Psych Congress Elevate

Patient Perspectives in the Management of Major Depressive Disorder (MDD): Optimizing Care When First-Line Antidepressants Fail

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St. Louis, Missouri

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Faculty Disclosures

- **Dr. Rakesh Jain:** Advisory Board—Adamas, Alkermes, Corium, Eisai, Indivior, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Supernus, Takeda, Teva, Tris Pharmaceuticals; Advisory Board (spouse)—Otsuka; Consultant—AbbVie (Allergan), Acadia, Adamas, Alfasigma USA, Inc., Axsome, Corium, Cingulate Therapeutics, Eisai, Evidera, Impel NeuroPharma, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Osmotica, Otsuka, Pamlab, Pfizer, Sage Therapeutics, Shire, Sunovion, Supernus, Takeda, Teva; Consultant (spouse)—Lilly, Otsuka, Pamlab, Sunovion; Grant/Research Support— AbbVie (Allergan), Lilly, Lundbeck, Otsuka, Pfizer, Shire, Takeda; Speakers Bureau—AbbVie (Allergan), Alkermes, Axsome, Corium, Eisai, Indivior, Intracellular Therapies, Ironshore Pharmaceuticals, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Takeda, Teva, Tris Pharmaceuticals; Speakers Bureau (Spouse)—Lilly.

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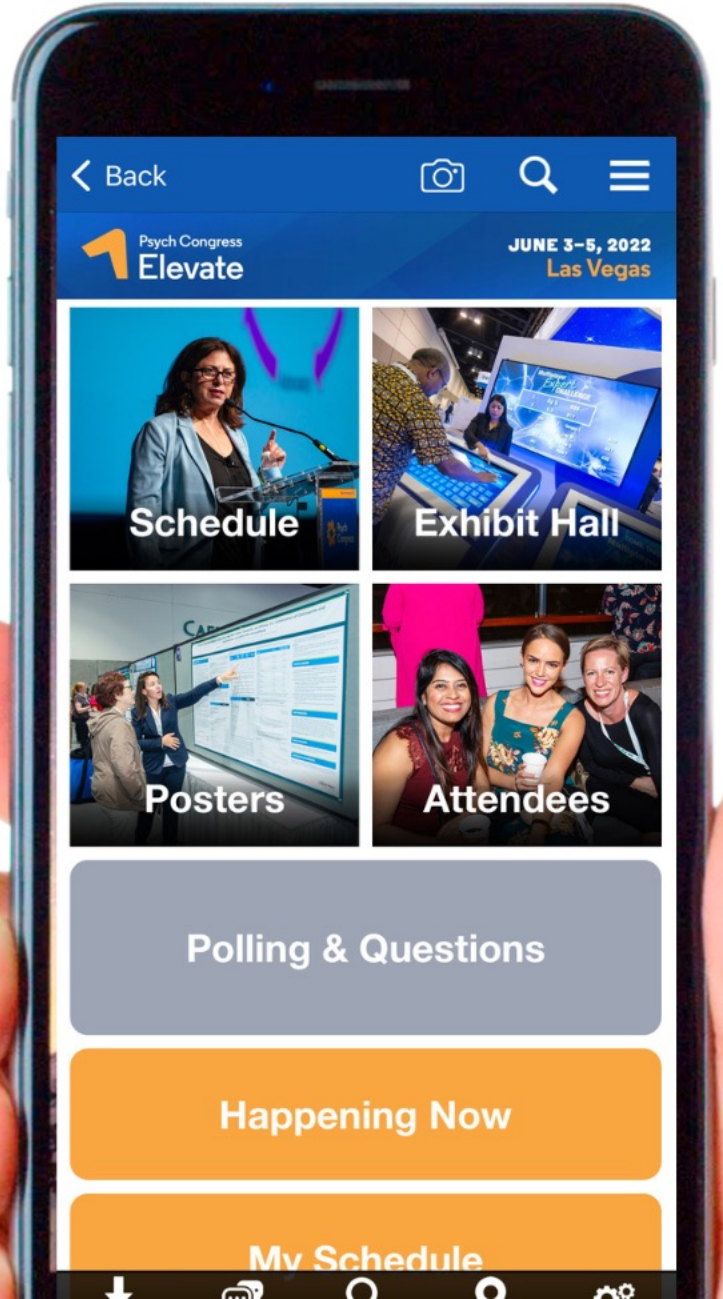
Learning Objectives

- Identify barriers to optimal treatment response and medication adherence in MDD
- Assess safety/efficacy data and mechanisms of action of newer antidepressants for the treatment of MDD
- Implement optimal antidepressant switching strategies into clinical practice after first-line treatment failure based on evidence-based guidance and collaborative care



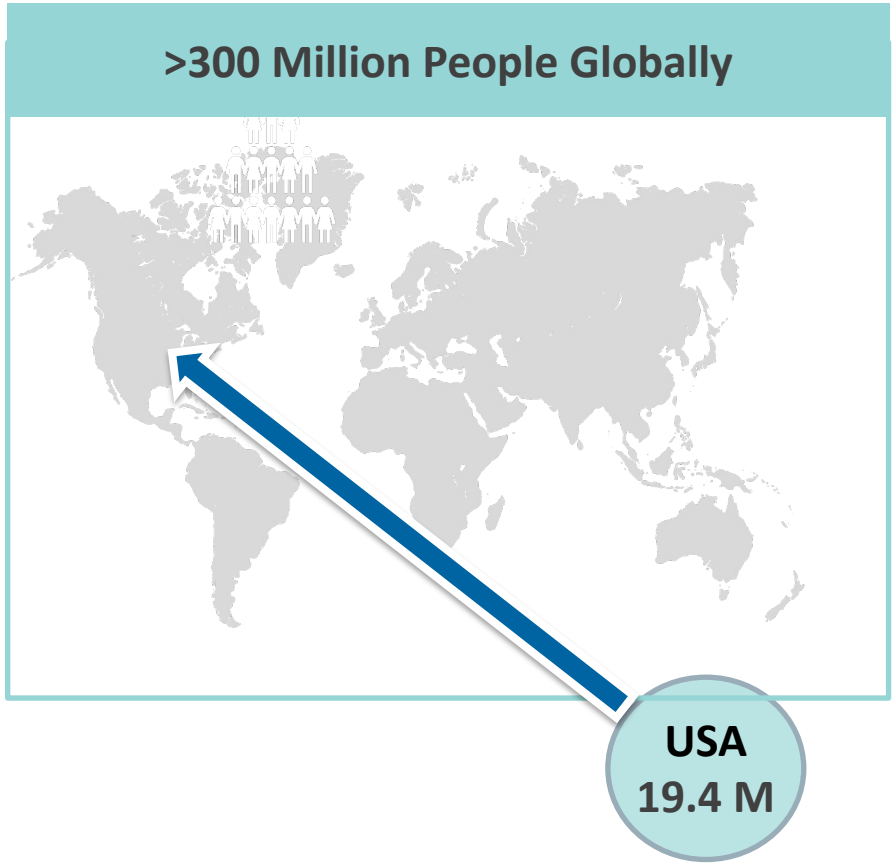
Click on Polling & Questions in the App to Participate in this Session

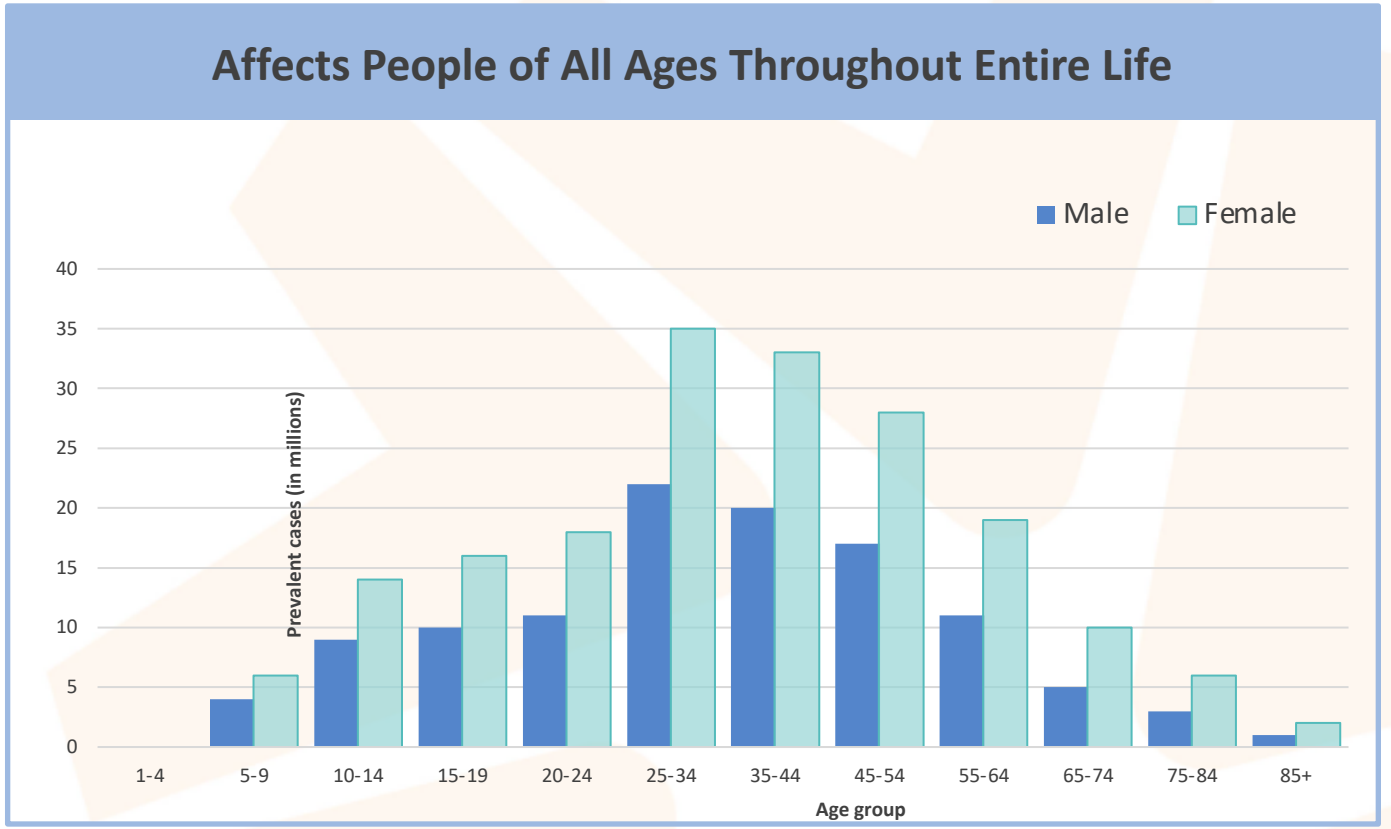
PSYCHOPHARMACOLOGY (OCTAVIUS 11)

You can also scan this QR code

MDD Overview

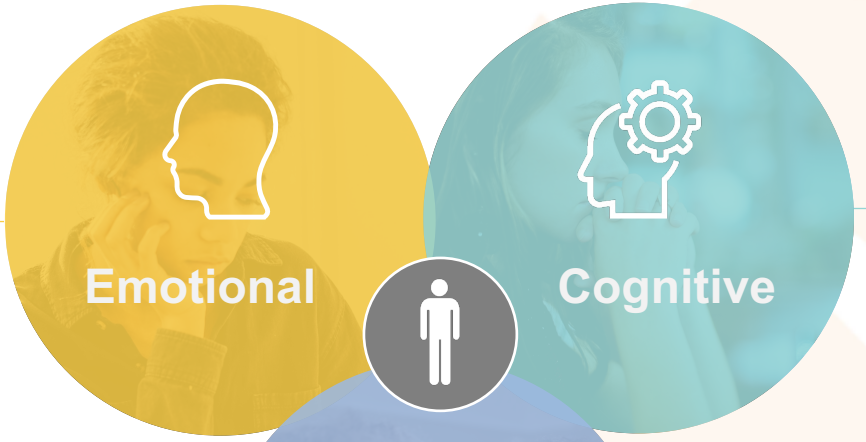
MDD – The Great 'Pandemic' Disorder Sweeps The World and Shows No Signs of Letting up





WHO. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017; Ferrari AJ, et al. *PLoS One*. 2013;8(7):e69637. US HHS. Results from the 2019 National Survey on Drug Use and Health. Accessed 5/29/22:www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR1PDFW090120.pdf

MDD: Heterogenous Disorder That Can Present Differently in Each Patient



- Anxiety
- Sadness
- Irritability
- Lack of enjoyment
- Suicidal ideation

Difficulties with:

- Attention and concentration
- Memory
- Thinking
- Decision-making
- Planning and organization

Symptom presentation varies from patient to patient with >1000 combinations of symptoms possible

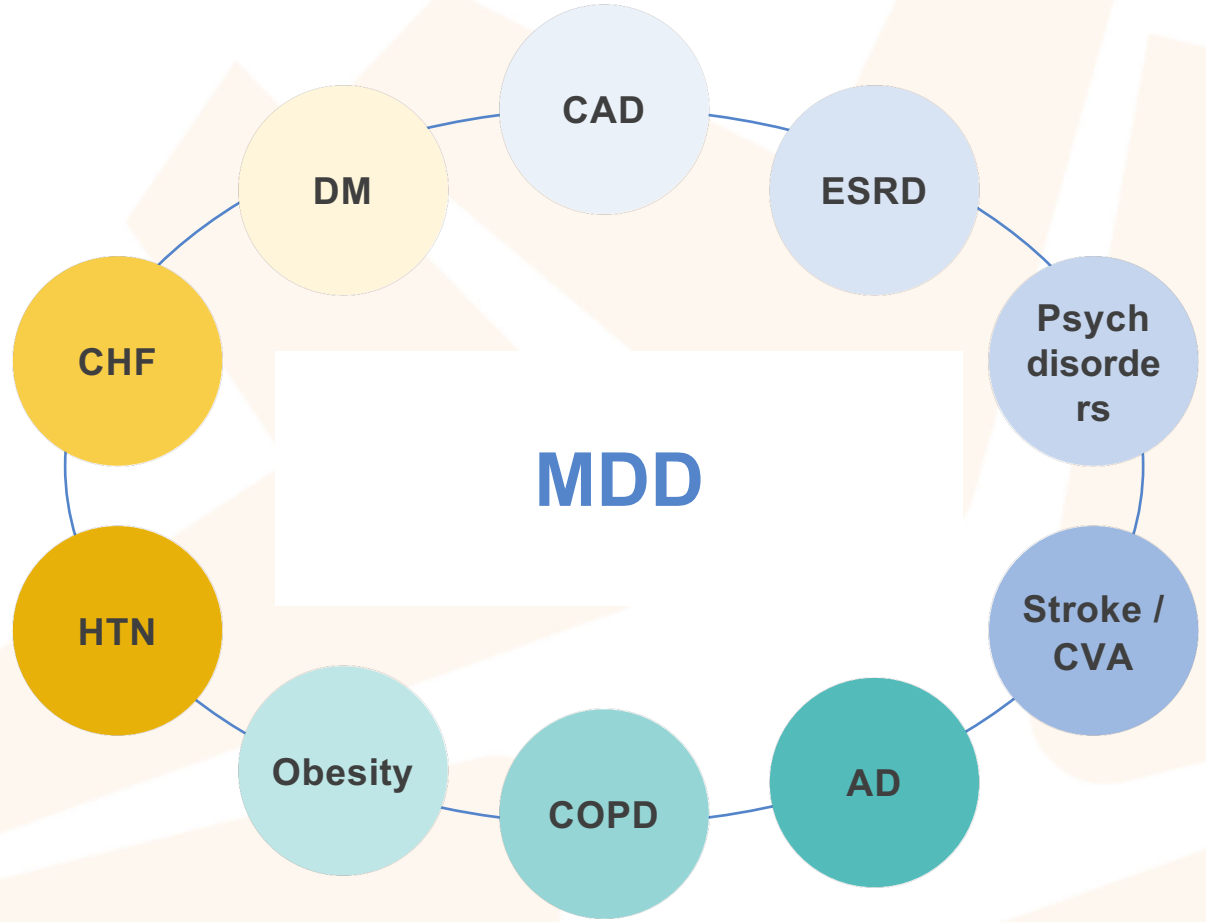
- Appetite/Weight changes
- Sexual dysfunction
- Pain
- Fatigue
- Insomnia/ Hypersomnia

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC: American Psychiatric Association,2013. Fehnel SE, et al. *CNS Spectr.* 2016;21(1):43-52. Marazziti D, et al. *Eur J Pharmacol.* 2010;626(1):83-86. Fried EI, et al.. *J Affect Disord.* 2015;172:96-102.

‘Trouble Everywhere I See’ - Major Depression And Its impact on Mortality and Morbidity

Major Depression

- 60% increased mortality rate
- 8-year reduction in life expectancy



Pratt LA, et al. *Gen Hosp Psychiatry*. 2016;39:39-4.; Egede LE. *Gen Hosp Psychiatry*. 2007;29(5):409-416. Thaipisuttikul P, et al. *Neuropsychiatr Dis Treat*. 2014;10:2097-2103. Luppino FS, et al. *Arch Gen Psychiatry*. 2010;67(3):220-229. Byers AL, Yaffe K. *Nat Rev Neurol.* 2011;7(6):323-331.

