

Beyond Depressive Symptoms: Addressing Cognitive Effects, Sexual Dysfunction, and Weight Gain in Major Depressive Disorder

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Faculty Disclosure

- **Dr. Rakesh Jain:** Advisory Board—Addrenex, Alkermes, Avanir, Forum, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, Teva; Consultant—Addrenex, Allergan, Avanir, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, Teva; Consultant (spouse)—Lilly, Otsuka, Pfizer, Sunovion; Grant/Research Support—Allergan, AstraZeneca, Lilly, Lundbeck, Otsuka, Pfizer, Shire, Takeda; Speakers Bureau—Addrenex, Alkermes, Allergan, Lilly, Lundbeck, Merck, Otsuka, Pamlab, Pfizer, Rhodes, Shionogi, Shire, Sunovion, Takeda, Tris Pharmaceuticals.

Disclosure

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- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Describe the latest advances in the diagnosis and assessment of major depressive disorder (MDD) and impact of cognitive dysfunction on outcomes
- Evaluate current MDD treatments in terms of mechanism of action, safety and efficacy, effect on cognitive dysfunction, and side effect profiles (eg, sexual dysfunction, weight gain)
- Integrate the latest assessment tools and clinical data surrounding newer multimodal therapies into individualized management plans that address the spectrum of cognitive symptoms and mitigates adverse treatment effects

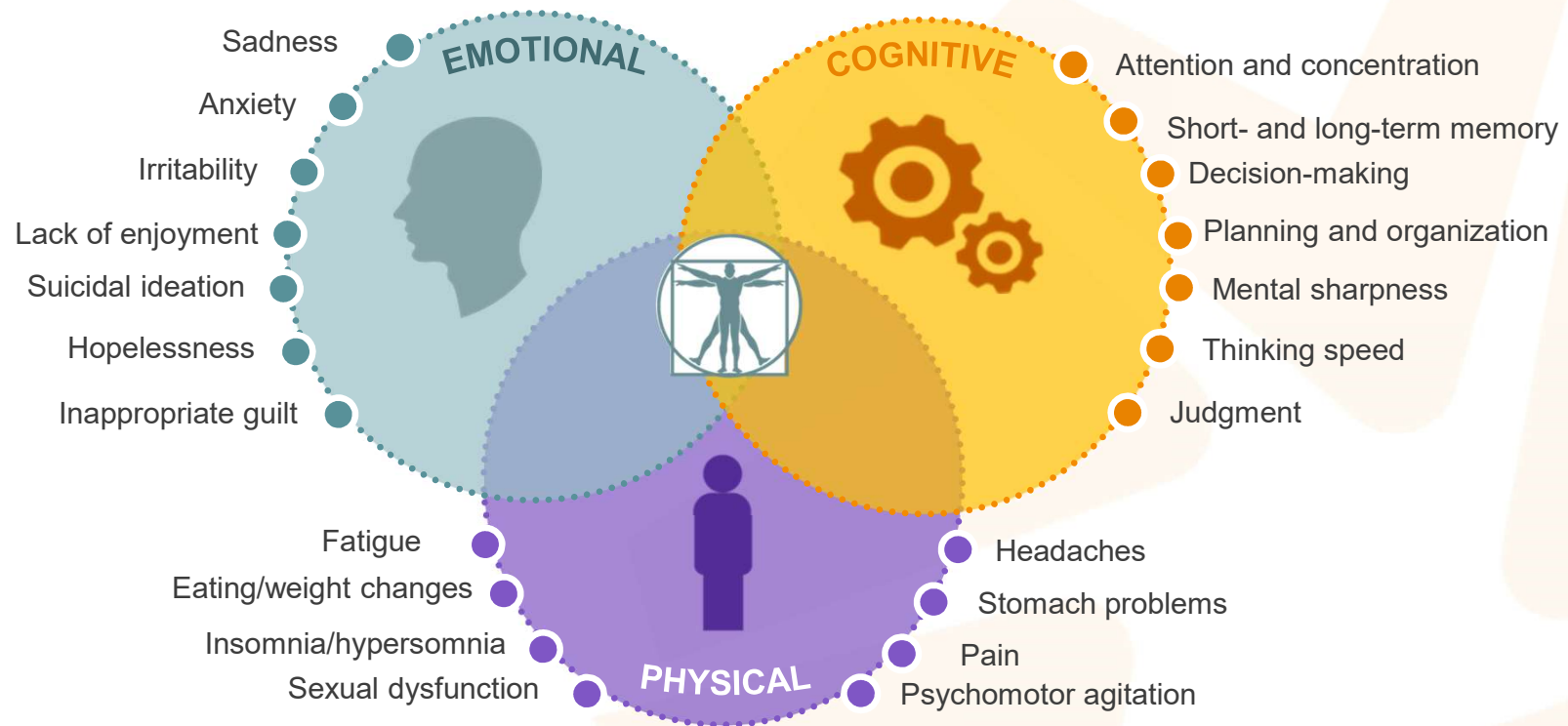
3 Unmet Needs in Major Depressive Disorder

Cognitive Dysfunction
Weight Gain
Sexual Dysfunction

The background features several large, semi-transparent orange geometric shapes, including rectangles and trapezoids, scattered across the white space. A solid blue horizontal band is positioned in the upper middle section of the slide.

Cognitive Dysfunction

MDD Has 3 Sets of Symptom Domains – Emotional, Physical, and Cognitive



MDD = major depressive disorder.

