:564-583. 5. Nugent AC, et al. *J Psychopharmacol.* 2013;27(10):894-902. 6. Andrews PW, et al. *Front Psychol.* 2011;2(159).7. Artigas F. *Pharmacol Ther.* 2013;137(1):119-131.

Long-term SSRI Antidepressant Treatment May Alter NE and DA Neurotransmission

SSRI treatment can result in a sustained increase of 5HT activity and thus an increased inhibitory tone, which may lead to a decrease in both NE and DA neurotransmission and a negative outcome in task performance measures

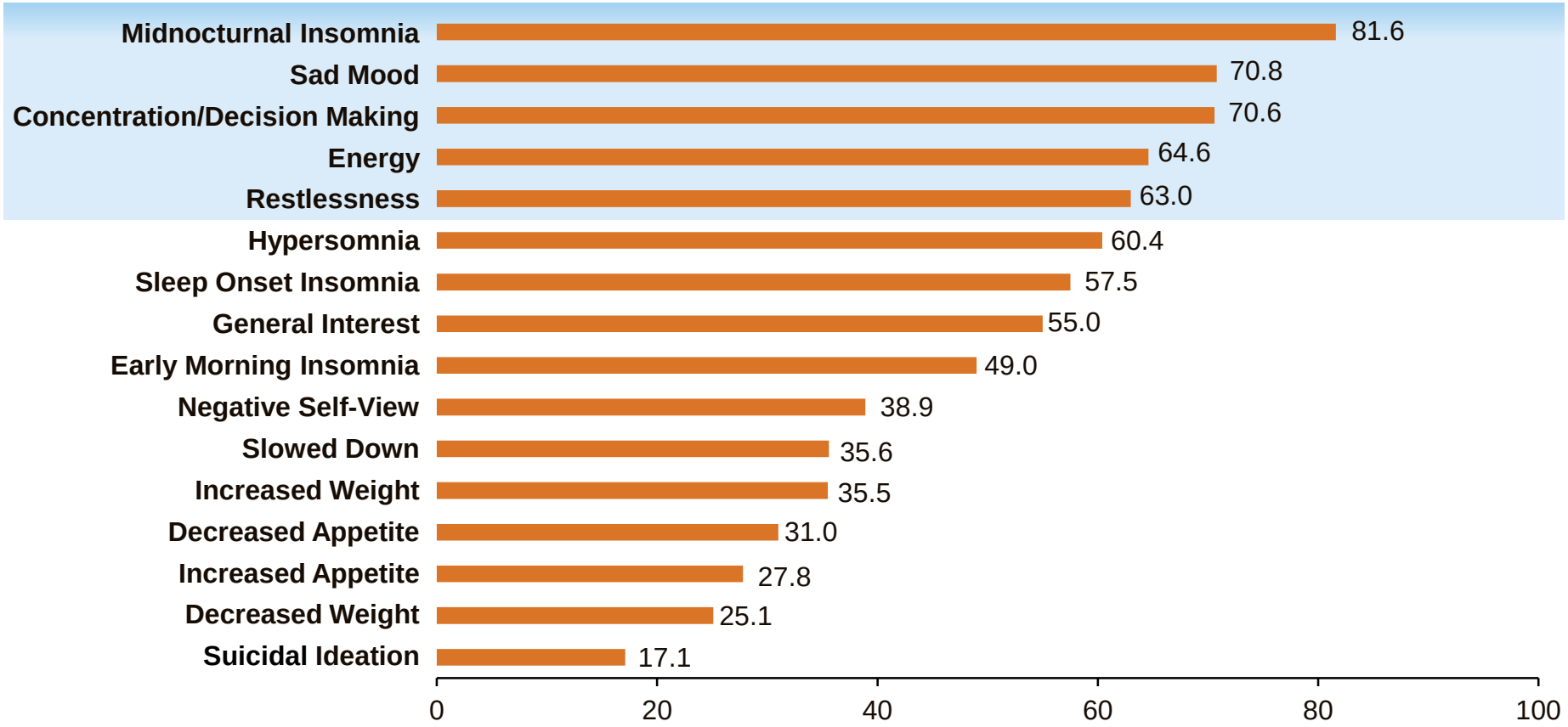


NE and DA neurotransmission in the prefrontal cortex and executive function; NE and DA in arrows represent increasing levels of stimulation

1. Blier P, Briley M. *Neuropsychiatr Dis Treat*. 2011;7(Suppl 1):15-20.

What Does Inadequate Response to an Antidepressant Look Like?