MDD is a Debilitating and Potentially Life-Threatening Condition

Wide Array of Physical, Mental, and Economic Burdens

- **2017 WHO report: MDD is leading cause of disability worldwide**
  - Nearly 2/3 patients with MDD are severely impaired

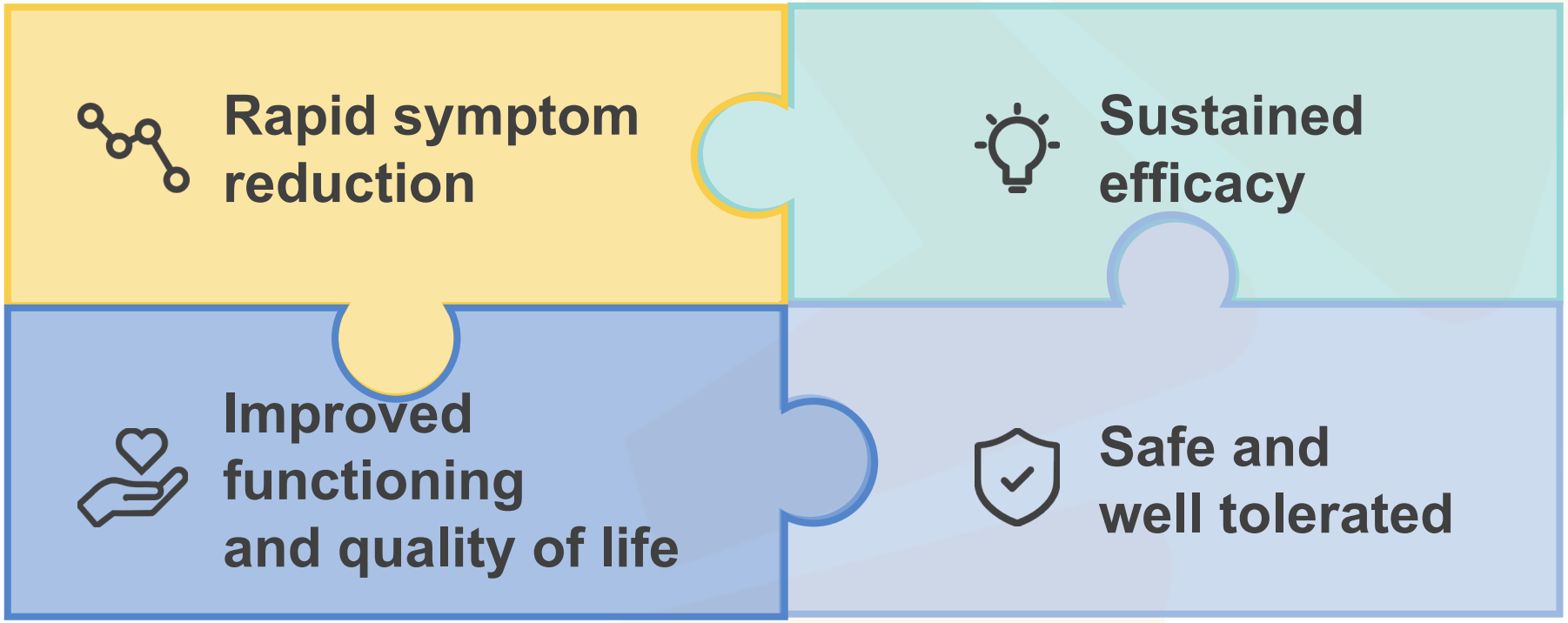
- **Patients with MDD:**
  - 20 times more likely to commit suicide than the public at large
  - Frequent psychiatric comorbidities tend to worsen the overall outcome

- **2020: Economic impact of depression (US): $326.2 billion**
  - Includes: healthcare costs, suicide-related costs, workplace absenteeism and presenteeism
  - National Comorbidity Survey Replication: mean loss of 27 workdays/year per employee due to depression alone

Pratt LA, et al. *Gen Hosp Psychiatry*. 2016;39:39-45. Egede LE. *Gen Hosp Psychiatry*. 2007;29(5):409-416. Thaipisuttikul P, et al. *Neuropsychiatr Dis Treat*. 2014;10:2097-2103. Luppino FS, et al. *Arch Gen Psychiatry*. 2010;67(3):220-229. Byers AL, Yaffe K. *Nat Rev Neurol.* 2011;7(6):323-331.

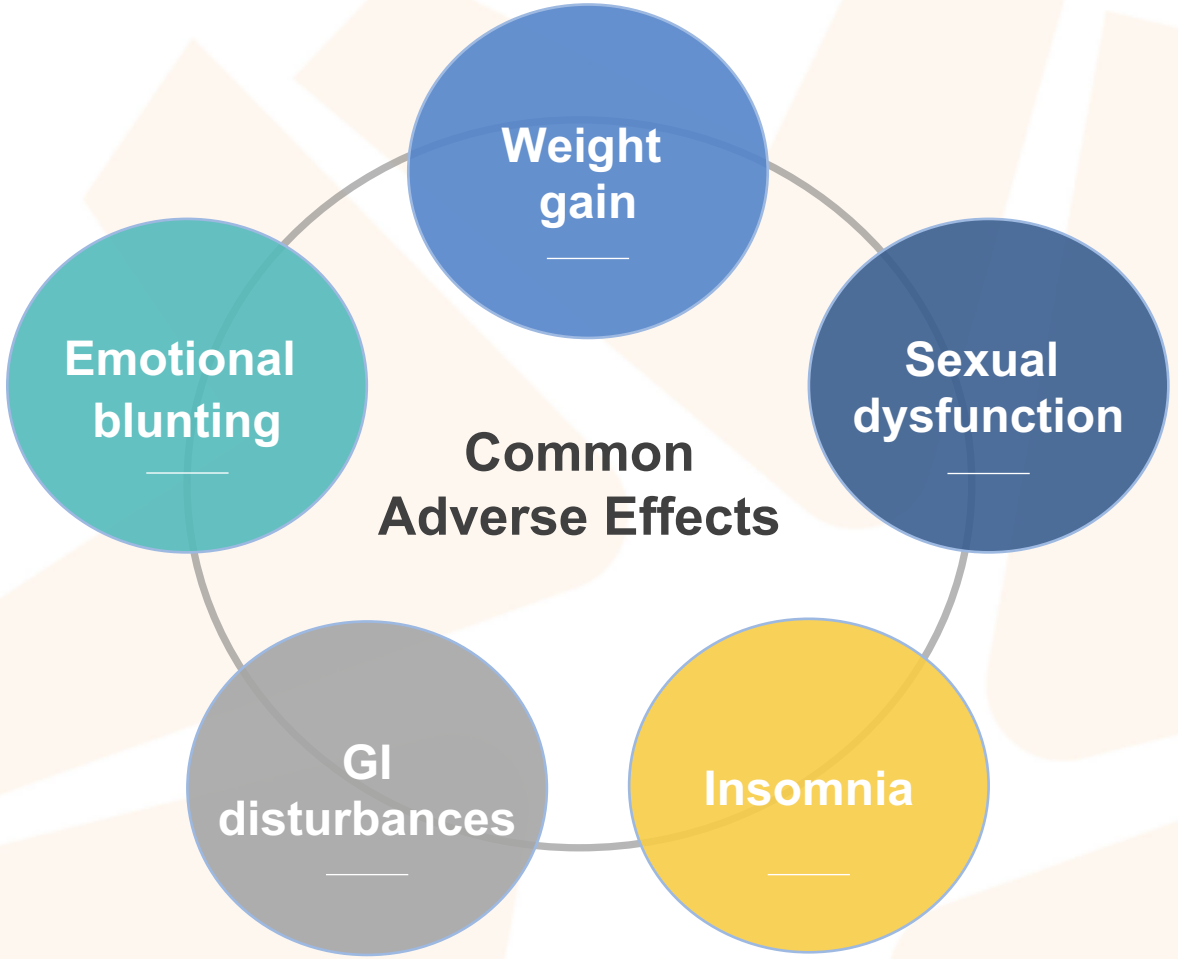
Antidepressant Treatment Should Address All Aspects of MDD

Key Requirements of an Effective Treatment



Richelson E. *Mayo Clin Proc.* 1994;69:1069-1081. Dzevlan A, et al. *Mater Sociomed*. 2019;31(1):14-18

Current Antidepressants
Distinct Tolerability Profiles



Solmi M, et al. *Braz J Psychiatry*. 2020;43(2):189-202. Ferguson JM. *Primary Care Companion J Clin Psychiatry*. 2001;3(1):22-27. Cartwright C, et al. *Patient Prefer Adherence*. 2016;10:1401-1417.

Adverse Events From Antidepressants Can Compromise Adherence

AEs can impact willingness to stay on treatment

Common reasons for nonadherence include

- Weight gain (27%)
- Sexual dysfunction (20%)

Balikci A, et al. *Bull Clin Psychopharmacol*. 2014;24(1):69-75. Zhou Q, et al. *CNS Neurosci Ther*. 2019;25(2):215-222. Ashton AK, et al. *Curr Ther Res Clin Exp*. 2005;66(2):96-106.

There Are Many Unmet Needs When The First Antidepressant Fails

EFFICACY	Inadequate response, low rates of remission, and substantial relapse rates remain challenges in managing MDD
FUNCTIONING AND QUALITY OF LIFE	Improvements in functioning and quality of life tend to lag behind symptomatic relief
SAFETY AND TOLERABILITY	Current therapies are associated with significant side effects, which can interfere with adherence

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. Sheehan DV, et al. *J Affect Disord*. 2017;215:299-313. Ferguson JM. *Primary Care Companion J Clin Psychiatry.* 2001;3(1):22-27. Masand PS. *Clinical Therapeutics.* 2003;25:2289-2304.

Factors to Consider When Response is Lacking

Potential Reasons for Treatment Nonresponse

- ✓ Inaccurate diagnosis
- ✓ Unaddressed co-occurring medical or psychiatric disorders, including substance use disorders
- ✓ Inappropriate selection of therapeutic modalities
- ✓ Inadequate dose of medication or frequency of psychotherapy
- ✓ Pharmacokinetic/pharmacodynamic factor affecting medication action
- ✓ Inadequate duration of treatment
- ✓ Nonadherence to treatment
- ✓ Persistent or poorly tolerated side effects
- ✓ Complicating psychosocial and psychological factors
- ✓ Inadequately trained therapist or poor “fit” between patient and therapist

American Psychiatric Association Work Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. Third Edition. American Psychiatric Association; 2010.

Meet Vanessa

Video Vignette #1

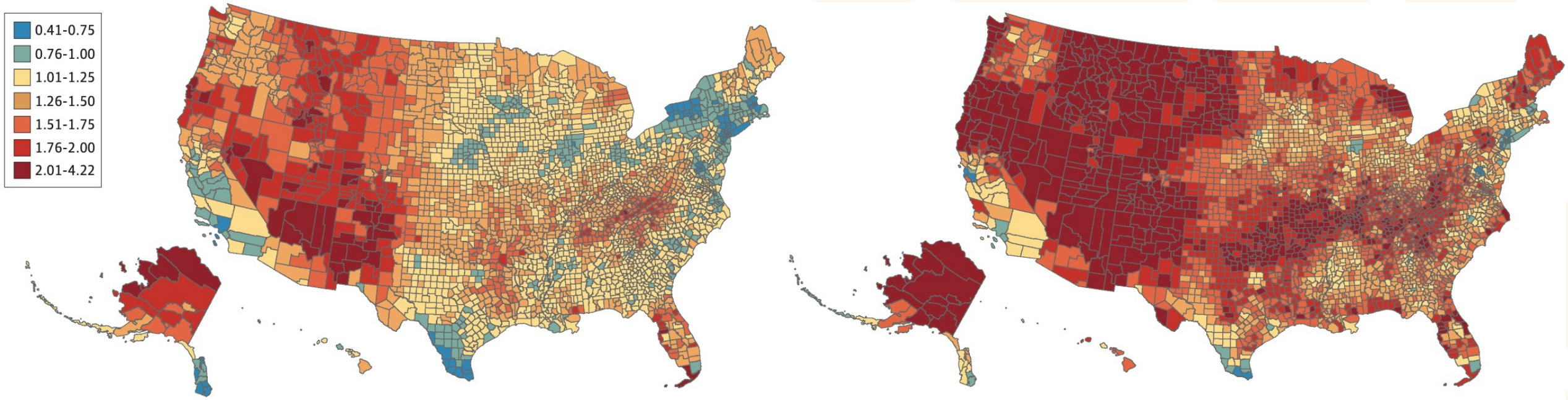
The Current MDD Treatment Landscape

A Heat Map of the United States

Suicide Rates By County

2002-2004

2014-2016



Steelesmith et al. *JAMA Netw Open*. 2019;2:e1910936.

Increasing Severity of Depression During COVID-19

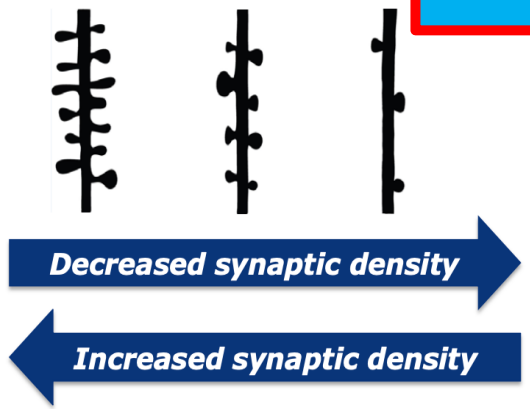
	% (95% CI)		Difference	
Depression Symptoms	**Before COVID-19**	**During COVID-19**	**Absolute, %**	**Relative**
None	75.3 (73.3-77.1)	47.5 (44.2-50.9)	−27.7	0.6
Mild	16.2 (15.1-17.4)	24.6 (21.8-27.7)	8.4	1.5
Moderate	5.7 (4.8-6.9)	14.8 (12.6-17.4)	9.1	2.6
Moderately severe	2.1 (1.6-2.8)	7.9 (6.3-9.8)	5.7	3.7
Severe	0.7 (0.5-0.9)	5.1 (3.8-6.9)	4.4	7.5

Ettman CK et al. *JAMA*. 2020;3:e2019686. Accessed May 29,2022.https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770146

What Happens in the Brain?
Reduced Neuroplasticity and Neurogenesis

What happens in the brain?
Reduced neuroplasticity and neurogenesis

- The brain has incredible **plasticity** which enables rapid creation and elimination of **synapses** and the alteration of functional circuits in learning and adaptation[1]
- **BDNF** is a neurotrophin that is needed for healthy **neuroplasticity** and reduced expression has been implicated in the pathophysiology of depression[1-3]
- It is thought that antidepressants can restore *a juvenile-like plastic state* in the brain, allowing a depressed individual to modify neural networks in response to external signals[1,4]

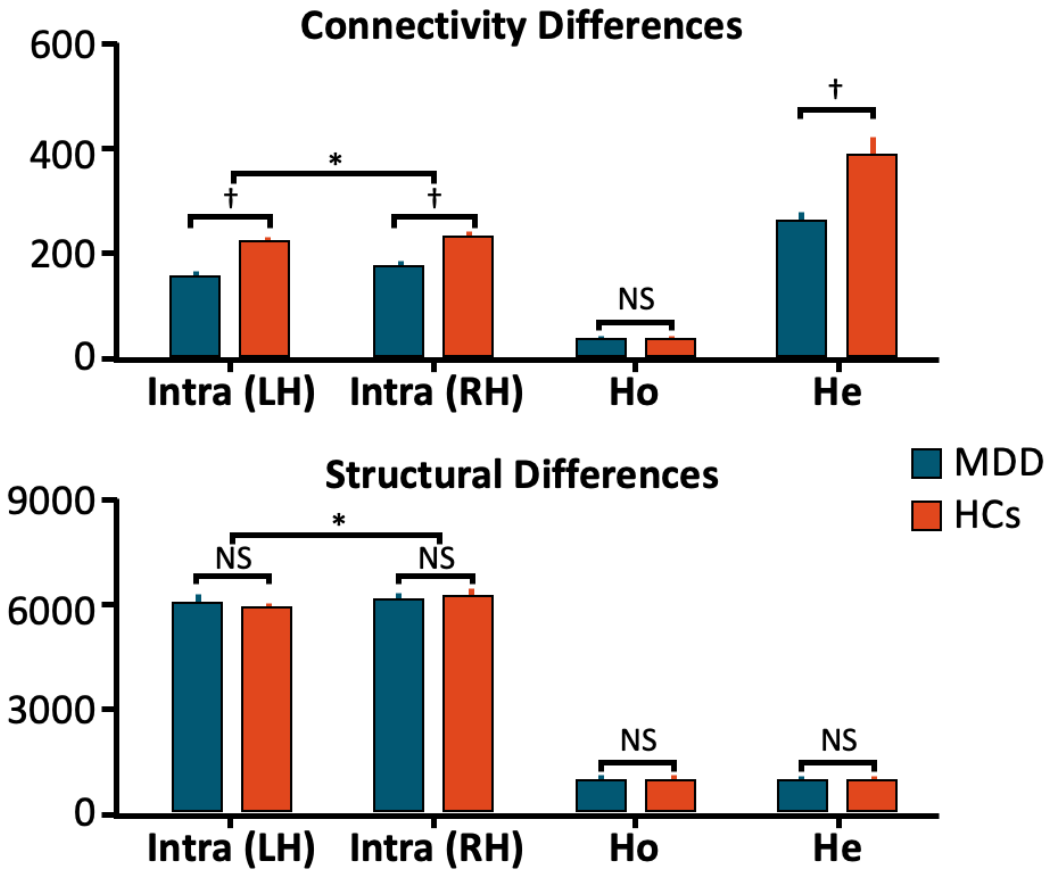


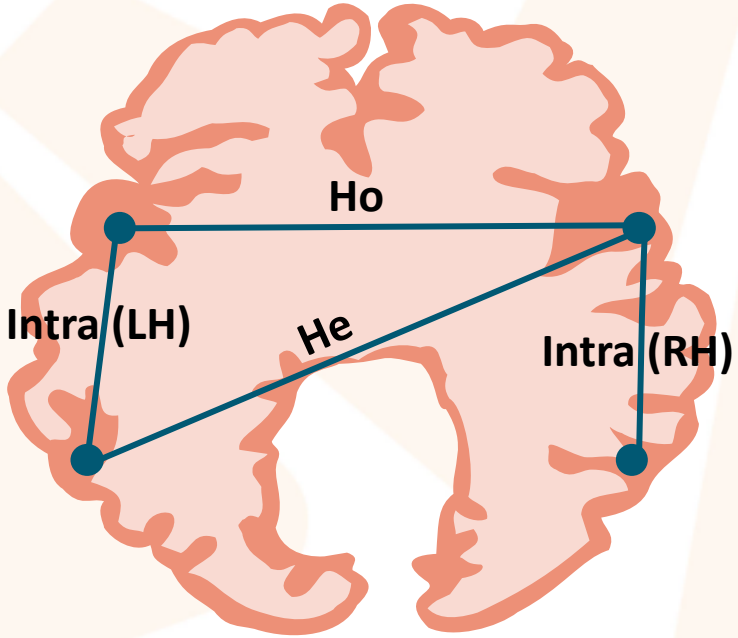
Individual synaptic connections are constantly being remodelled as a result of experience, emotional processing, learning, memory, and stress[5,6]

Individual synaptic connections are constantly being remodeled as a result of experience, emotional processing, learning, memory, and stress[5,6]

1. Dean et al. *Asian J Psychiatry*. 2017;27:101; 2. Monteleone et al. *Bipolar Disord*. 2008;10:95; 3.Taliaz et al. *Mol Psychiatry*. 2010;15:80; 4. Castren et al. *JAMA Psychiatry*. 2013;70:983; 5. Sanacora et al. Neuropharmacology. 2012;62:63; Holtmaat. *Nat Rev Neurosci.* 2009; 10:647.