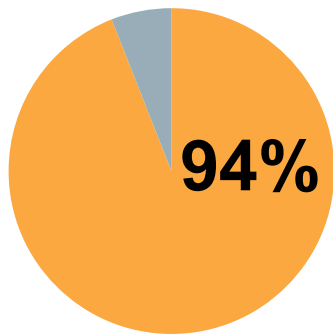
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA: American Psychiatric Association; 2013. Marazziti D, et al. *Eur J Pharmacol*. 2010;626(1):83-86. Hammar A, et al. *Front Hum Neurosci*. 2009;3:26. Fehnel SE, et al. *CNS Spectr*. 2016;21(1):43-52.

Cognitive Symptoms in Depression

Cognitive symptoms in depression are highly prevalent and persistent – *even after treatment*

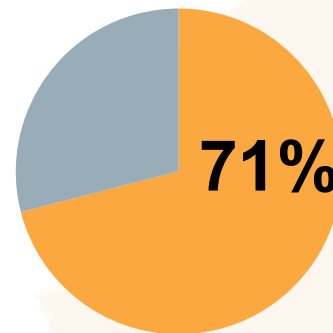
ACUTE

In one study, cognitive problems dominated and were **present for up to 94% of the time** during depressive episodes



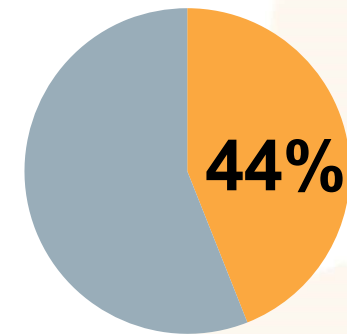
RESPONSE

Another study showed that **71% of patients who responded to treatments** still had cognitive symptoms

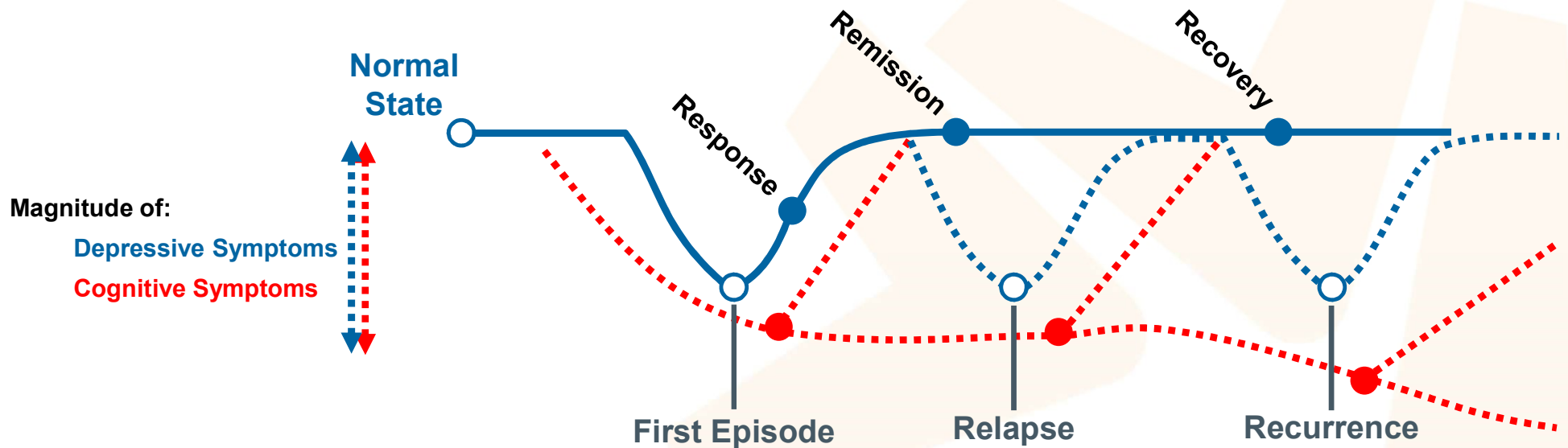


REMISSION

Even in patients thought to be in remission, cognitive symptoms were shown to be **present in patients with depression for an average of 44% of the time** during periods of remission