Proportion of Responders Who Had Symptoms at Baseline That Persisted at Exit*

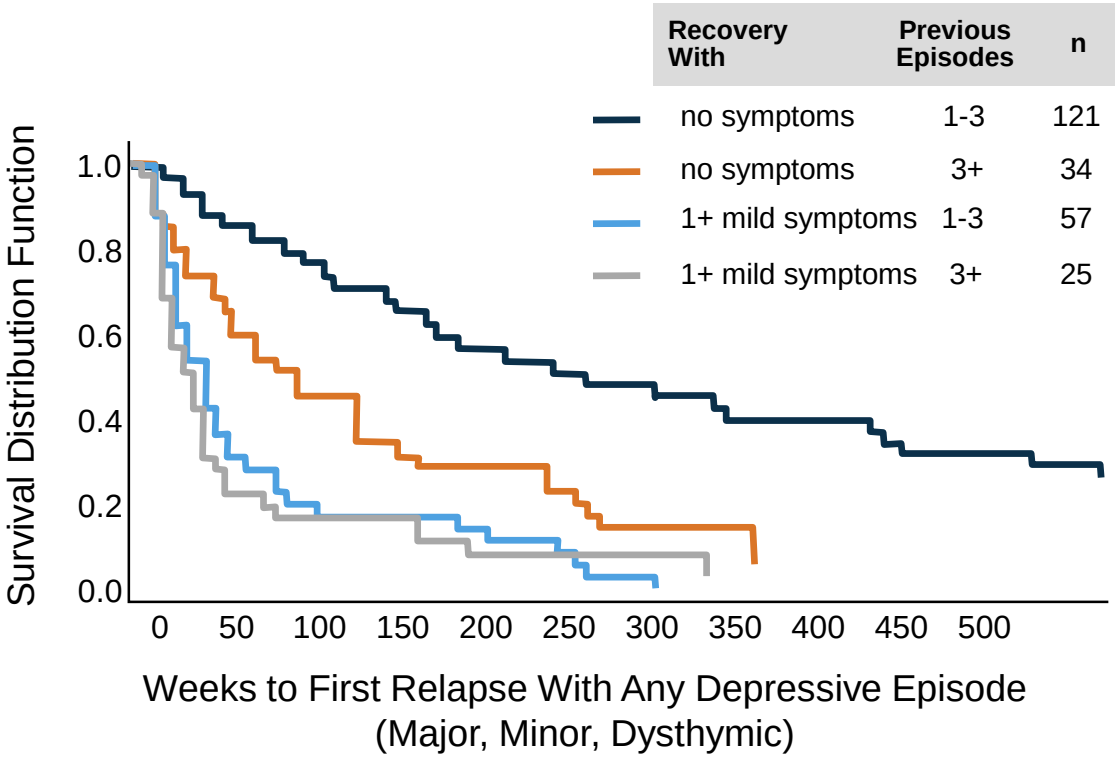


*Percentages are reported as the remaining percent of those with each symptom at baseline that continued to have the symptom at exit. Response was defined as ≥50% reduction in QIDS-SR16. Presence of symptoms was indicated by a QIDS-SR16 domain score ≥1.

1. McClintock SM, et al. *J Clin Psychopharmacol*. 2011;31(2):180-186.

Residual Symptoms and Repeated Episodes Predict Worse Outcomes for Patients With MDD

In a 10-Year Naturalistic Study, Patients With No Symptoms and Fewer Episodes Remained Well Longer



- Patients with asymptomatic recovery remained well for a median of 231 weeks compared to 68 weeks for those with residual symptoms
  - Patients with more residual symptoms relapsed faster

Survival Distribution Function=cumulative proportion of cases surviving to given time interval.

1. Judd LL, et al. *J Affect Disord*. 1998;50(2-3):97-108.

Images: Reprinted from *J Affect Disord*. 1998;50(2-3):97-108, Judd LL, et al., Copyright 1998 with permission from Elsevier.