Impaired "Connectivity" in Depression





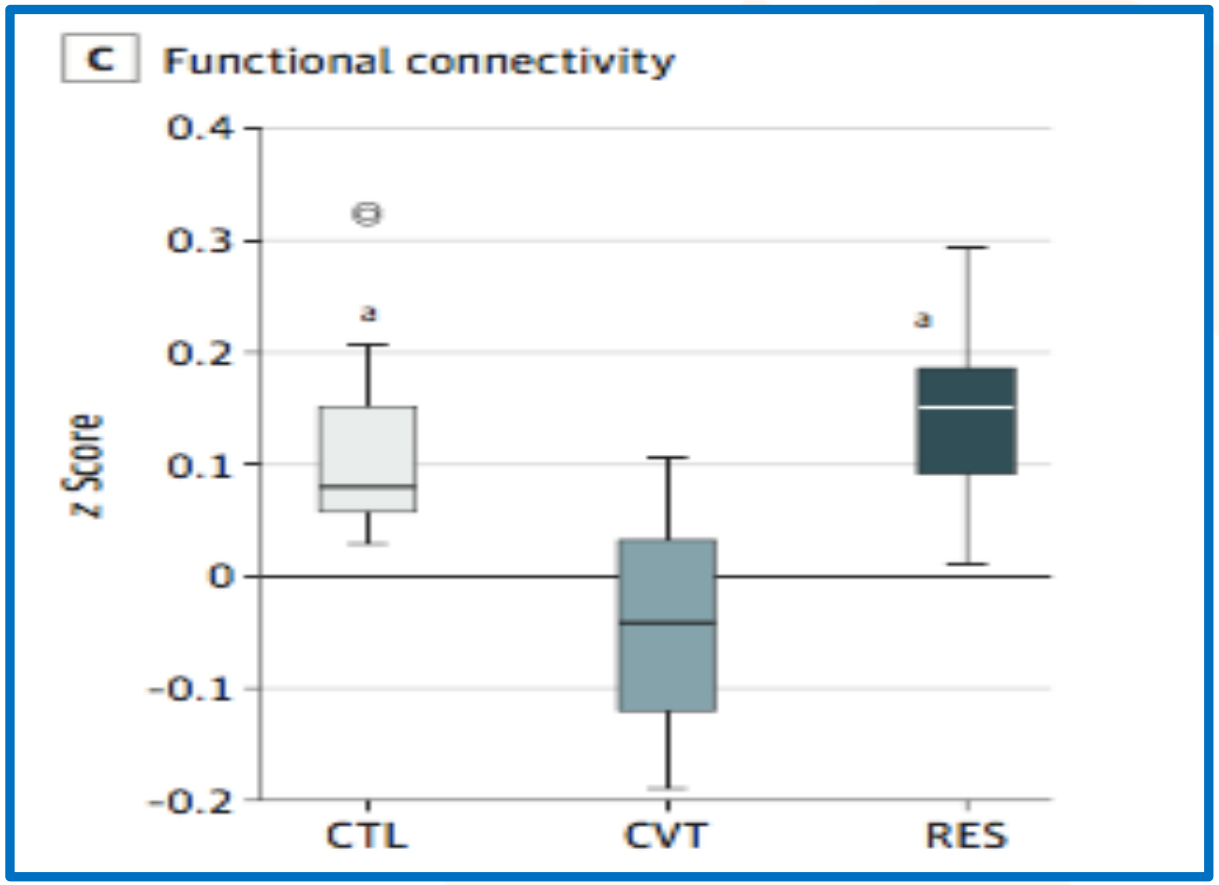
Connecton types:

- Interhemispheric (Intra)
- Interhemispheric homotopic (Ho)
- Interhemispheric heterotopic (He)

*P <.01; †P <.001

Jiang X, et al. *Transl Psychiatry*. 2019;9:136.

Poor Neural Connectivity:
Associated With Development of Depression in Adolescent Females at High Genetic Risk



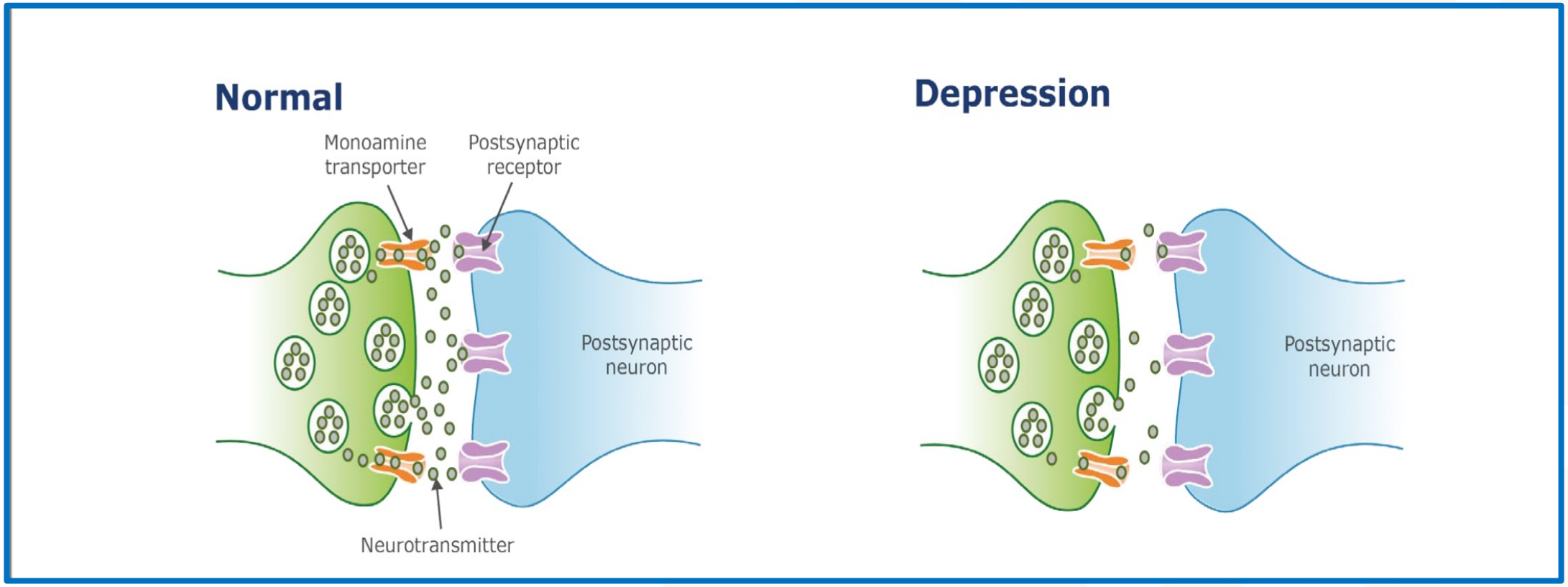
******P* **<.001 compared with CVT.**

Fischer AS, et al. *JAMA Psychiatry*. 2018;75:493.

Traditional Antidepressants

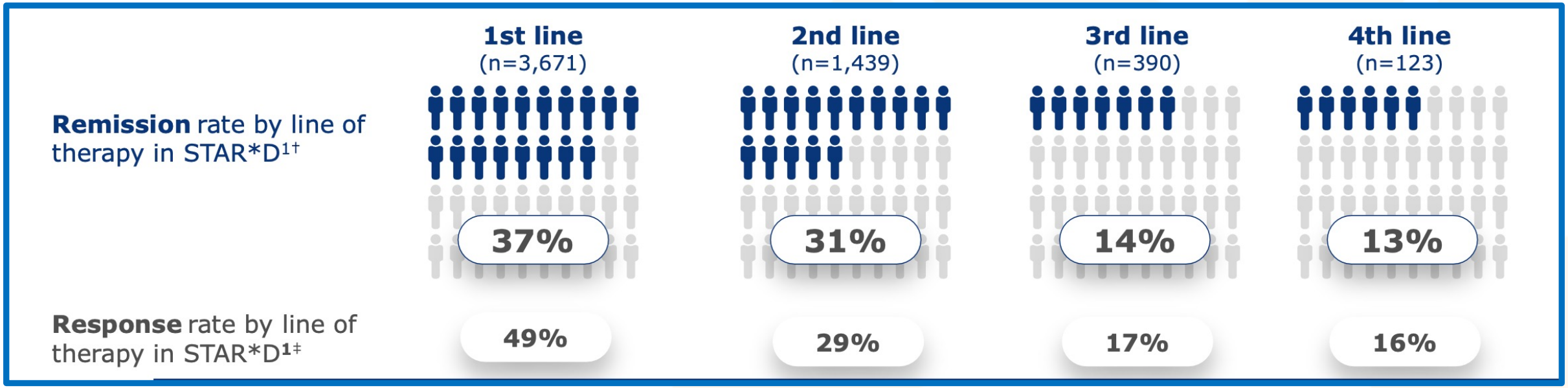
The Monoamine Hypothesis of Depression

- Reduction in the availability of **monoamine neurotransmitters** in the **synaptic cleft** leads to the symptoms of MDD



Hattori N,et al. *Mol Psychiatry*. 2005;10:719.

STAR*D



STAR*D = **Sequenced Treatment Alternatives to Relieve Depression**

Rush AJ, et al. Am J Psychiatry. 2006;163:1905.

STAR-D Step 2: Switch or Augment?

	Response
Step 2 (N = 1439)	28.5
Switch strategy (N = 789)	27.3
Bupropion SR (N = 239)	26.1
Cognitive therapy (N = 62)	30.6
Sertraline (N = 238)	26.7
Venlafaxine XR (N = 250)	28.2
Augmentation strategy (N = 650)	29.9
Bupropion (N = 279)	31.8
Buspirone (N = 286)	26.9
Cognitive therapy (N = 85)	34.1

Response
28.5% Switch
29.9% Augment

Rush AJ, et al. Am J Psychiatry. 2006;163:1905.

Pharmacologic Treatments for Depression

Antidepressants

- SSRIs (fluoxetine, sertraline, paroxetine, citalopram, and escitalopram)
- SNRIs (venlafaxine, desvenlafaxine, duloxetine)
- Others (bupropion, mirtazapine, vortioxetine, vilazodone, levomilnacipran, trazodone)
- Tricyclic and tetracyclics, MAOIs

Second-generation antipsychotics (as augmentation)

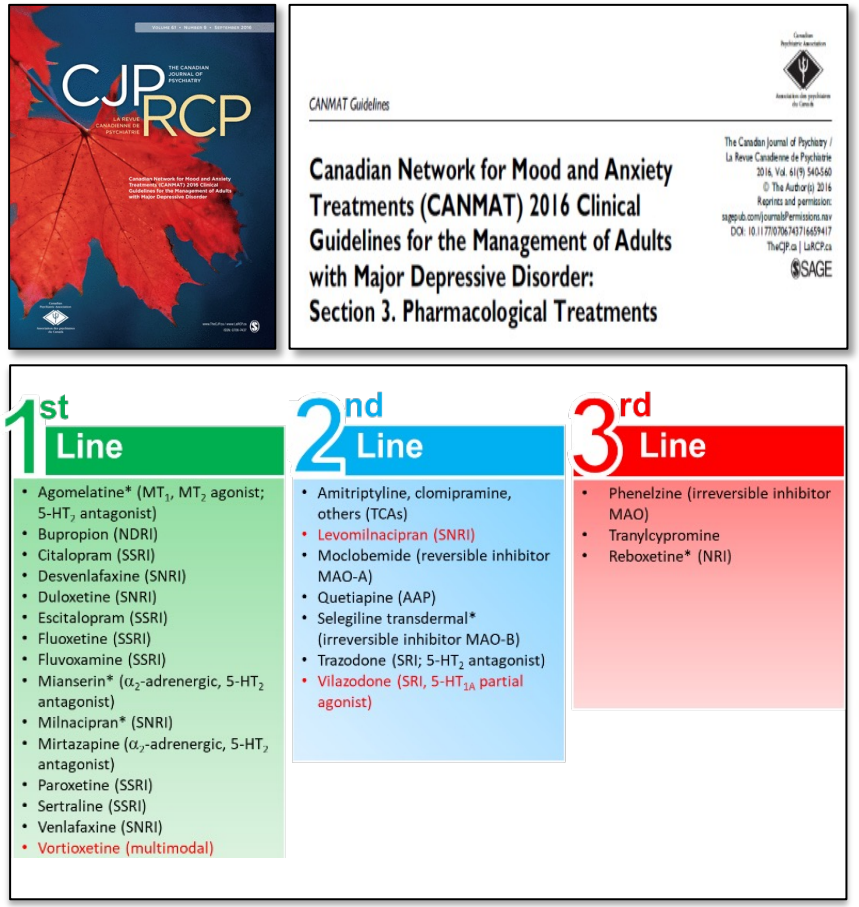
Intranasal esketamine

Off-label and experimental: nutraceuticals, ketamine, pramipexole, anti-inflammatory medications

MAOI = monoamine oxidase inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Jha MK, et al. Experimental Therapies for Treatment-Resistant Depression: Deciding When to Go to an Unproven or Experimental Therapy. Focus. 2018;16(3):279-284.

Contemporary Perspective of Antidepressant Medication



Over 30 antidepressants available

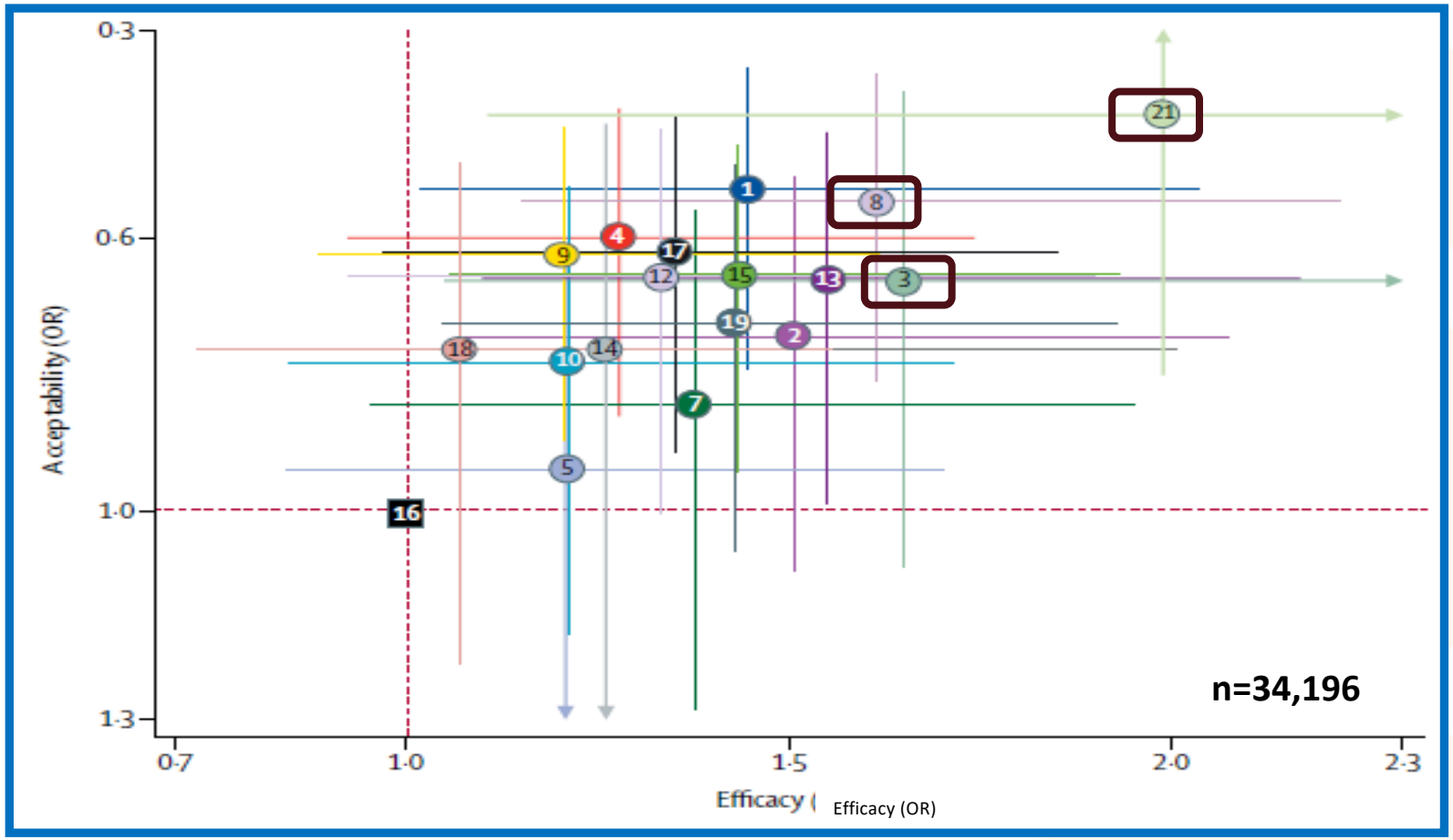
Unmet Needs

- Fast onset
- Treatment of residual symptoms
- Cognition
- Functional improvement
- Novel mechanisms

Kennedy SH, et al. Can J Psychiatry. 2016;61:540. Moser et al. Pink Sheet. 2018. Goldberg et al. Expert Opin Pharmacother. 2017;18:1417.

Depression: A Quick Look at the Data

Head-to-head Studies of Efficacy and Acceptability



In **head-to-head** studies, 3 antidepressants had the most favourable profile for efficacy and acceptability:

1. Vortioxetine (21) had the greatest net clinical benefit
   - Highest OR for efficacy
   - Lowest OR for all-cause discontinuation
2. Escitalopram (8)
3. Bupropion (3)

1=agomelatine *(not available in Canada)*. 2=amitriptyline. 3=bupropion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. 7=duloxetine. 8=escitalopram. 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12=milnacipran 13=mirtazapine. 14=nefazodone. 15=paroxetine. 16=reboxetine 17=sertraline. 18=trazodone. 19=venlafaxine. 20=vilazodone. 21=vortioxetine.