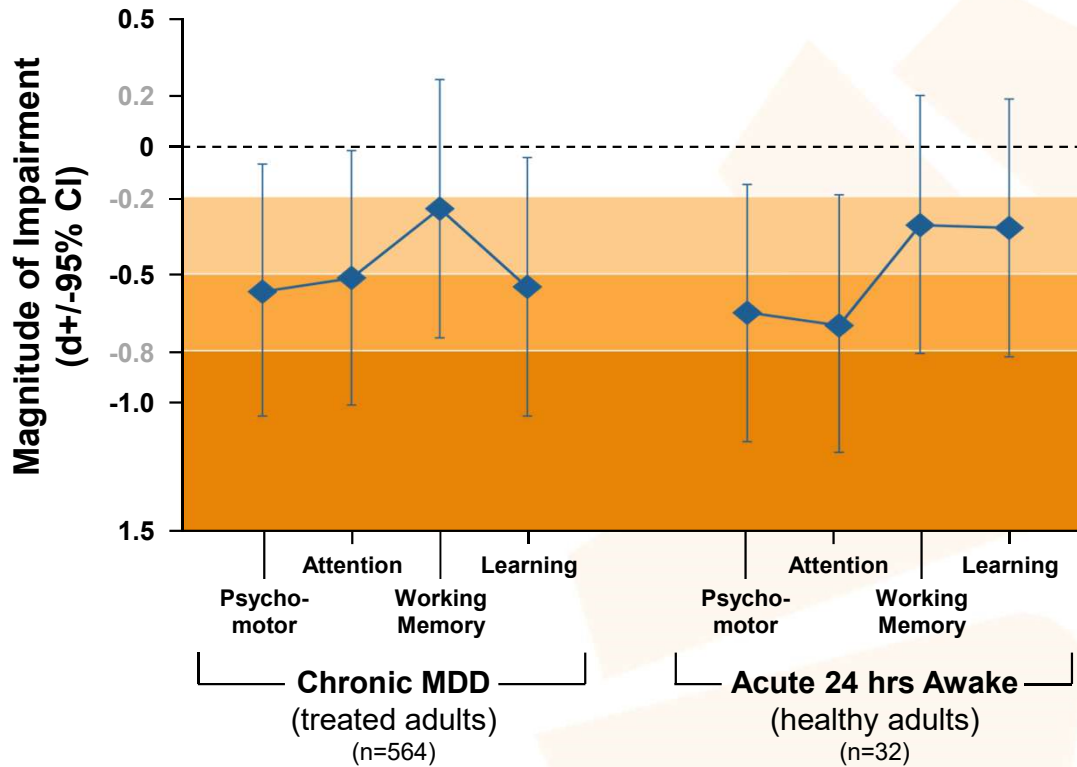


Cognitive Symptoms and the Long-Term Course of MDD

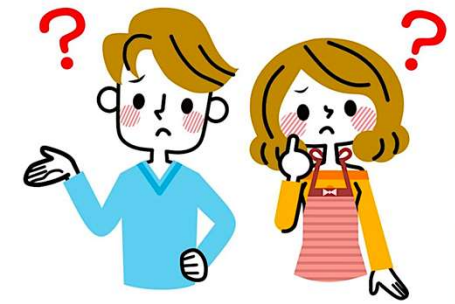


The red dotted line represents the magnitude of cognitive symptoms associated to MDD pathology according to MDD state. An early onset of cognitive symptoms in depression has been reported before the clinical diagnosis.

Cognitive Symptoms Cause Significant Impairment in MDD



- Small Effect Size (.2)
- Medium Effect Size (.5)
- Large Effect Size (.8)

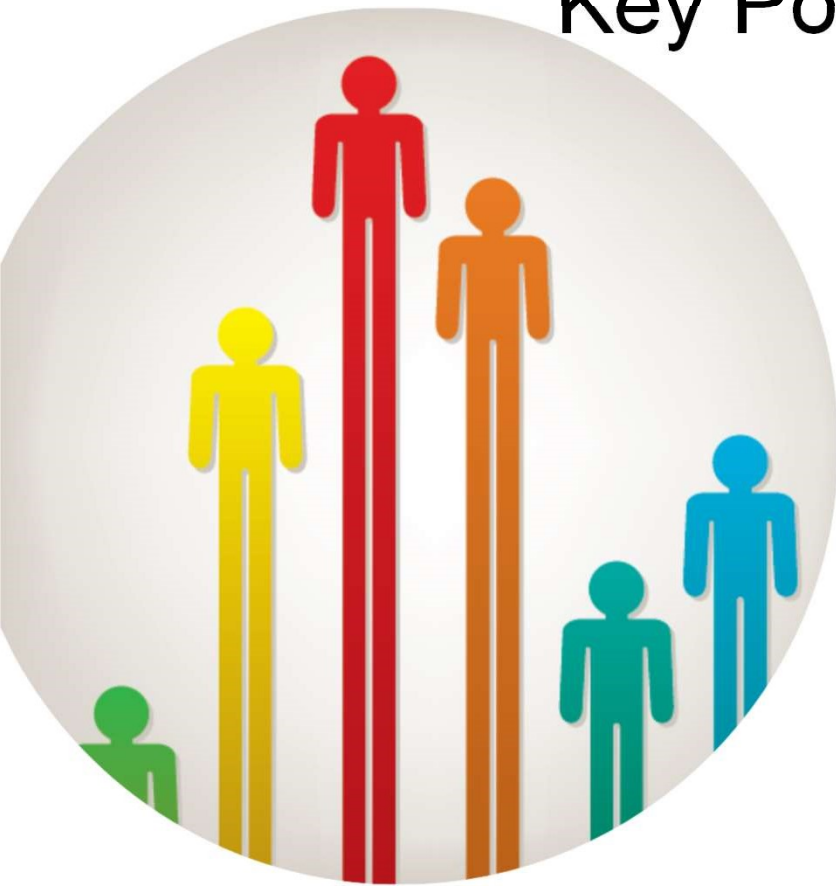


Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Second Edition. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
 McIntyre R (Ed). *Cognitive Impairment in Major Depressive Disorder: Clinical Relevance, Biological Substrates, and Treatment Opportunities*. Cambridge, United Kingdom: Cambridge University Press; 2016.