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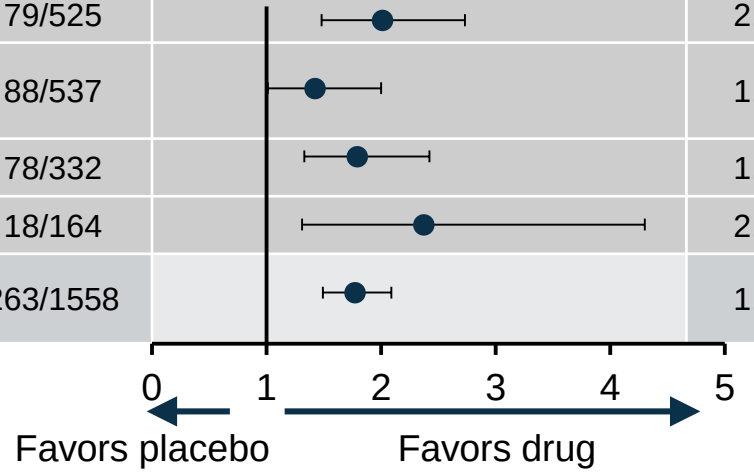
TREATING MDD: THE ROLE OF ATYPICAL ANTIPSYCHOTIC AUGMENTATION

Rakesh Jain, MD, MPH

Adjunctive Atypical Antipsychotics in MDD: Clinical Evidence Supports Their Use

Efficacy of Adjunctive Treatment With Atypical Antipsychotics (N=3549)[2,*]

Drug	Treatment n/N	Placebo n/N	Odds Ratio (95% CI)
Atypical Antipsychotic 1	142/540	79/525	2.01 (1.48–2.73)
Atypical Antipsychotic 2/SSRI	135/584	88/537	1.42 (1.01–2.00)
Atypical Antipsychotic 3	231/645	78/332	1.79 (1.33–2.42)
Atypical Antipsychotic 4	48/199	18/164	2.37 (1.31–4.30)
Overall	556/1968	263/1558	1.77 (1.49–2.09)