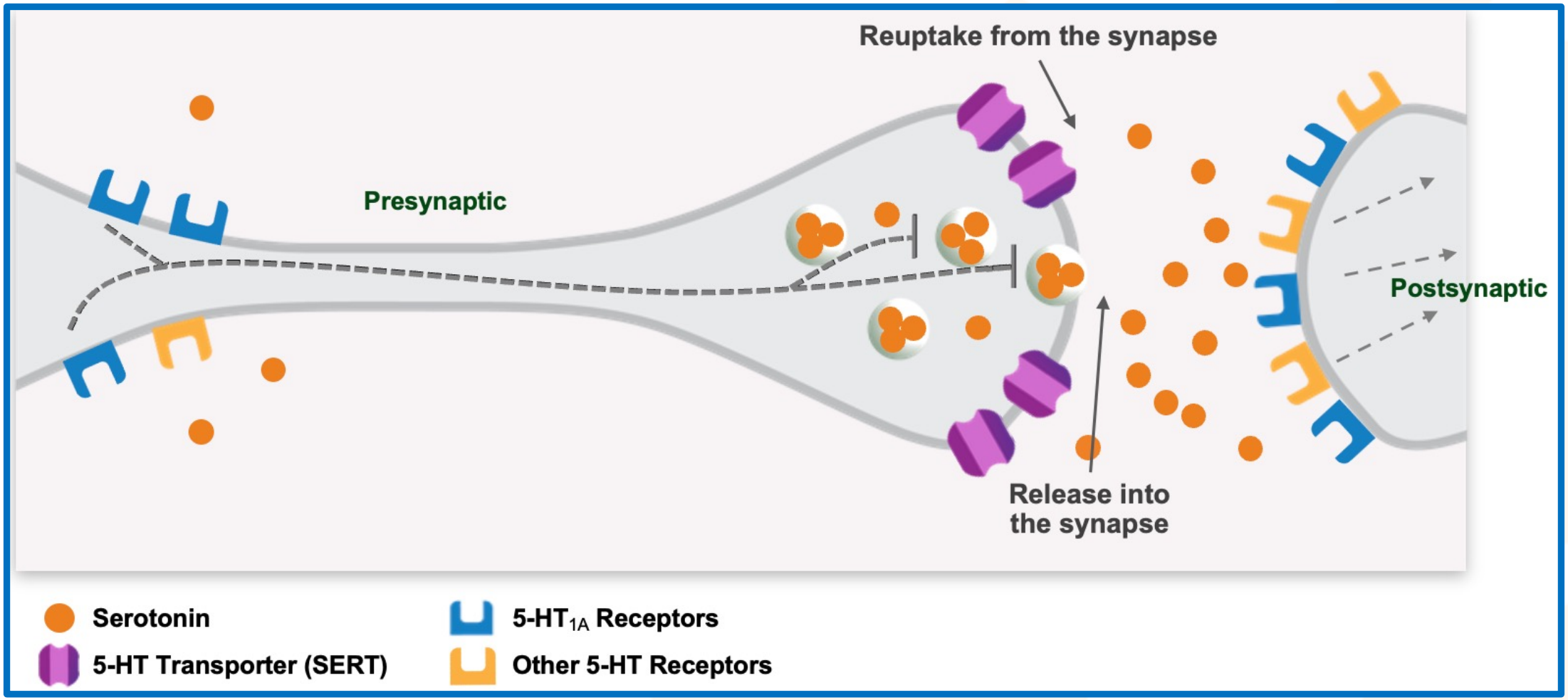
Cipriani A, et al. *Lancet*. 2018;391:1357.

5HT1a Receptors Modulate Anxiety and Mood

- 5HT1a partial agonists-Buspirone, Gepirone, Tandospirone
- SERT + 5HT1a partial agonist-Vilazodone
- SERT + 5HT1a full agonist-Vortioxetine

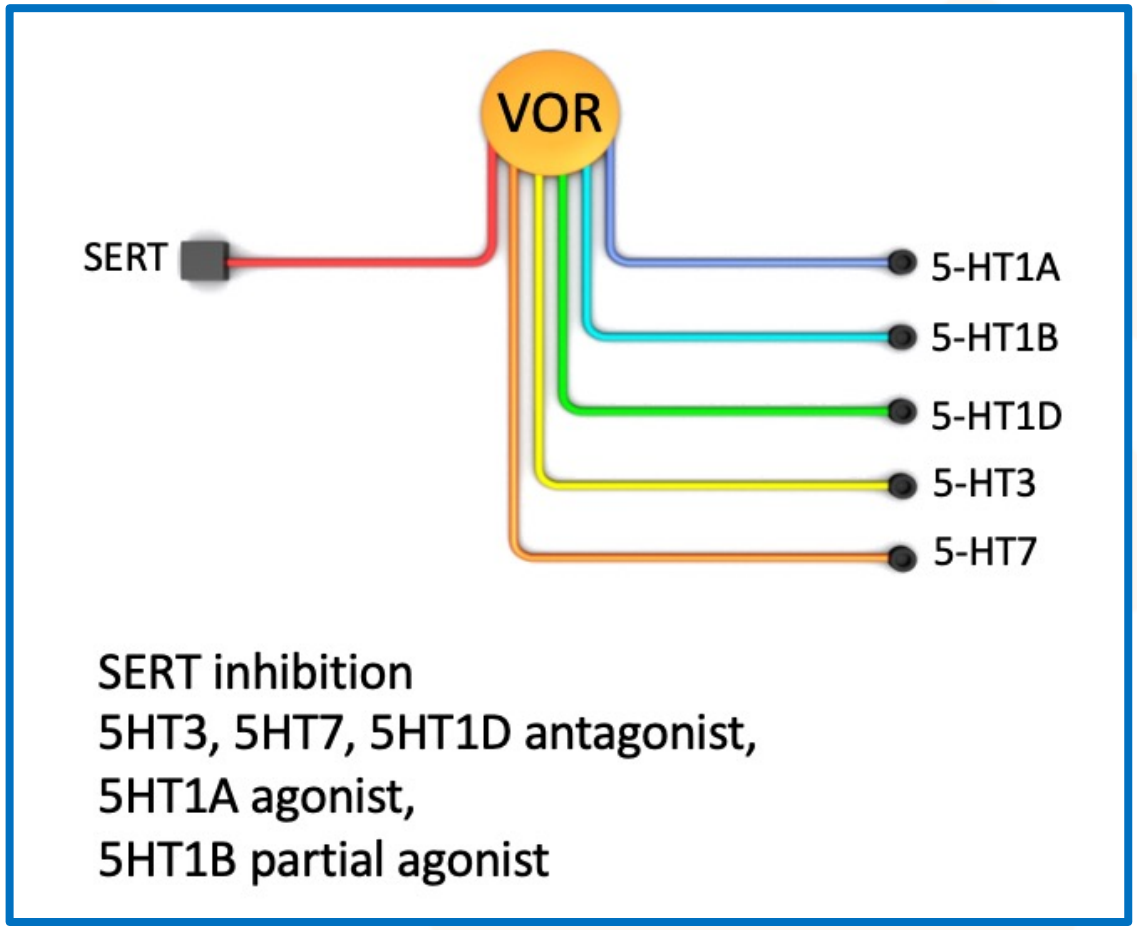
Frankel J, et al. *Ther Adv Psychopharmacol. 2017;*7(1):29–41.

5HT1a Receptors
Pre and Post Synaptic



Belmaker & al. New England Journal of Medicine, 2008. 2. Blier. Journal of Psychiatry and Neuroscience, 2001. 3. Savitz J et al. Prog Neurobiol. 2009;88:17-31.

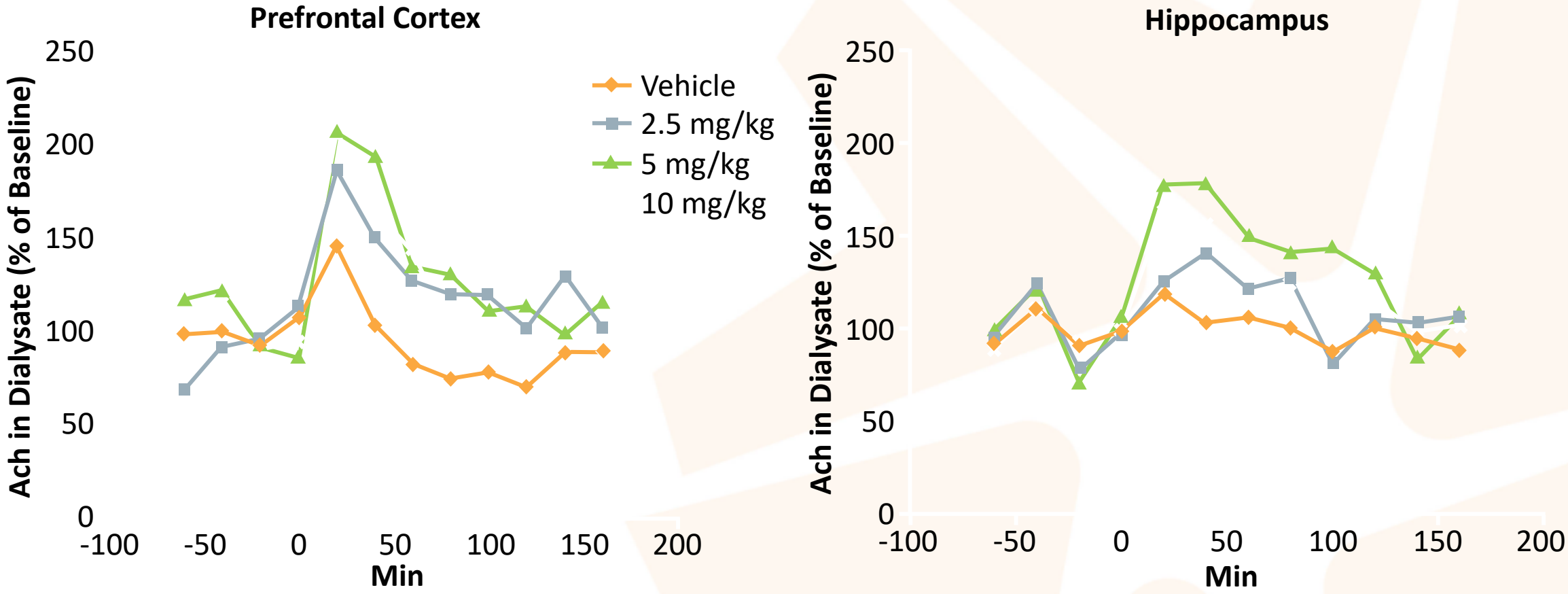
Vortioxetine- 5HT1a+



Guilloux JP, et al. *Neuropharmacology.* 2013;73:147–159. Pehrson AL, et al. *Eur Neuropsychopharmacol*. 2013;23(2):133–145. Mørk A, et al. *Pharmacol Biochem Behav.* 2013;105:41–50.

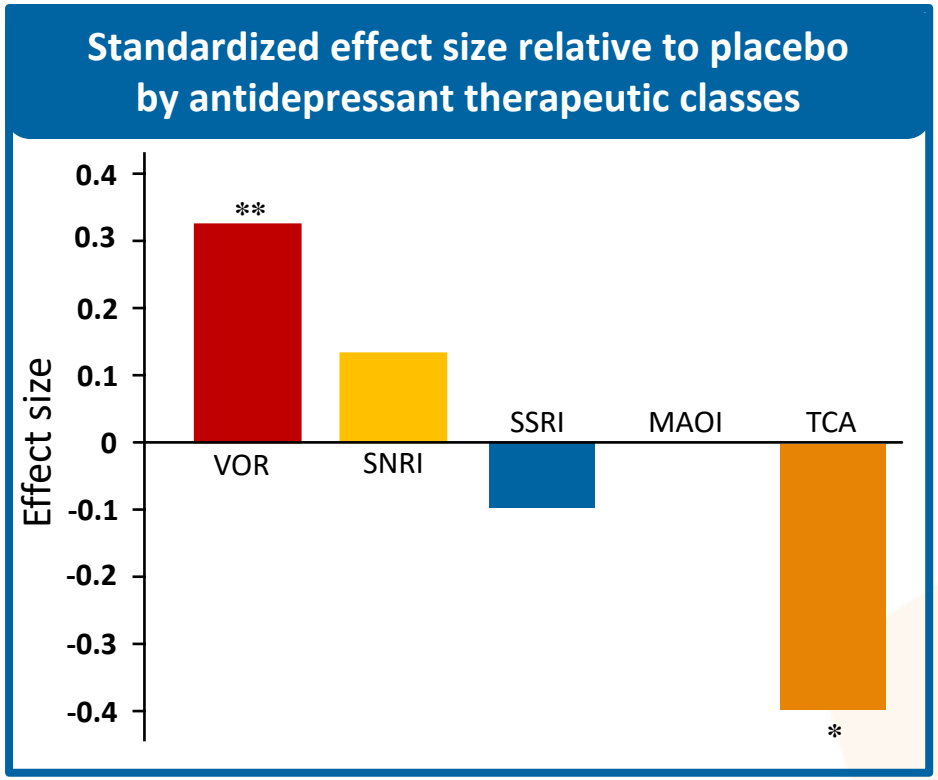
A Compound Which Stimulates 5-HT_{1A} and Blocks 5-HT_3

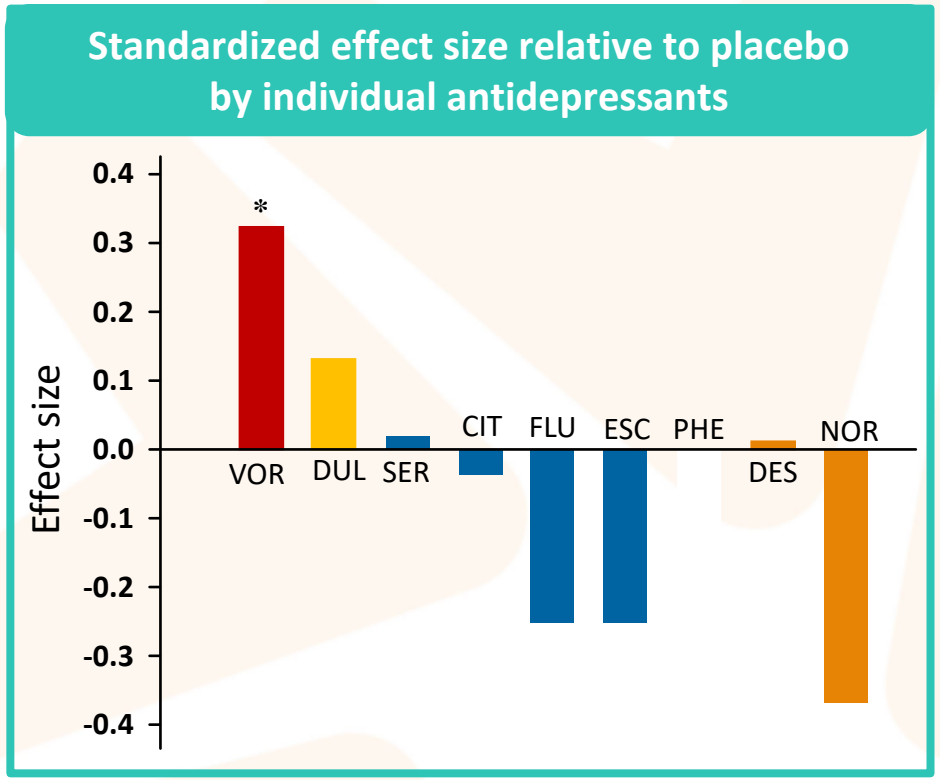
Increases Acetylcholine in the Prefrontal Cortex and the Hippocampus



Vortioxetine. US 9,278,096 Patent. March 8, 2016.

Comparing Effects of Antidepressants on DSST





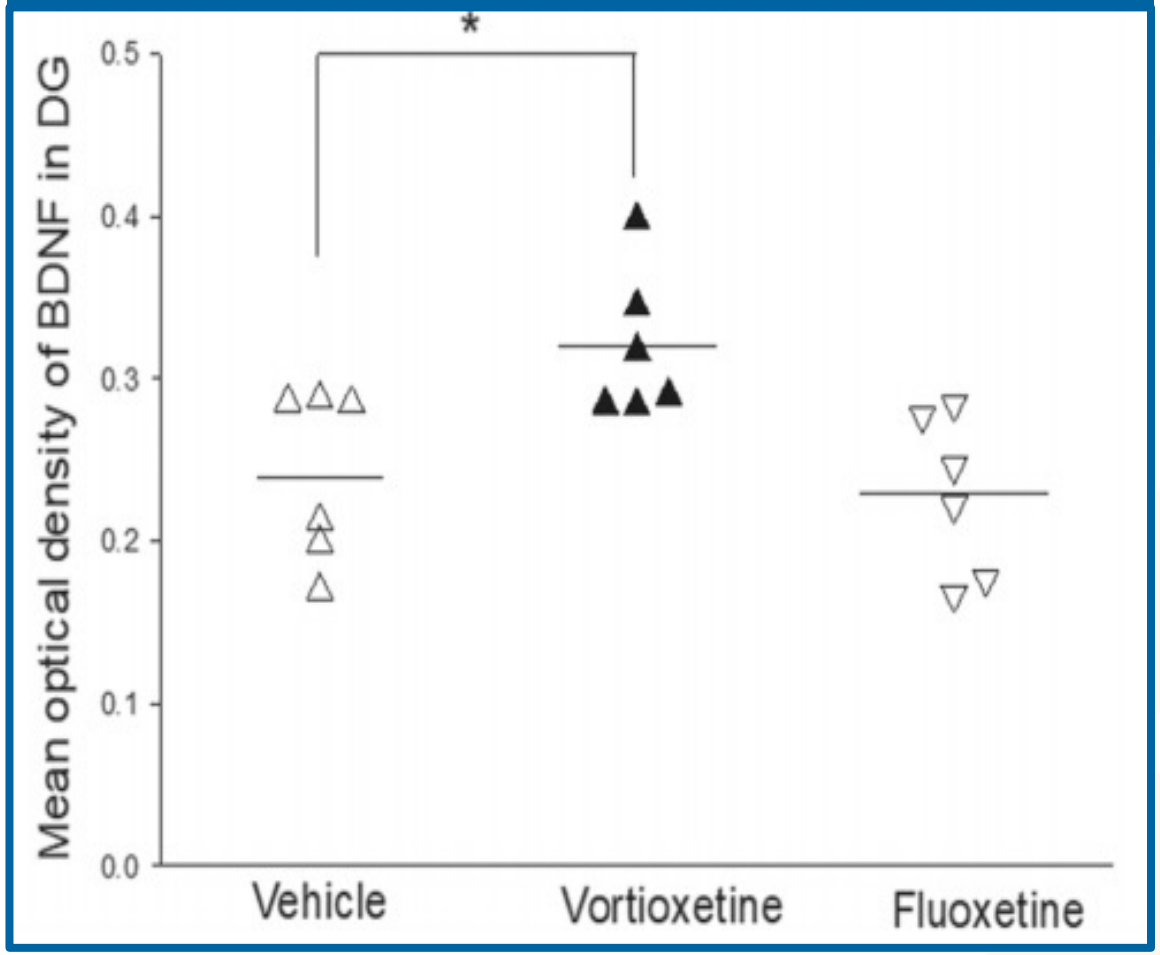
DSST = Digit Symbol Substitution Test

Baune BT, et al. *Int J Neuropsychopharmacol*. 2018;21:97. Mattingly G. *Postgraduate Medicine*. 2016;8:665.