Key Points to Remember:

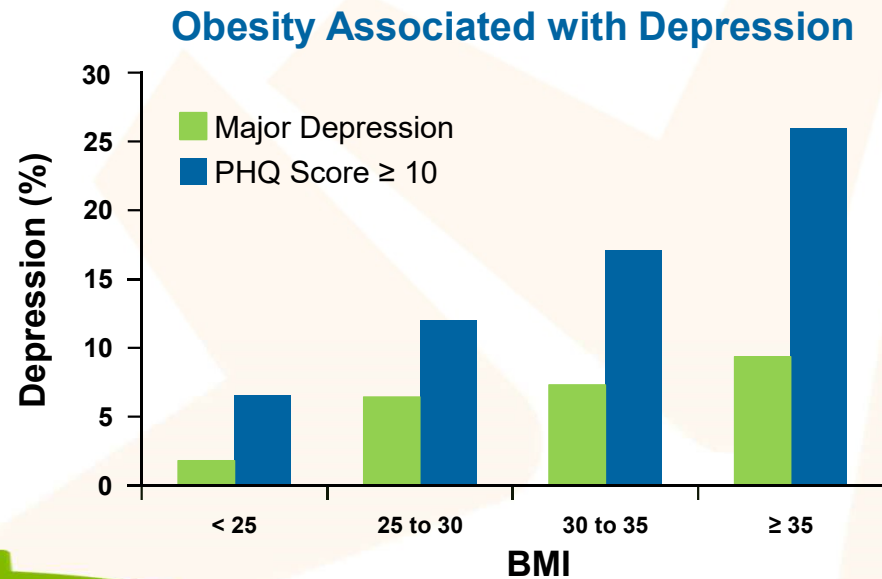
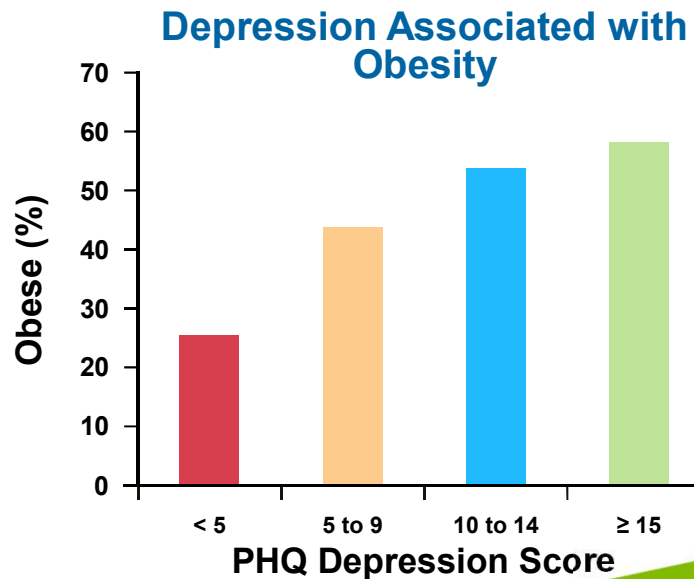