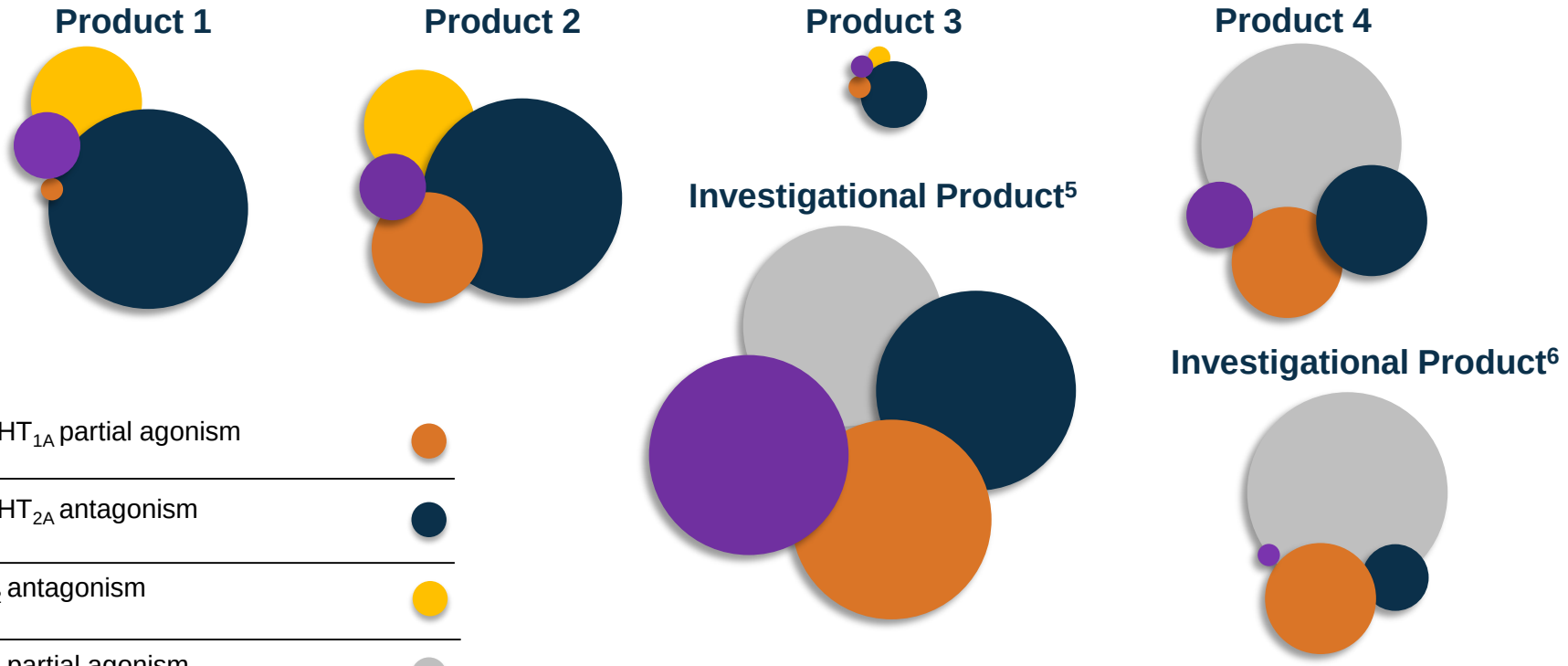


- Patients with MDD receiving adjunctive antipsychotics were more likely to show efficacy and remission† compared to placebo however, the effect sizes were small or small-to-moderate in magnitude[2]
- However, use of atypical antipsychotics adjunctive therapy in MDD has been associated with akathisia, weight gain, abnormal metabolic lab results, and sedation[2]

*Data are from a systematic review of the efficacy and safety profiles of atypical antipsychotic medications used for the adjunctive treatment of depression. †Definition of remission varied across 14 studies.

1. Connolly KR, Thase ME. *Drugs*. 2011;71(1):43-64; 2. Spielmans GI, et al. *PLoS Med*. 2013;10(3):e1001403.

Binding Affinities of Select Atypical Antipsychotics Demonstrate Receptor Targeting Differences



Size of circle indicates affinity, with higher affinity represented by larger circle.

- Largest circle = Ki <1 nM
- Medium circle = Ki ≥1 nM thru <10 nM
- Small circle = Ki ≥10 nM thru <100 nM
- Smallest circle= Ki ≥100 nM thru <1000 nM

1. **Product 1.** Full Prescribing Information; 2014. 2. **Product 2.** Full Prescribing Information; 2013. 3. **Product 3.** Full Prescribing Information; 2013. 4. **Product 4.** Full Prescribing Information; 2012. 5. Maeda K, et al. *J Pharmacol Exp Ther.* 2014;350(3):589-604. 6. Citrome L. *Adv Ther.* 2013;30(2):114-126. 7. Michl J, et al. *Eur Neuropsychopharmacol.* 2014;24(9):1463-1474. 8. Richtand NM, et al. *Neuropsychopharmacology.* 2007;32(8):1715-1726.

Augmentation Therapy May Double the Chance of Remission

Pooled Response and Remission Rates (10 RCTs, N = 1500)

Treatment Group	Response Rate, % of patients	Remission Rate, % of patients
Atypical antipsychotic + antidepressant	57.2	47.4
Placebo + antidepressant	35.4	22.3

Meta-analysis of randomized, double-blind, placebo-controlled clinical trials assessed adjunctive treatment of standard antidepressants with an atypical antipsychotic for MDD; studies had to meet all of the following inclusion criteria:

1) used the HAM-D or the MADRS as their primary outcome measure
2) studies that exclusively focused on treatment-resistant depression.

Remission was defined by either a HAM-D-17 < 8 or MADRS < 11.

1. Papakostas GI, et al. *J Clin Psychiatry*. 2007;68(6):826-831.

Helping to Narrow the MDD Treatment Gap[1-6]

Unmet Needs Still Exist

5% to 26%

OF ADULTS ARE AFFECTED BY MDD LIFETIME PREVALANCE[1,2]

33% to 66%

OF PATIENTS WITH MDD DO NOT RESPOND TO INITIAL TREATMENT[3]