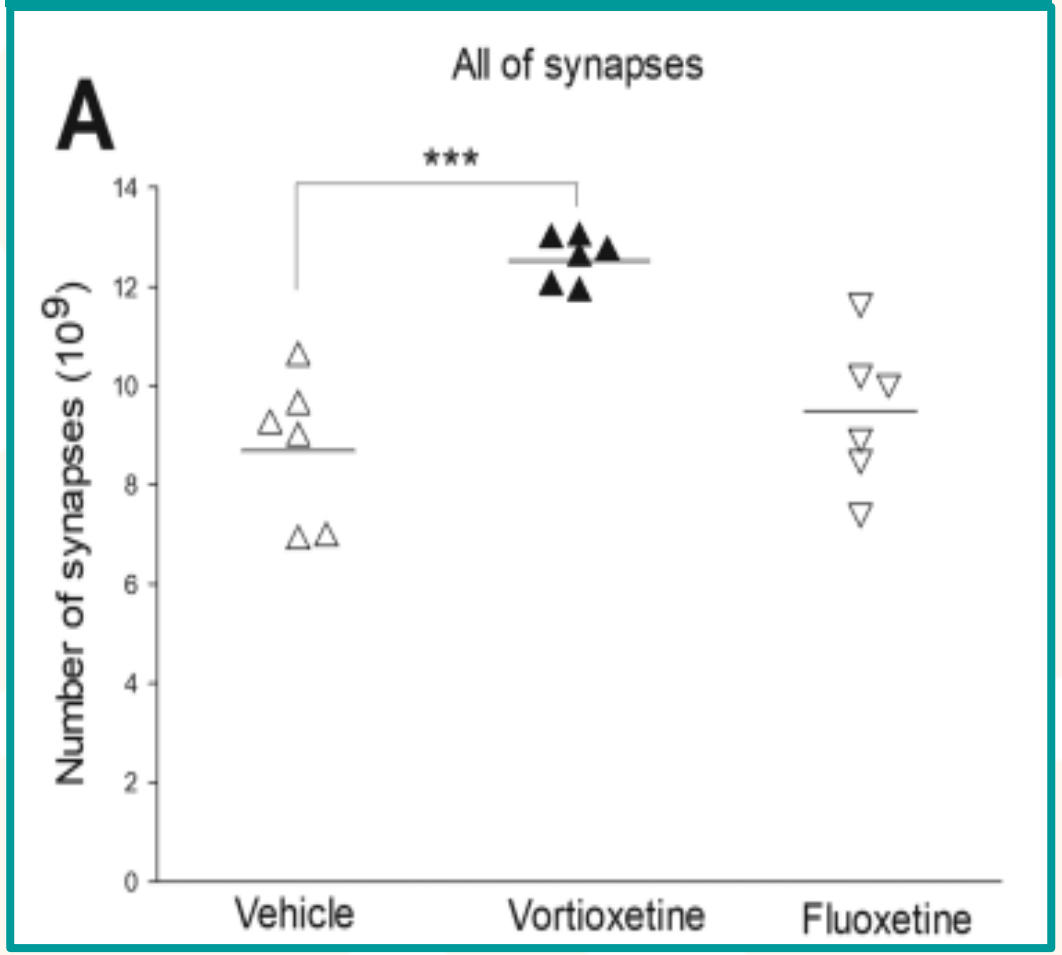
Changes in BDNF and Synaptic Number

After 1 Week of Vortioxetine or Fluoxetine

BDNF Levels



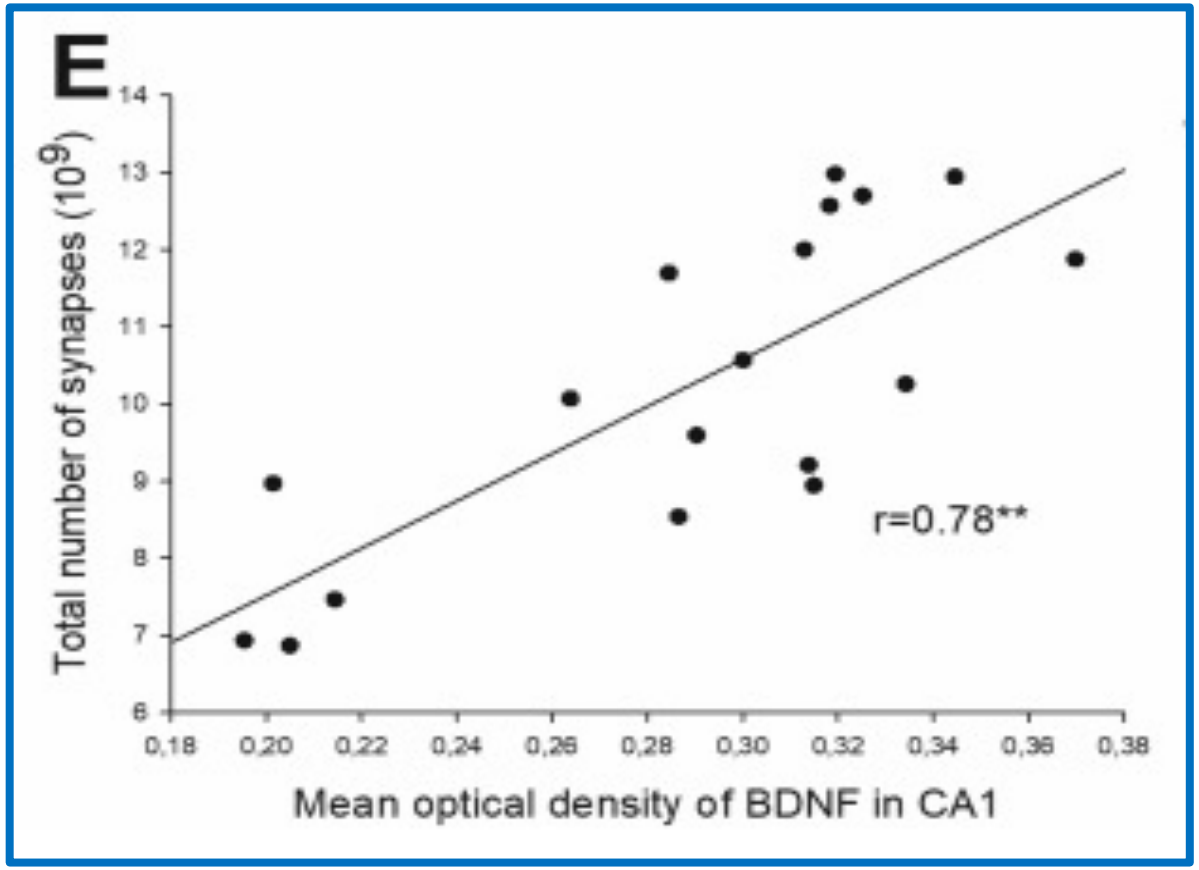
Number of Synapses



International Journal of Neuropsychopharmacology. 2018;21(6): 603–615.

Vortioxetine

BDNF Increase and Synaptic Number

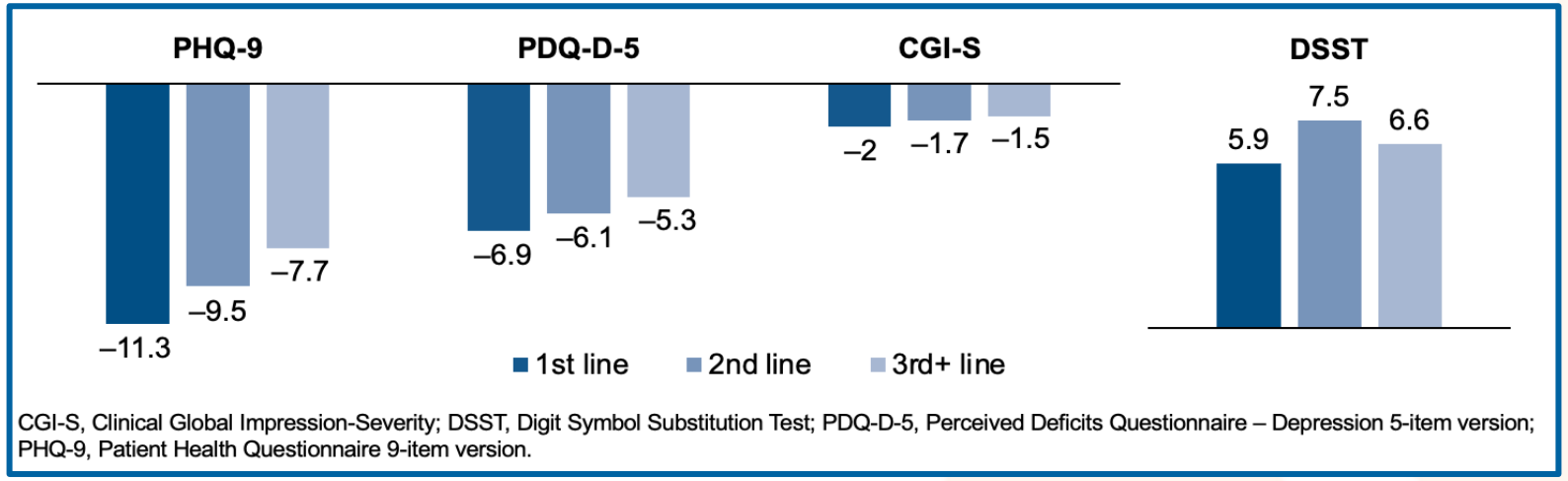


*.

International Journal of Neuropsychopharmacology. 2018;21(6):603–615.

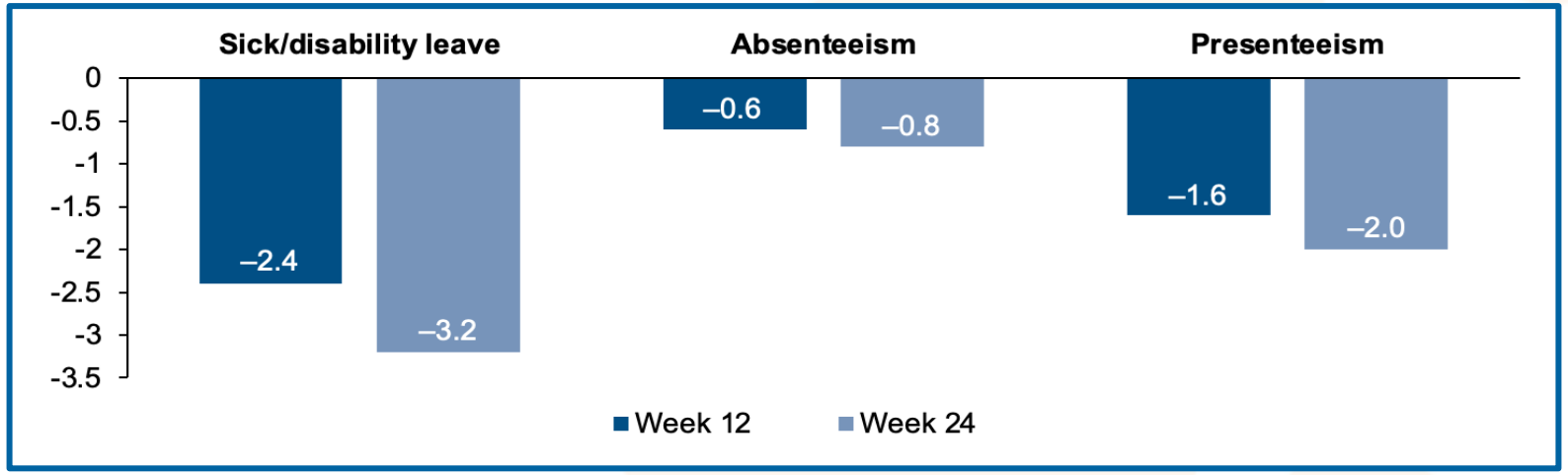
Relieve Study

"Real World" Global Study of 862 Patients Starting Vortioxetine



CGI-S, Clinical Global Impression-Severity; DSST, Digit Symbol Substitution Test; PDQ-D-5, Perceived Deficits Questionnaire – Depression 5-item version; PHQ-9, Patient Health Questionnaire 9-item version.

Improved Depressive Symptoms and More Productive at Work



Mattingly. EPA. 2021.

Other Receptor Modulators

Atypical Antipsychotics Approved for MDD Treatment

	Dose		Side Effects
	Initial	Recommended	
Aripiprazole	2-5 mg	5 -15 mg	Weight gain, sedation, akathisia
Quetiapine / Quetiapine XR	50 mg	150-300 mg	Sedation, weight gain
Olanzapine/Fluoxetine	6/25 mg	6/25-12/50 mg	Sedation, weight gain, appetite, metabolics
Brexpiprazole	0.5-1 mg	2-3 mg	Weight gain

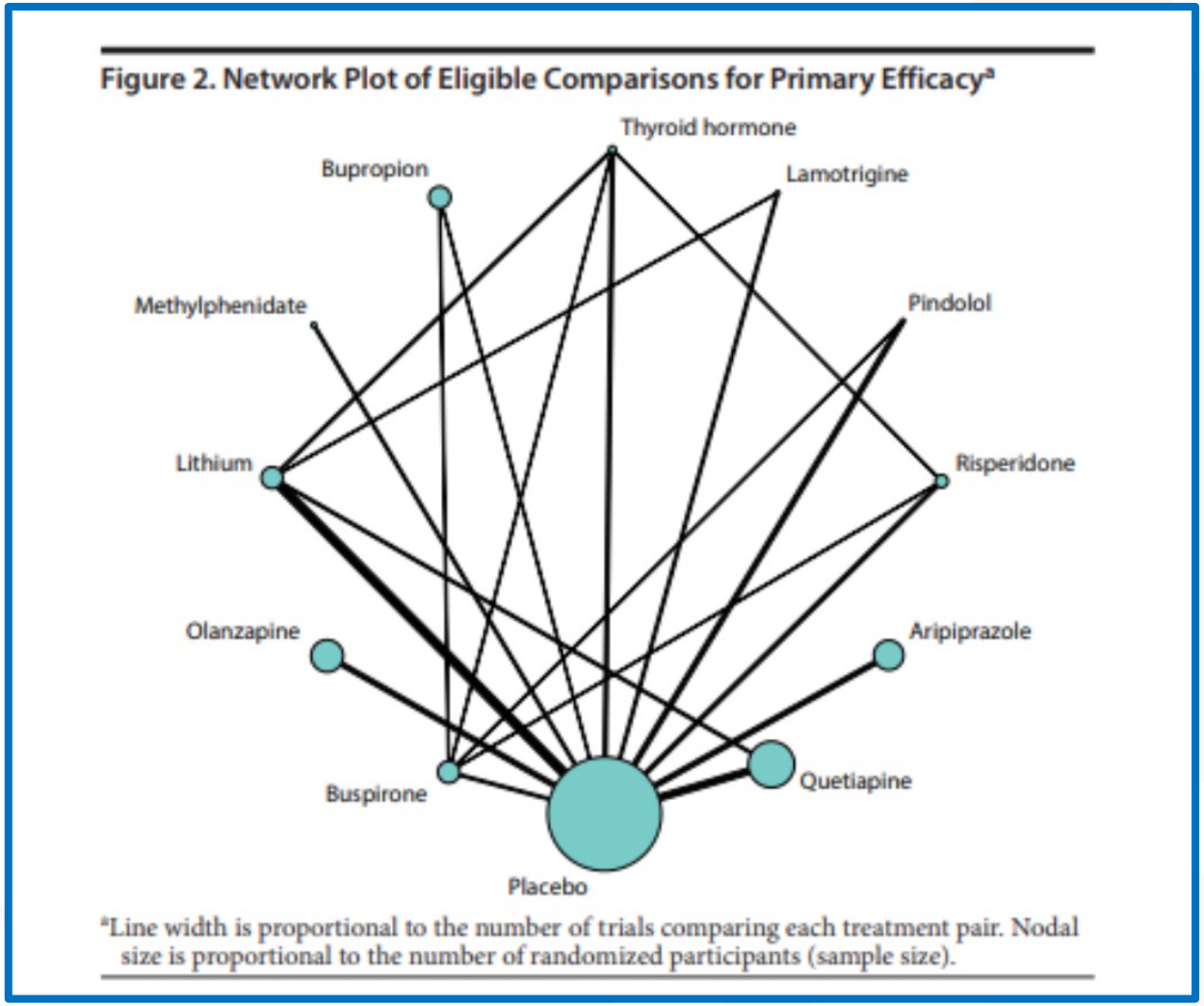
*There are no head-to-head clinical studies comparing the safety and efficacy of these products. This chart is descriptive of the FDA-approved indications.

Aripiprazole PI. Quetiapine PI. Quetiapine XR PI. Olanzapine/fluoxetine PI. Brexpiprazole PI.