In MDD, *Cognitive Dysfunction*
is COMMON
&
IMPAIRING



Weight Gain

Bidirectional Relationships between Obesity and Depression

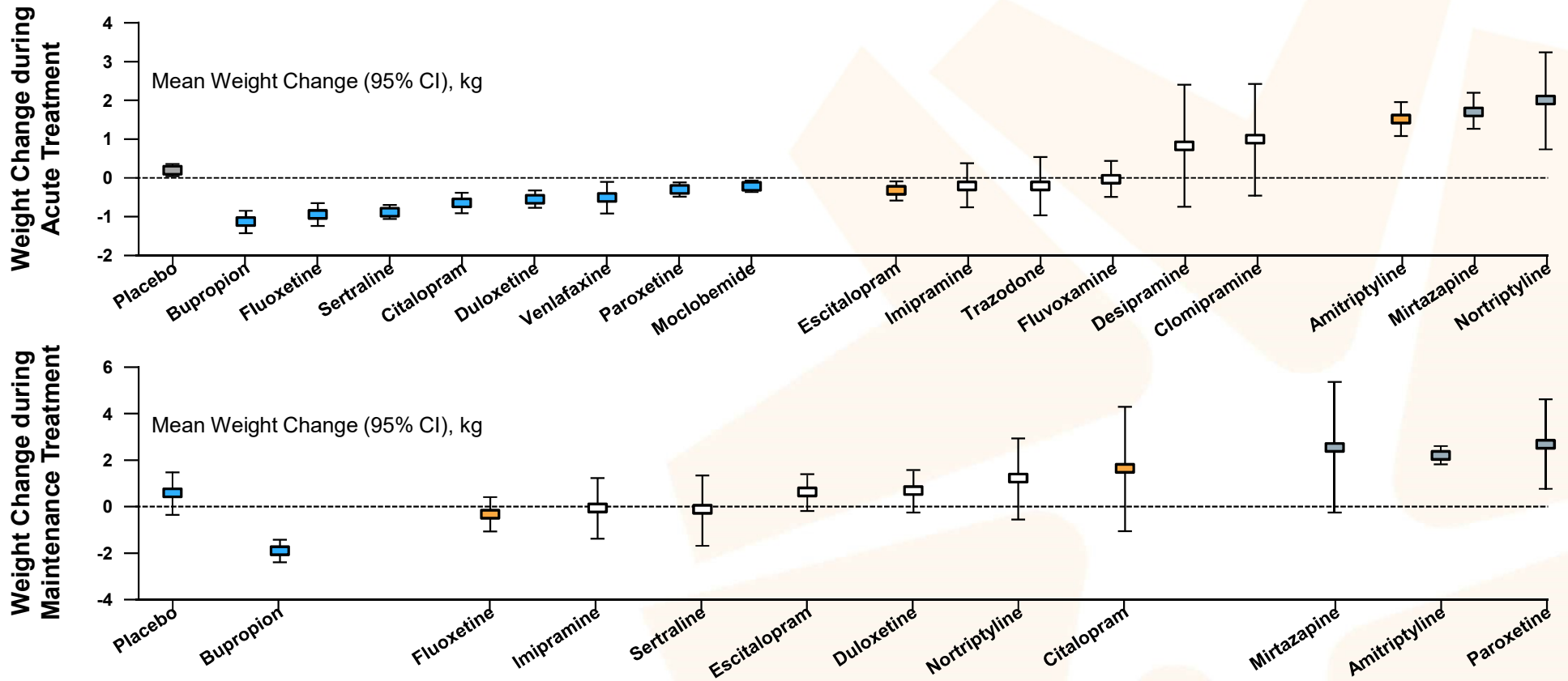


In a sample of 4641 female health plan enrollees aged 40 to 65, depression was associated with obesity and obesity was associated with depression. Prevalence of moderate or severe depression increased from 6.5% among those with BMI < 25 to 25.9% among those with BMI > 35. Prevalence of obesity increased from 25.4% among those with no depressive symptoms to 57.8% among those with moderate to severe depression. These cross-sectional data have been confirmed in longitudinal studies in women showing that depression at baseline independently predicts weight gain over time (OR 1.38, 95% CI 1.24–1.53) and that obesity predicted increased risk of depression on follow up (OR 1.11, 95% CI 1.03–1.18).

BMI = body mass index; PHQ = Patient Health Questionnaire.

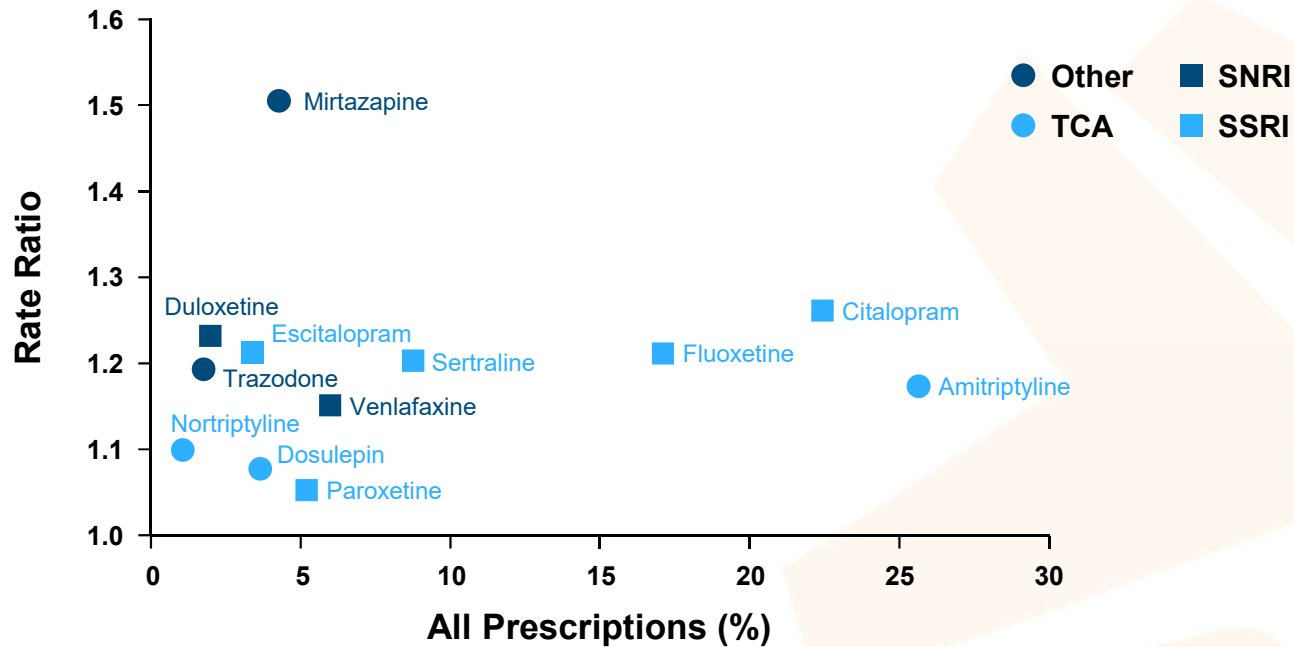
Simon GE, et al. *Gen Hosp Psychiatry*. 2008;30(1):32-39. Pan A, et al. *Int J Obes*. 2012;36(4):595-602.

Weight Change during Antidepressant Treatment



Serretti A, et al. *J Clin Psychiatry*. 2010;71(10):1259-1272.

What about Long-Term? A 10-Year Follow-up Study



The risk of weight gain remained increased during at least 6 years of follow-up.

In people who were initially of normal weight, the adjusted rate ratio for transition to overweight or obesity was 1.29 (1.25 to 1.34); in people who were initially overweight, the adjusted rate ratio for transition to obesity was 1.29 (1.25 to 1.33).

Scatter plot of adjusted rate ratios for $\geq 5\%$ weight gain by number of prescriptions. Rate ratios were adjusted for sex, body mass index category, age, age², diabetes, coronary heart disease, stroke, cancer, depression, smoking status, coprescribing of antiepileptics or antipsychotics, diet advice, year, region, and fifth of deprivation.