Earlier Use of Augmentation Needed

2X

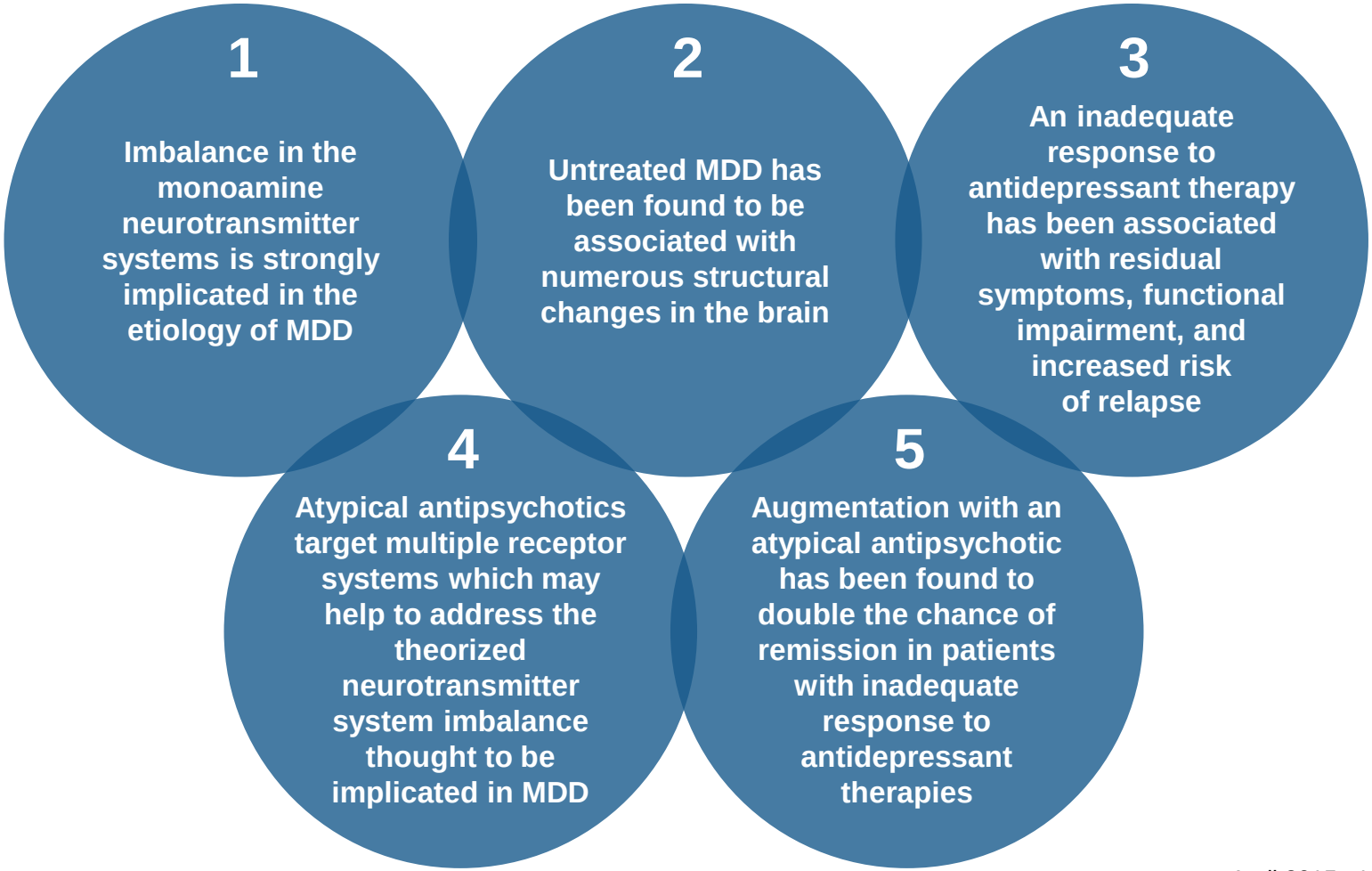
Augmentation with an atypical antipsychotic has been found to double the rate of remission in patients with inadequate response to antidepressant therapies[4]

More Proactive Focus on Neurotransmitters

Atypical antipsychotics target multiple receptor systems that may help to address the theorized neurotransmitter system imbalance thought to be implicated in MDD[5]

1. Wright BM, et al. *Pharmacotherapy*. 2013;33(3):344-359. 2. Kessler RC, et al. *JAMA*. 2003;289(23):3095-3105. 3. Little A. *Am Fam Physician*. 2009;80(2):167-172. 4. Papakostas GI, et al. *J Clin Psychiatry*. 2007;68(6):826-831. 5. Stahl SM. Chapter 5. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed; 2013:129-236. 6. Judd LL, et al. *J Affect Disord*. 1998;50(2-3):97-108.

Key Takeaways



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DISCUSSION

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QUESTIONS

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CLOSING

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The Evolving Psychopharmacology of Major Depressive Disorder:

Narrowing the Treatment Gap

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