Tolerability of Augmentation Strategies

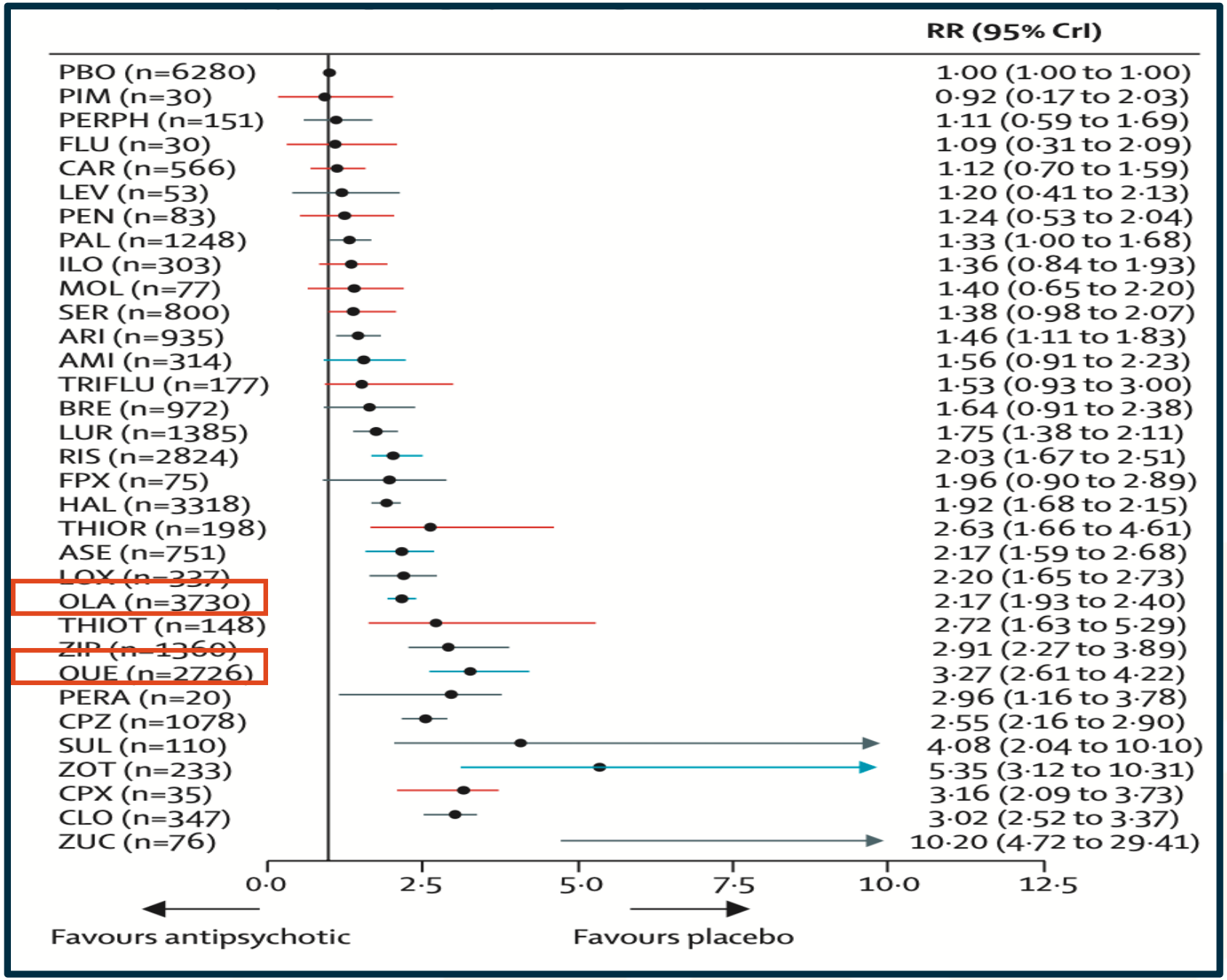
Less Tolerability:

- Quetiapine OR = 3.85
- Olanzapine OR = 3.36
- Aripiprazole OR = 2.51
- Lithium OR = 2.30



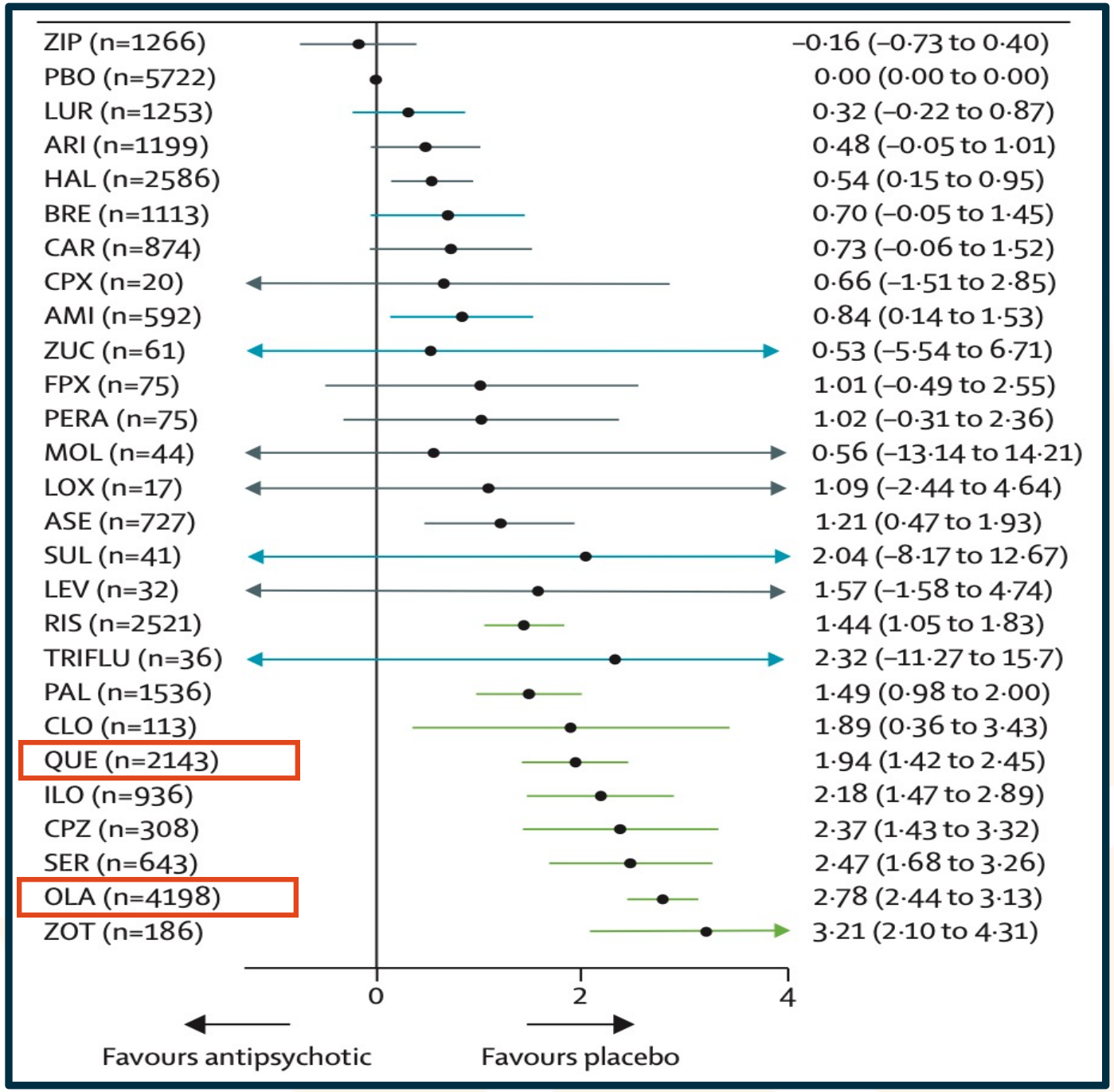
Zhou X, et al. *J Clin Psychiatry*. 2015;76(4):3423. :e487.

Sedation



Huhn M, et al. Lancet. 2019;394:939.

Weight Gain



Huhn M, et al. Lancet. 2019;394:939.

Olanzapine/Fluoxetine Weight Gain

Amount Gained kg (lb)	Up to 8 Weeks (N = 881) (%)	Up to 20 Weeks (N = 651) (%)	Up to 47 Weeks (N = 220) (%)
≤0	19.8	14.9	19.1
0 to ≤5 (0-11 lb)	64.1	47.2	37.7
>5 to ≤10 (11-22 lb)	15.1	30.3	27.7
>10 to ≤15 (22-33 lb)	0.9	5.8	10.0
>15 to ≤20 (33-44 lb)	0.1	1.2	3.2
>20 to ≤25 (44-55 lb)	0.0	0.6	1.4
>25 to ≤30 (55-66 lb)	0.0	0.0	0.5
>30 (>66 lb)	0.0	0.0	0.5

With Long-Term Use: **7% Weight gain 64%**
15% Weight gain 32%
25% Weight gain 12%

Olanzapine/fluoxetine PI.

Comparison of Antidepressant and Common Side Effects

Class	Drug	Nausea	Constipation	Diarrhoea	Dry mouth	Headache	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased appetite	Weight gain	Male sexual dysfunction
SSRI	• Citalopram	10–29%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Escitalopram	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%
	• Fluoxetine	10–29%	0–9%	0–9%	10–29%	0–9%	0–9%	10–29%	10–29%	10–29%	0–9%	10–29%	0–9%	0–9%	0–9%	10–29%	10–29%	0–9%	0–9%	0–9%
	• Fluvoxamine	≥30%	10–29%	0–9%	10–29%	10–29%	10–29%	10–29%	0–9%	0–9%	10–29%	10–29%	0–9%	10–29%	0–9%	10–29%	10–29%	0–9%	0–9%	0–9%
	• Paroxetine	10–29%	10–29%	10–29%	10–29%	10–29%	10–29%	10–29%	0–9%	0–9%	0–9%	10–29%	0–9%	10–29%	10–29%	0–9%	0–9%	0–9%	0–9%	10–29%
	• Sertraline	10–29%	0–9%	10–29%	10–29%	10–29%	10–29%	10–29%	0–9%	0–9%	0–9%	10–29%	10–29%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	10–29%
SNRI	• Desvenlafaxine	10–29%	0–9%	0–9%	10–29%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Duloxetine	10–29%	10–29%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%
	• Levomilnacipran	10–29%	0–9%	0–9%	10–29%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%
	• Milnacipran	10–29%	0–9%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Venlafaxine	≥30%	10–29%	0–9%	10–29%	10–29%	10–29%	10–29%	10–29%	0–9%	0–9%	10–29%	0–9%	10–29%	10–29%	0–9%	10–29%	0–9%	0–9%	10–29%
Other	• Agomelatine	0–9%	0–9%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Bupropion	10–29%	0–9%	0–9%	10–29%	≥30%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Mirtazapine	0–9%	10–29%	0–9%	10–29%	0–9%	0–9%	≥30%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%	10–29%	0–9%
	• Moclobemide	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Vilazodone	10–29%	0–9%	10–29%	0–9%	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%
	• Vortioxetine	10–29%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%

0–9%

10–29%

≥30%

* Based on unadjusted rates from product monographs

Kennedy SH, et al. *Can J Psychiatry*. 2016 Sep;61(9):540-60.

Side Effects with Continued Treatment

Some side effects may emerge later in the course of antidepressant treatment and affect adherence with treatment

Weight Gain

- More common with TCAs and MAOIs than SSRIs
- Among SSRIs, more common with paroxetine
- Mirtazapine has higher weight gain potential than other atypical antidepressants
- Bupropion and levomilnacipran have lower weight gain potential than SSRIs and SNRIs
- Consider weight gain potential when using SGAs for augmentation, especially olanzapine and quetiapine
- Vilazodone and vortioxetine similar to placebo

TCA = tricyclic antidepressant.

Fava M. *J Clin Psychiatry*. 2000;61 Suppl 11:37-41. Park LT, et al. *N Engl J Med*. 2019;380(6):559-568.

Side Effects: *Sexual Dysfunction*

Important to establish baseline sexual function before initiating antidepressants

Dysfunction may be a symptom of depression

Dysfunction may emerge after several weeks of antidepressant treatment

Tools to measure sexual function include:

- Massachusetts General Hospital Sexual Function Inventory (MGH SFI)
- Arizona Sexual Experiences Scale (ASEX)
- Changes in Sexual Functioning Questionnaire (CSFQ)

Cleaner agents would include- Mirtazapine, Buproprion, Vilazodone and Vortioxetine*

***Vortioxetine package insert demonstrates with significant improvement in SSRI induced sexual dysfunction.**
Clayton AH, et al. *Int Clin Psychopharmacol*. 2015;30(4):216-223. Park LT, et al. *N Engl J Med*. 2019;380(6):559-568.

Antidepressant Discontinuation Syndrome

May occur after abrupt discontinuation (even with missed doses or sharp dose reduction with some drugs such as paroxetine)

FINISH

- Flu-like, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation)

Gained recent media attention

Highest likelihood with **paroxetine** among SSRIs and **venlafaxine** among SNRIs

Lowest likelihood with fluoxetine among SSRIs

Jha MK, et al. *Am J Psychiatry*. 2018;175(12):1176-1184.

Initializing Therapy in MDD

After Treatment – Benefits to Daily Life and Continuing Struggles

Video Vignette #2

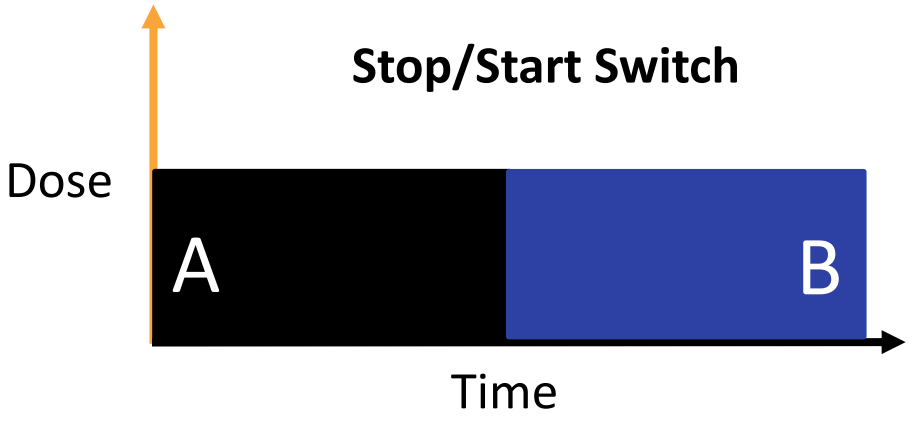
Guidance on Antidepressant Switching

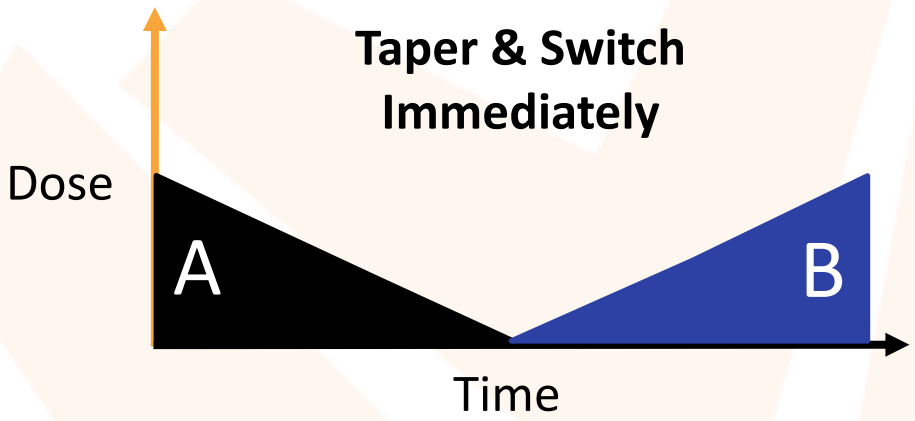
Which Antidepressant Would you Start?

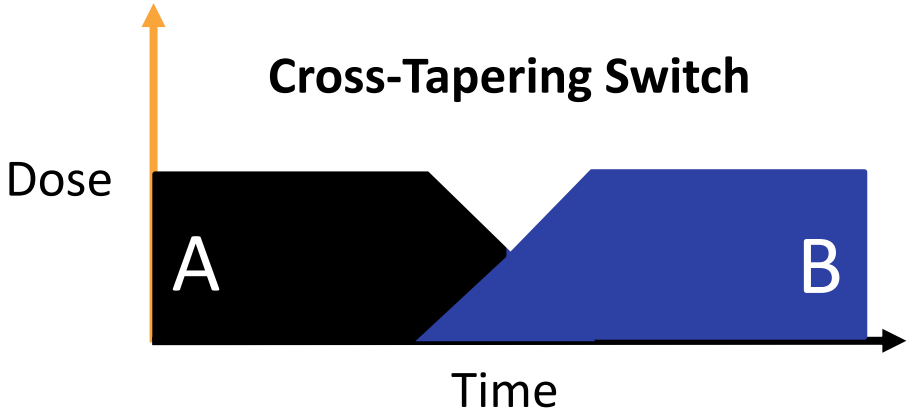
AD Class	Examples	Side effects
SSRIs	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram	GI, activation, insomnia, sexual dysfunction, migraines, falls, weight gain, potential for serotonin syndrome, discontinuation syndrome[1,2]
SNRIs	Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran	GI, activation, sexual dysfunction, increased pulse rate, dry mouth, excessive sweating, increased blood pressure, potential for serotonin syndrome, discontinuation symptoms[1,2]
TCAs	Amitriptyline, nortriptyline, imipramine, desipramine, doxepin	Cardiovascular effects, arrhythmias, orthostatic hypotension, dry mouth, sexual dysfunction, tachycardia, impaired vision, memory and concentration impairments, sedation, weight gain, myoclonus[1,2]
MAOIs	Phenelzine, tranylcypromine, isocarboxazid, selegiline	Hypertensive crisis, potential for serotonin syndrome, orthostatic hypotension, weight gain, sexual dysfunction, headaches, insomnia[1,2]
Others	Bupropion, nefazodone, trazodone, mirtazapine, agomelatine	Nausea, headaches, dizziness, insomnia, somnolence, tremors, seizures, dry mouth, sedation, weight gain[1-3]
Multimodal Antidepressants	Vilazodone, vortioxetine	Nausea, diarrhea[4]

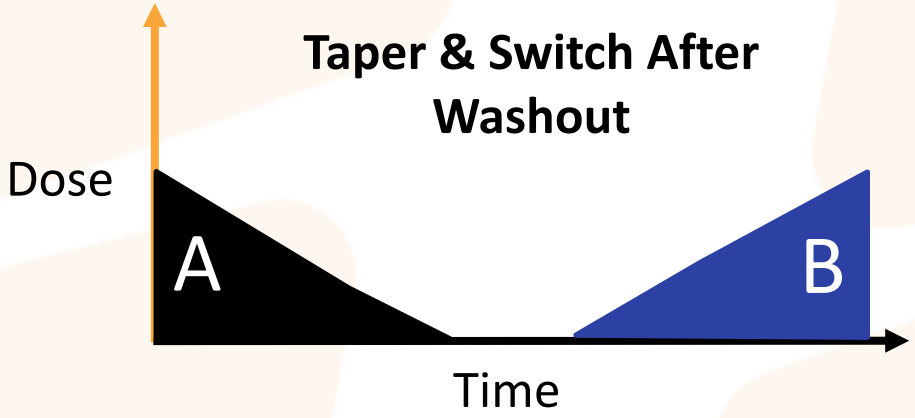
AD = antidepressant; GI = gastrointestinal; MAOI = monoamine oxidase inhibitor; SNRI = serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

How Do You Switch?