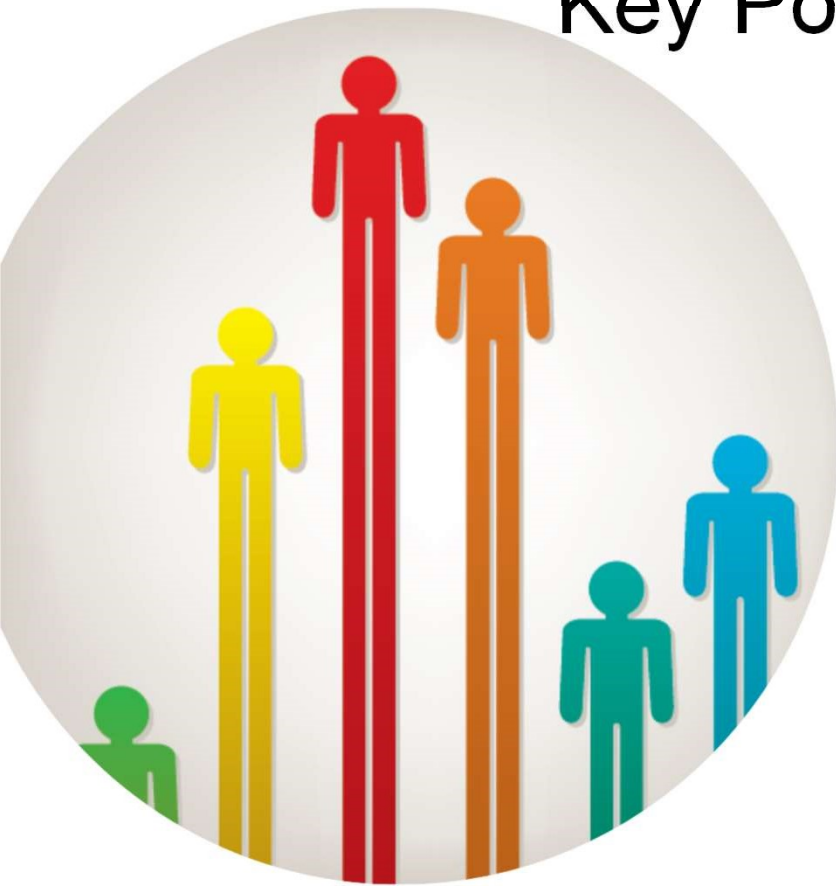
SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic and related antidepressants.

Gafoor R, et al. *BMJ*. 2018;361:k1951.

Key Points to Remember:



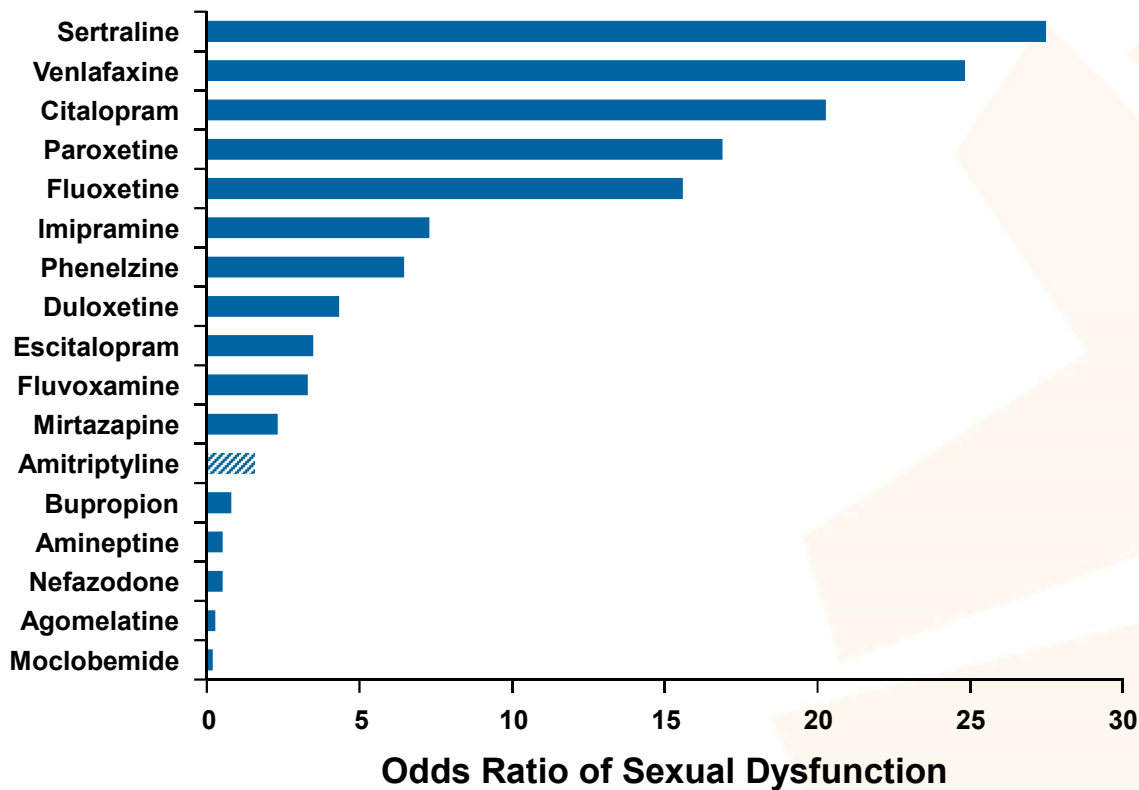
Antidepressants **OFTEN** cause
Weight Gain,
BUT
DIFFERENT antidepressants
appear to have **DIFFERENT**
Weight Gain profiles





Sexual Dysfunction

Recent Data Continues to Highlight Risk of Sexual Dysfunction with Antidepressants



A total of 14 publications, including 8 qualified randomized clinical trials, were eligible. The frequency of SD in overall, male and female patients was 5.7%, 11.9%, and 1.7%, respectively. SD was six-fold higher in men than women.

SD = sexual dysfunction.

Chen LW, et al. *Am J Mens Health*. 2018;12(2):370-379. Serretti A, et al. *J Clin Psychopharmacol*. 2009;29(3):259-266.

Patient-Reported Reasons for Nonadherence to Antidepressants

Nonadherence (22%)

- Trouble remembering to take medication (43%)
- Gained a lot of weight (27%)
- Couldn't have an orgasm (20%)
- **Lost my sex drive** (20%)

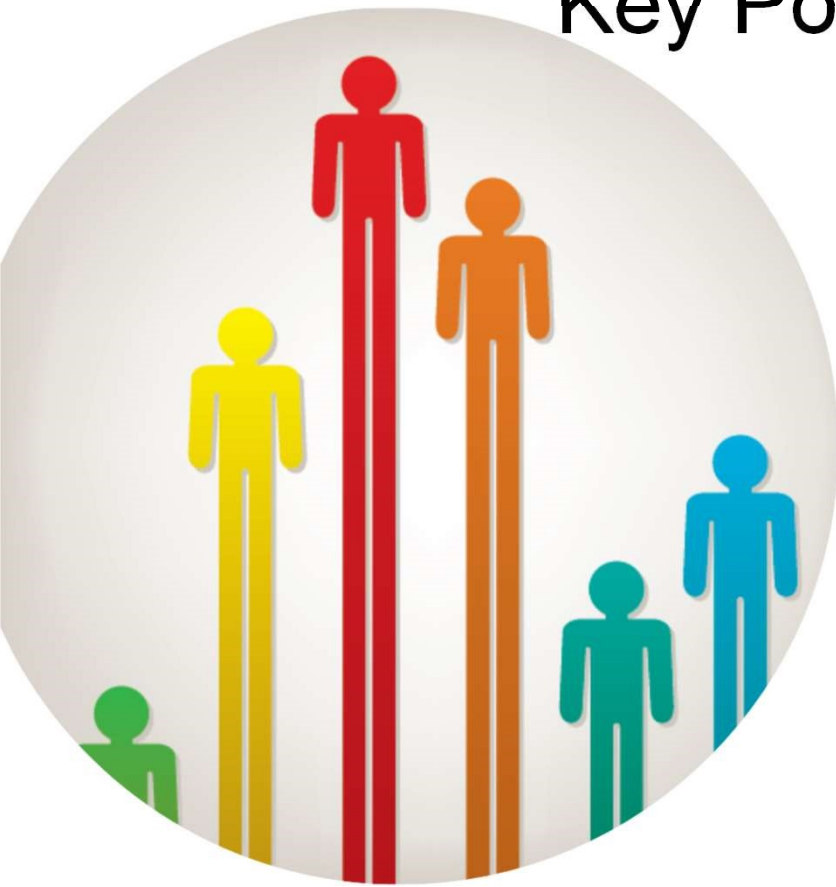
Adverse Effects Extremely Difficult to Tolerate

- **Weight gain** (31%)
- Unable to have an erection (25%)
- Difficulty reaching orgasm (24%)
- Tired during the day/no energy (21%)

Key Points to Remember:



Antidepressants **OFTEN** Induce
Sexual Dysfunction,
and this **OFTEN** leads to
adherence challenges





Assessment and Monitoring of Cognitive and Sexual Dysfunction

The Perceived Deficits Questionnaire (PDQ) provides a subjective assessment of cognitive function

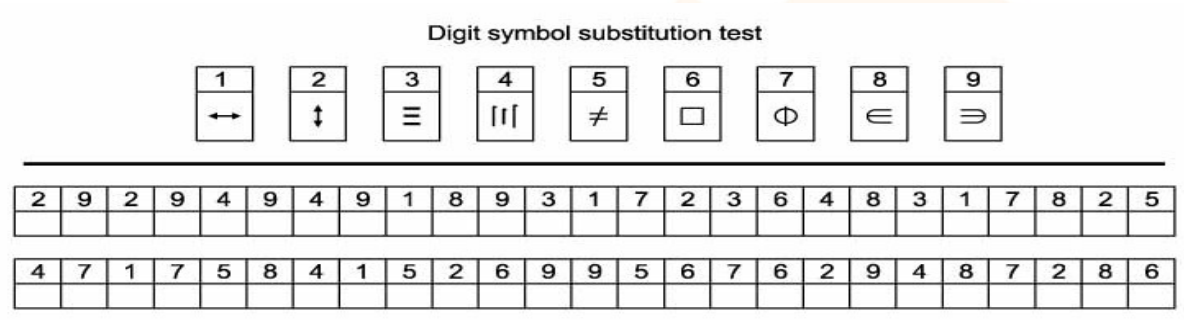
	Example PDQ questions: During the past 4 weeks, how often did you ...	(0) Never	(1) Rarely	(2) Sometimes	(3) Often	(4) Almost Always
1	Lose your train of thought when speaking?					
2	Have difficulty remembering the names of people. Even ones you have met several times?					
4	Have trouble getting things organized ?					
8	Have difficulties planning what to do in the day?					
9	Have trouble concentrating on things like watching a television program or reading a book?					
18	Forget what you did last weekend?					
20	Have trouble making decisions ?					

Mahabeshwarkar AR, et al. *Neuropsychopharmacology*. 2015;40(8):2025-2037. The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee. MSQI: A User's Manual. (1997). www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/MSQI_-_A-User-s-Manual.pdf. Accessed February 20, 2019.