Case #1: Chris

Chris is a 29-year-old man with a 9-month history of MDD. His PHQ-9 score on diagnosis was 18 (moderate-severe). Fluoxetine was initiated and titrated to 40 mg qd over 6 months, at which point his PHQ-9 score had dropped to 8 (mild).

Today, his PHQ-9 score is 7. When his clinician asks if Chris feels that his goals for therapy have been met, Chris says, “I don’t feel depressed the way I did before, but my energy is really low.” Chris asks if there are any options that might improve this daily fatigue.

Current Antidepressants: A Range of Side Effects

AD Class	Examples	Side effects
SSRIs	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram	GI, activation, insomnia, sexual dysfunction, migraines, falls, weight gain, potential for serotonin syndrome, discontinuation syndrome[1,2]
SNRIs	Venlafaxine, desvenlafaxine, duloxetine , levomilnacipran	GI, activation, sexual dysfunction, increased pulse rate, dry mouth, excessive sweating, increased blood pressure, potential for serotonin syndrome, discontinuation symptoms[1,2]
TCAs	Amitriptyline, nortriptyline, imipramine, desipramine, doxepin	Cardiovascular effects, arrhythmias, orthostatic hypotension, dry mouth, sexual dysfunction, tachycardia, impaired vision, memory and concentration impairments, sedation, weight gain, myoclonus[1,2]
MAOIs	Phenelzine, tranylcypromine, isocarboxazid, selegiline	Hypertensive crisis, potential for serotonin syndrome, orthostatic hypotension, weight gain, sexual dysfunction, headaches, insomnia[1,2]
Others	Bupropion, nefazodone, trazodone, mirtazapine, agomelatine	Nausea, headaches, dizziness, insomnia, somnolence, tremors, seizures, dry mouth, sedation, weight gain[1-3]
Multimodals	Vilazodone , vortioxetine	Nausea, diarrhea[4]

Increases NE and DA

1. APA. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: APA;2010; 2.Taylor et al. Maudsley Prescribing Guidelines,10th Edition,2009; 3.EMA. Summary of Product Characteristics for Valdoxan (agomelatine).2009. Accessed October 27, 2014; 4.Forest Laboratories Inc. Prescribing Information for Viibryd (vilazodone hydrochloride). 2014.

Case #2: Carolyn

Carolyn is a 73-year-old woman with a 5-year history of MDD and 15-year history of hypertension. Her first episode of MDD was treated with paroxetine 20 mg qd. She achieved remission (PHQ-9 score 4) on this regimen and maintained remission until last year. When she experienced a relapse (PHQ-9 score 17), she was switched from paroxetine to citalopram 40 mg qd.

Her PHQ-9 score today is 8 (mild). Her highest scores are on trouble falling asleep (score of 2) and lack of appetite (2). When her clinician asks about sleep and appetite, Carolyn says, “I stay up late many nights hoping to get sleepy, and I’m just not hungry. I think I’ve lost some weight.” Current medications include citalopram 20 mg qd and lisinopril 20 mg qd.

Current Antidepressants: A Range of Side Effects

AD Class	Examples	Side effects
SSRIs	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram	GI, activation, insomnia, sexual dysfunction, migraines, falls, weight gain, potential for serotonin syndrome, discontinuation syndrome[1,2]
SNRIs	Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran	GI, activation, sexual dysfunction, increased pulse rate, dry mouth, excessive sweating, increased blood pressure, potential for serotonin syndrome, discontinuation symptoms[1,2]
TCAs	Amitriptyline, nortriptyline, imipramine, desipramine, doxepin	Cardiovascular effects, arrhythmias, orthostatic hypotension, dry mouth, sexual dysfunction, tachycardia, impaired vision, memory and concentration impairments, sedation, weight gain, myoclonus[1,2]
MAOIs	Phenelzine, tranylcypromine, isocarboxazid, selegiline	Hypertensive crisis, potential for serotonin syndrome, orthostatic hypotension, weight gain, sexual dysfunction, headaches, insomnia[1,2]
Others	Bupropion, nefazodone, trazodone, mirtazapine, agomelatine	Nausea, headaches, dizziness, insomnia, somnolence, tremors, seizures, dry mouth, sedation, weight gain[1-3]
Multimodals	Vilazodone, vortioxetine	Nausea, diarrhea[4]

Helps sleep and appetite

1. APA. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: APA ; 2010; 2.Taylor et al. Maudsley Prescribing Guidelines, 10th Edition, 2009; 3.EMA. Summary of Product Characteristics for Valdoxan (agomelatine). 2009. Accessed October 27, 2014; 4.Forest Laboratories Inc. Prescribing Information for Viibryd (vilazodone hydrochloride). 2014.

Managing Insomnia in MDD

- Subjects with MDD and insomnia (N=19)
- Randomized to 8 weeks of treatment with mirtazapine or fluoxetine
- Sleep evaluated by polysomnography
- Significant improvements in objective sleep physiology with mirtazapine at 8 weeks
  - Sleep latency, sleep efficiency, and wake after sleep significantly better after 2 weeks
- No significant changes in sleep continuity measures with fluoxetine

Winokur A, et al. *J Clin Psychiatry.* Oct 2003;64(10):1224-1229.

Case #3: Larry

Larry is a 40-year-old man with a 2-year history of MDD. His PHQ-9 score on diagnosis was 19 (moderate-severe). After 6 months of treatment with escitalopram 10 mg qd, his PHQ-9 score dropped to 10 (moderate). He has maintained the SSRI since diagnosis, with no relapses.

Today, his PHQ-9 score is 6 (mild). Workup identifies 15-lb weight gain over the last year. His clinician notes that the recent weight gain could be a side effect of the SSRI and asks Larry about other potential side effects, such as sexual dysfunction. Larry reports that his wife thinks their sex life has suffered since he started treatment for depression. During the discussion, Larry describes reduced interest in sex, occasional trouble maintaining an erection, and delayed ejaculation when he does have sex.

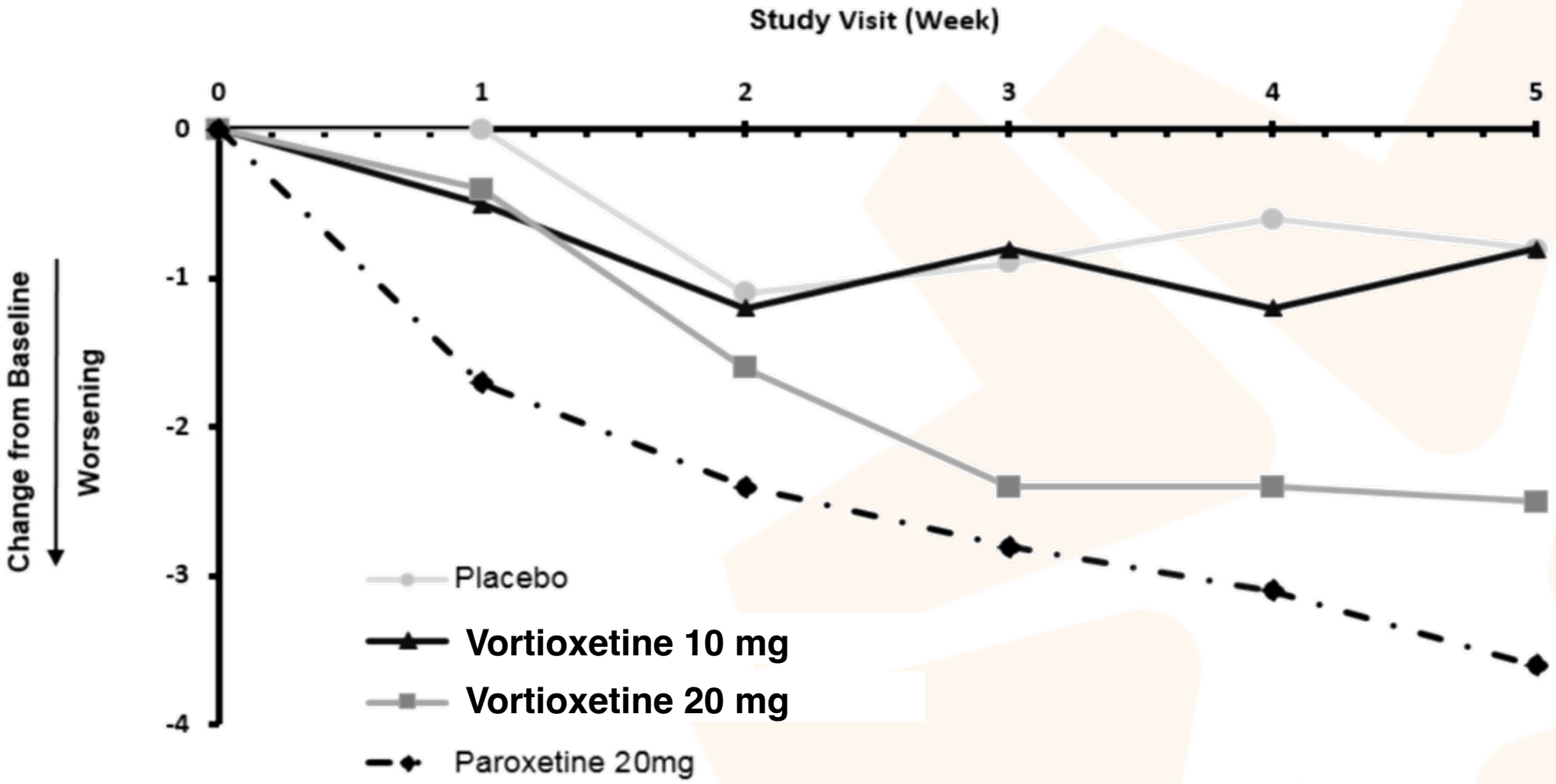
Current Antidepressants: A Range of Side Effects

AD Class	Examples	Side effects
SSRIs	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram	GI, activation, insomnia, sexual dysfunction, migraines, falls, weight gain, potential for serotonin syndrome, discontinuation syndrome[1,2]
SNRIs	Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran	GI, activation, sexual dysfunction, increased pulse rate, dry mouth, excessive sweating, increased blood pressure, potential for serotonin syndrome, discontinuation symptoms[1,2]
TCAs	Amitriptyline, nortriptyline, imipramine, desipramine, doxepin	Cardiovascular effects, arrhythmias, orthostatic hypotension, dry mouth, sexual dysfunction, tachycardia, impaired vision, memory and concentration impairments, sedation, weight gain, myoclonus[1,2]
MAOIs	Phenelzine, tranylcypromine, isocarboxazid, selegiline	Hypertensive crisis, potential for serotonin syndrome, orthostatic hypotension, weight gain, sexual dysfunction, headaches, insomnia[1,2]
Others	Bupropion, nefazodone, trazodone, mirtazapine, agomelatine	Nausea, headaches, dizziness, insomnia, somnolence, tremors, seizures, dry mouth, sedation, weight gain[1-3]
Multimodals	Vilazodone, vortioxetine	Nausea, diarrhoea[4]

5HT Receptor Modulators

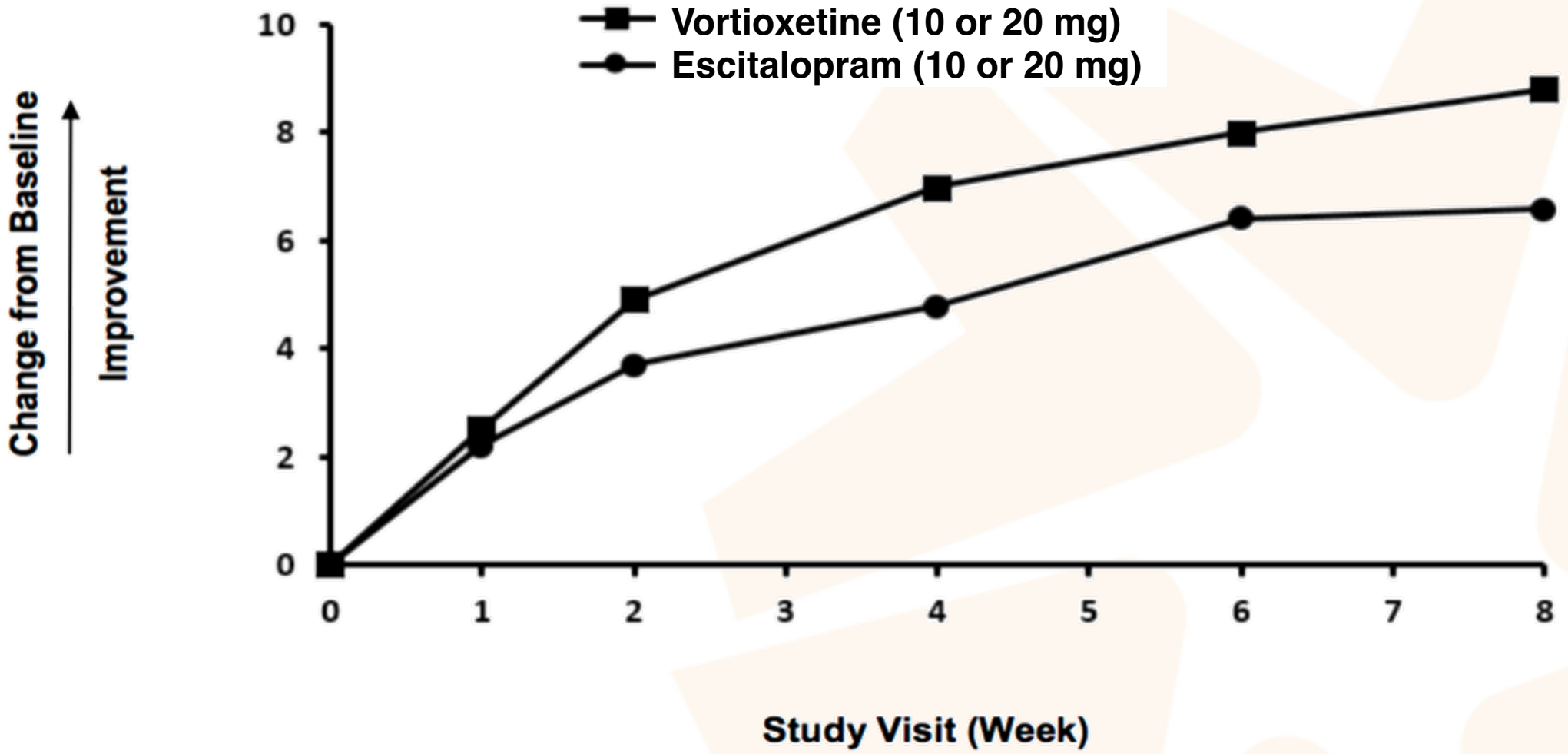
1. APA. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: APA ; 2010; 2.Taylor et al. Maudsley Prescribing Guidelines, 10th Edition, 2009; 3.EMA. Summary of Product Characteristics for Valdoxan (agomelatine). 2009. Accessed October 27, 2014; 4.Forest Laboratories Inc. Prescribing Information for Viibryd (vilazodone hydrochloride). 2014.

Sexual Side Effects of SSRI vs Vortioxetine



Vorioxetine Package Insert

Improvement in Sexual Dysfunction



Vorioxetine Package Insert

Case #5: Linda

Linda is a 42-year-old woman with a 2-year history of MDD, 20-year history of polycystic ovary syndrome (PCOS), and 3-year history of chronic back pain related to a motor vehicle accident. Current medications include paroxetine 50 mg qd, oral contraceptives, and naproxen 200 mg bid.

Linda presents today for a checkup. Her PHQ-9 score is 9 (mild), unchanged from her last visit. Her main concern today is frustration with her persistent back pain. Previously, she declined surgical intervention but engages in daily physiotherapy.

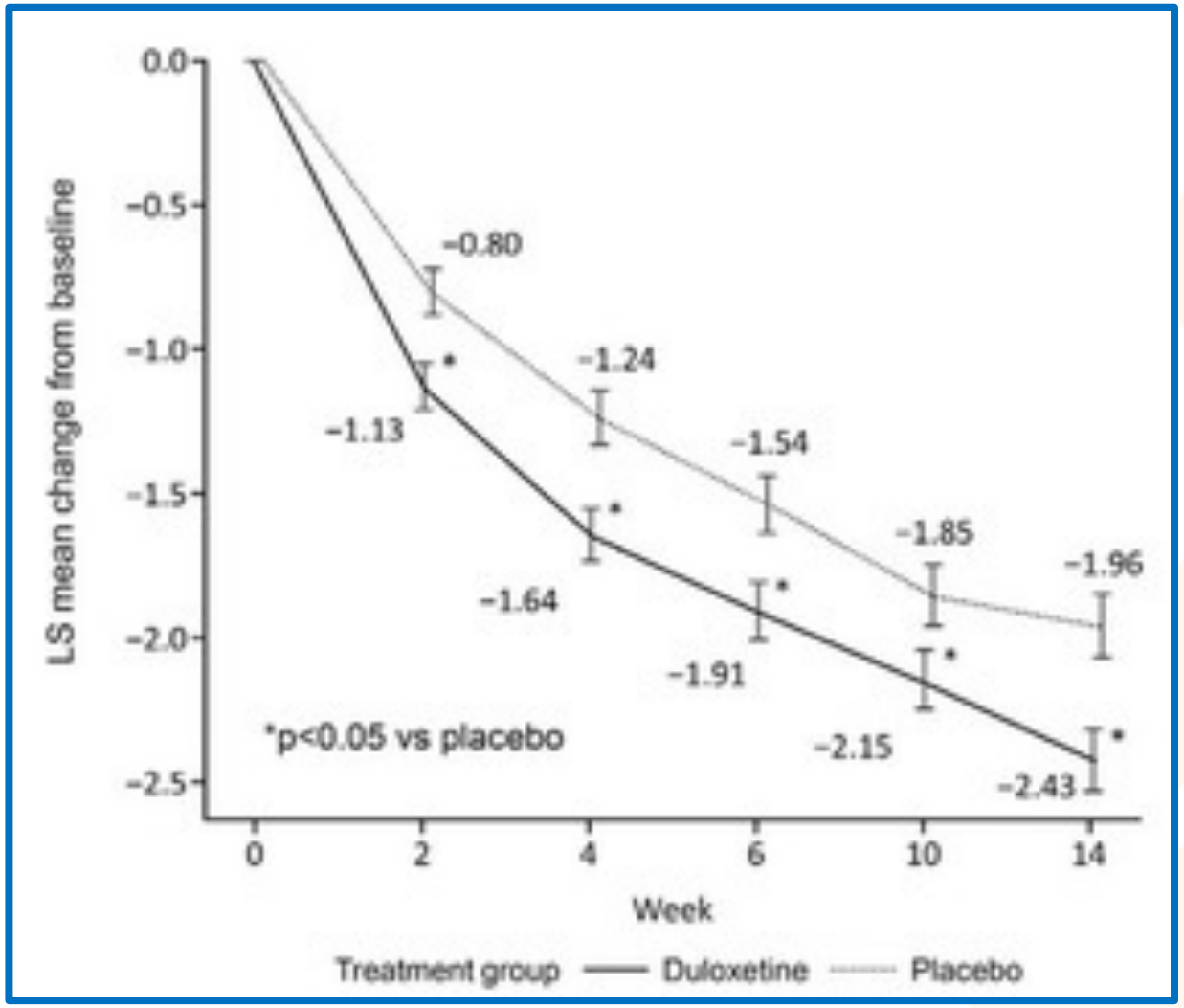
Current Antidepressants: A Range of Side Effects

AD Class	Examples	Side effects
SSRIs	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram	GI, activation, insomnia, sexual dysfunction, migraines, falls, weight gain, potential for serotonin syndrome, discontinuation syndrome[1,2]
SNRIs	Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran	GI, activation, sexual dysfunction, increased pulse rate, dry mouth, excessive sweating, increased blood pressure, potential for serotonin syndrome, discontinuation symptoms[1,2]
TCAs	Amitriptyline, nortriptyline, imipramine, desipramine, doxepin	rdiovascular effects, arrhythmias, orthostatic hypotension, dry mouth, sexual unction, tachycardia, impaired vision, memory and concentration impairments, n, weight gain, myoclonus[1,2]
MAOIs	Phenelzine, tranylcypromine, isocarboxazid, selegiline	ive crisis, potential for serotonin syndrome, orthostatic hypotension, weight es, insomnia[1,2]
Others	Bupropion, nefazodone, trazodone, mirtazapine, agomelatine	omnia, somnolence, tremors, seizures, dry mouth, sedation, weight gain[1-3]
Multimodals	Vilazodone, vortioxetine	Nausea, diarrhea[4]

Raise 5HT and NE

1. APA. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: APA ; 2010; 2.Taylor et al. Maudsley Prescribing Guidelines, 10th Edition, 2009; 3.EMA. Summary of Product Characteristics for Valdoxan (agomelatine). 2009. Accessed October 27, 2014; 4.Forest Laboratories Inc. Prescribing Information for Viibryd (vilazodone hydrochloride). 2014.

Improvement in Chronic Pain



- 458 Japanese patients with chronic low back pain
- Randomized to duloxetine 60 mg qd or placebo
- 14 weeks of treatment
- Brief Pain Inventory (BPI) scores improved significantly with duloxetine compared to placebo

Konno S, et al. *Spine (Phila Pa 1976).* Nov 15 2016;41(22):1709-1717.

Shared Decision-Making

Team Approach to Management Decisions

Shared Decision-Making

To make an optimal decision when no unequivocally superior option exists

Bidirectional exchange of information

Clinician: available options

Patient: values and preference

Use of decisional aids for exchange of information

Assessment and re-assessment of patients' comfort with making treatment decisions

Barry MJ, et al. *N Engl J Med*. 2012;366(9):780-781. Elwyn G, et al. *J Gen Intern Med*. 2012;27(10):1361-1367.

Shared Decision-Making

Choice Talk

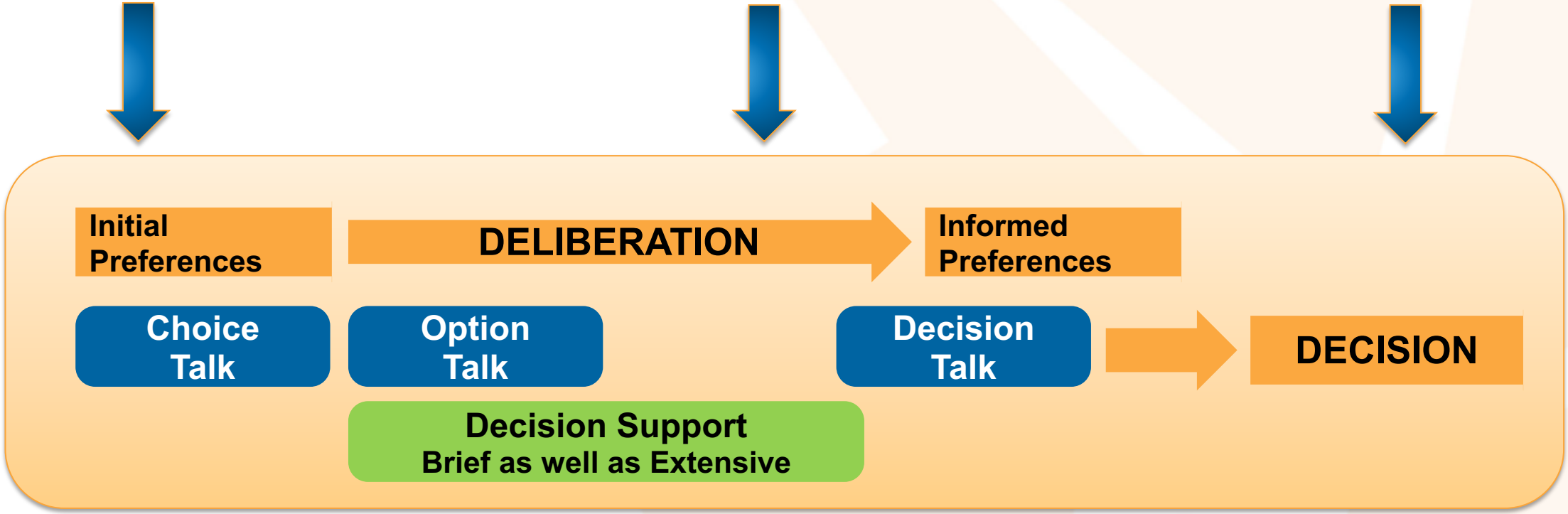
- Step back
- Offer choice
- Justify choice – preferences matter
- Check reaction
- Defer closure

Option Talk

- Check knowledge
- Describe options – explore preferences
- Harms and benefits
- Provide patient decision support

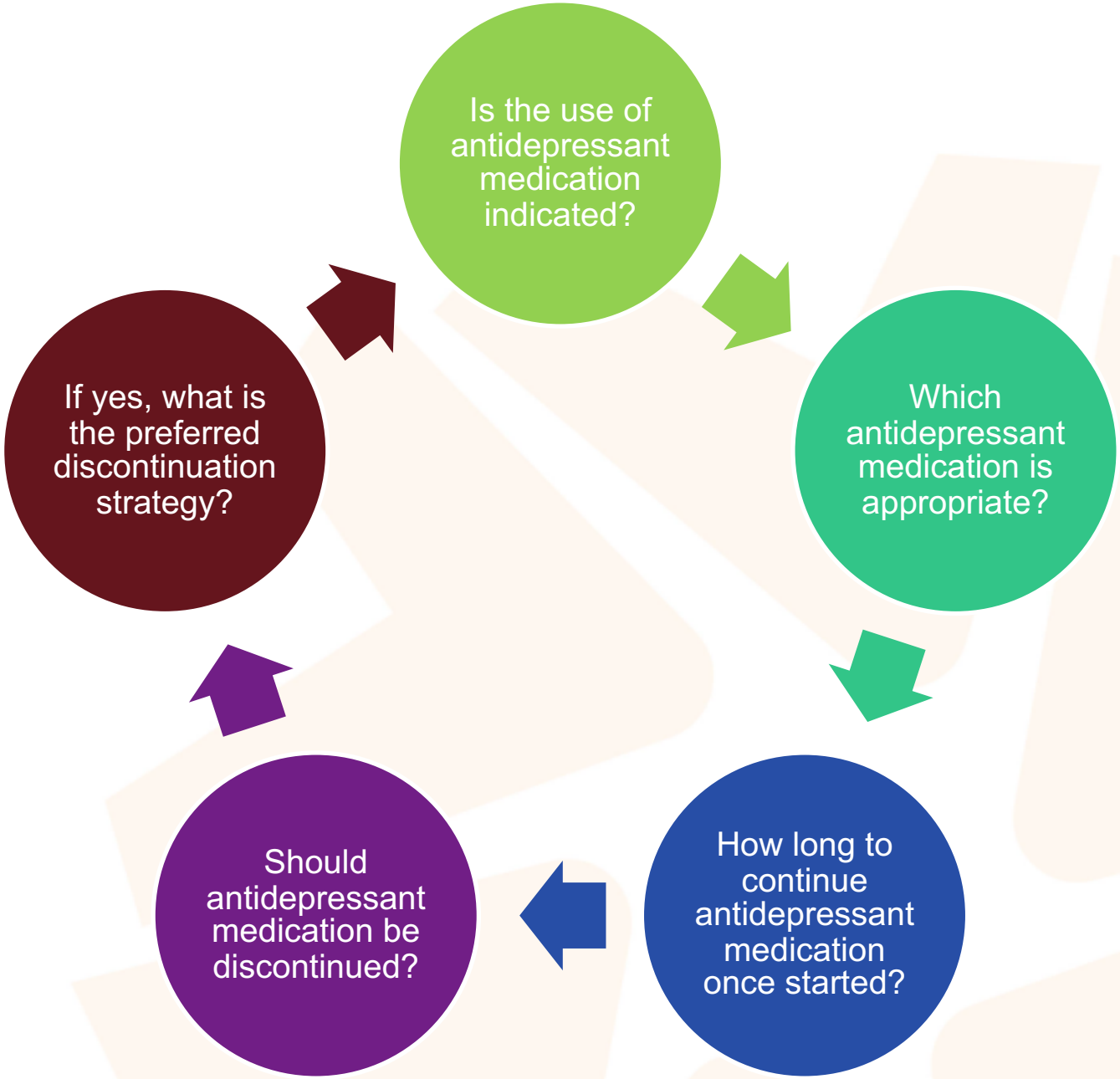
Decision Talk

- Focus on preferences
- Elicit preferences
- Move to a decision
- Offer review



Elwyn G, et al. *J Gen Intern Med*. 2012;27(10):1361-1367.

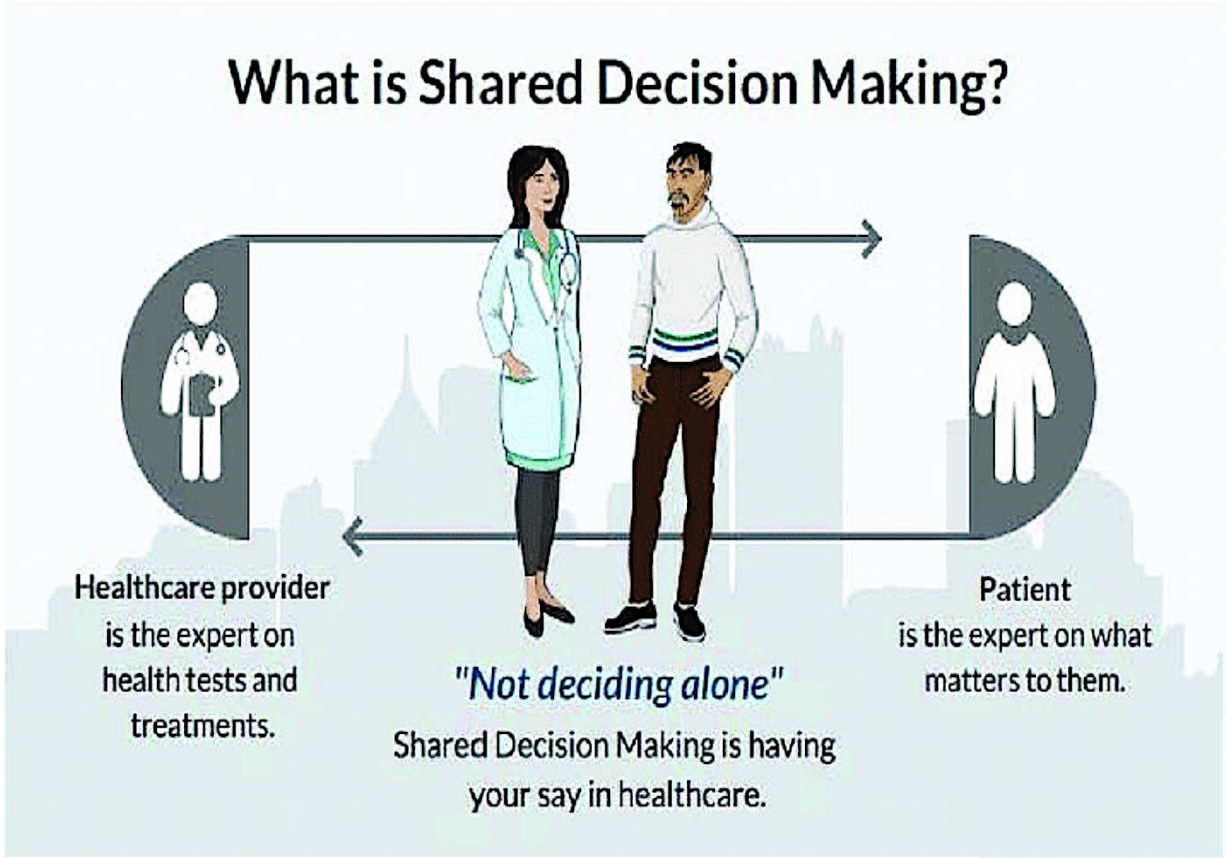
Shared Decision-Making Relevant to Depression Treatment



Jha MK. *J Clin Psychiatry*. 2019;80(6):19com13047.

The Process of Shared Decision Making

Three Stages of Shared Decision Making (SDM)



How to do Shared Decision Making

STAGE 1
Preparation

Think about these questions with people who support you.

- *Do you understand why you are going to the healthcare provider?*
- *What do you want help for? How does this affect you?*
- *What are your worries?*
- *What are you hoping will be better after seeing the healthcare provider?*
- *Are there traditional or cultural ways to heal that you use?*
- *What information do you need to make good health decisions?*

STAGE 2
Decision event

Meet with your healthcare provider and people who support you.

- *What is the **decision**?*
- *What are my **options**?*
- *What are the **risks and benefits** of the options?*
- *What **help do I need** to make my decision?*

STAGE 3
Follow up

Follow up with people who support you.

Jull J, et al. *Curr. Oncol.* 2019;*26*(3):192-204

And How is Shared Decision Making Relevant to Major Depression?

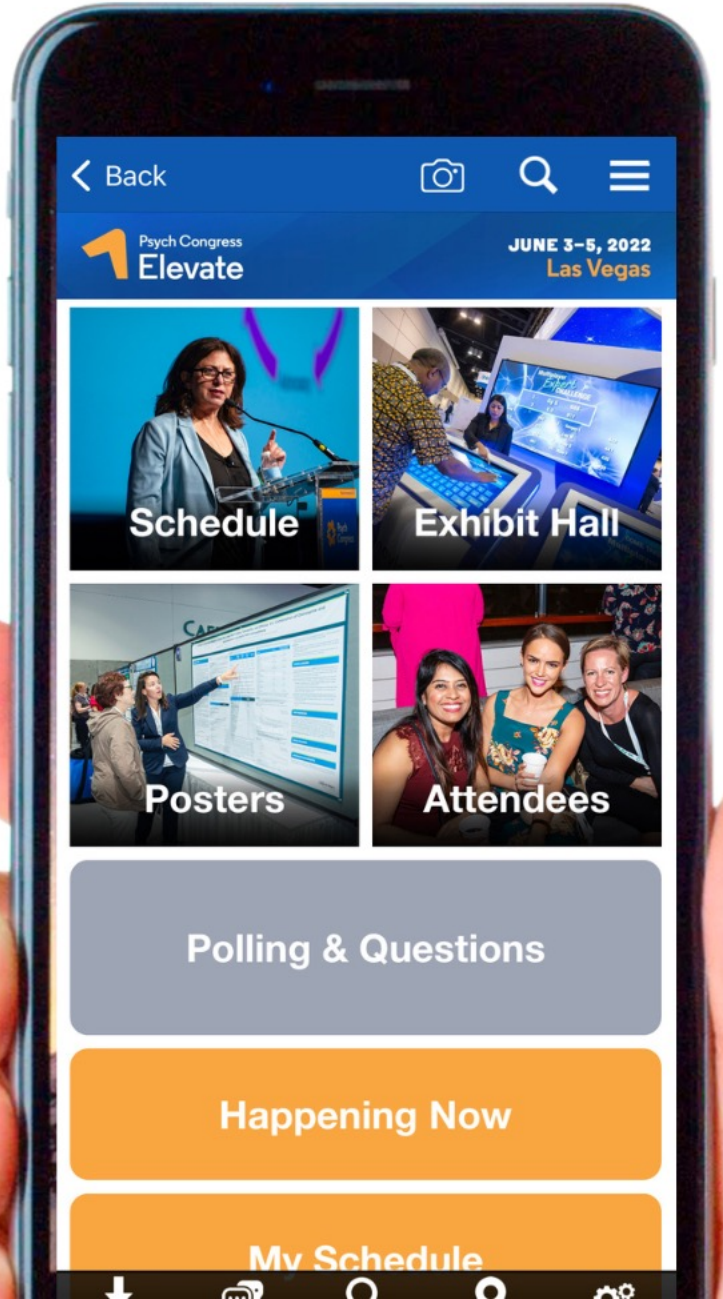
All Four Of These Unmet Needs with Antidepressants Can Be Addressed with SDM

Key Requirements of an Effective Treatment

Baldwin DS. *Hum Psychopharmacol*. 2001 Dec;16(S2):S93-S9. Jull J, et al. *Curr. Oncol.* 2019;*26*(3):192-204.

Clinician-Patient Collaboration for Improved Patient Outcomes

Video Vignette #3



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