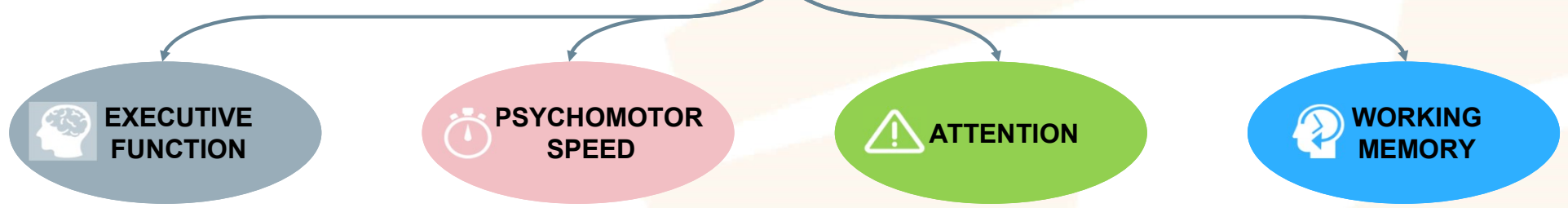
Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

<i>(a) How has your motivation/interest/enthusiasm been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent
<i>(b) How has your wakefulness/alertness been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent
<i>(c) How has your energy been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent
<i>(d) How has your ability to focus/sustain attention been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent
<i>(e) How has your ability to remember/recall information been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent
<i>(f) How has your ability to find words been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent
<i>(g) How has your sharpness/mental acuity been over the past month?</i>					
1 greater than normal	2 normal	3 minimally diminished	4 moderately diminished	5 markedly diminished	6 totally absent

The Digit Symbol Substitution Test (DSST) Captures the Function of Several Cognitive Domains Affected in MDD



The cognitive domains affected by MDD measured by the DSST



Katona C, et al. *Int Clin Psychopharmacol.* 2012;27(4):215-223. Wechsler D. Wechsler Adult Intelligence Scale, 3rd ed. San Antonio, Texas, Psychological Corporation, 1997. Harrison JE, et al. Poster presented at: ASCP Annual Meeting (NCDEU); June 16–19, 2014; Hollywood, Florida, USA. www.academia.edu/7144239/Cognitive_domains_impacted_by_vortioxetine_treatment_of_patients_with_major_depressive_disorder_MDD. Accessed February 20, 2019.

THINC-it

Integrated Computerized Cognitive Assessment Tool

Original Research

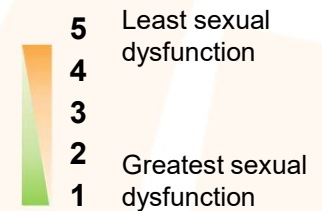
The THINC-Integrated Tool (THINC-it) Screening Assessment for Cognitive Dysfunction: Validation in Patients With Major Depressive Disorder

Roger S. McIntyre, MD, FRCPC^{a,b,c,d,e,*}; Michael W. Best, MSc^f; Christopher R. Bowie, PhD, CPsych^{f,g};
Nicole E. Carmona, HBSc^a; Danielle S. Cha, HBSc, MSc^{a,h}; Yena Lee, BSc^{a,e}; Mehala Subramaniapillai, MSc^a;
Rodrigo B. Mansur, MD^a; Harry Barry, MDⁱ; Bernhard T. Baune, PhD, MD, MPH, FRANZCP^j; Larry Culpepper, MD, MPH^k;
Philippe Fossati, MD^l; Tracy L. Greer, PhD^m; Catherine Harmer, DPhil, MA, DipLATHEⁿ; Esther Klag, PhD^o;
Raymond W. Lam, MD^p; Hans-Ulrich Wittchen, PhD^q; and John Harrison, PhD, CSci, CPsychol^{r,s,t}

Changes in Sexual Functioning Questionnaire (CSFQ-14)

Male and female versions

1. Compared with the most enjoyable it has ever been, **how enjoyable or pleasurable** is your sex life right now?
2. **How frequently** do you **engage** in sexual activity (sexual intercourse, masturbation, etc.) now?
3. **How often** do you **desire** to engage in sexual activity?
4. **How frequently** do you engage in **sexual thoughts** (thinking about sex, sexual fantasies) now?
5. Do you **enjoy books, movies, music, or artwork** with sexual content?
6. How much **pleasure** or enjoyment do you get from thinking about and **fantasizing** about sex?



Total score range **70–14**

Threshold of dysfunction

Females ≤ 41 Males ≤ 47

Female version

7. **How often** do you become sexually **aroused**?
8. Are you **easily aroused**?
9. Do you have **adequate vaginal lubrication** during sexual activity (get wet)?
10. How often do you become **aroused and then lose interest**?
11. How often do you experience an **orgasm**?
12. Are you able to have an **orgasm when you want to**?

Male version

7. **How often** do you have an **erection** related or unrelated to sexual activity?
8. Do you get an **erection easily**?
9. Are you able to **maintain an erection**?
10. How often do you experience **painful, prolonged erections**?
11. How often do you have an **ejaculation**?
12. Are you able to **ejaculate when you want to**?

13. How much **pleasure or enjoyment** do you get from your orgasms?
14. How often do you have **painful orgasm**?

Male and female versions

Arizona Sexual Experiences Scale (ASEX)

1. How strong is your sex drive?

1 2 3 4 5 6
extremely strong very strong somewhat strong somewhat weak very weak no sex drive

2. How easily are you sexually aroused (turned on)?

1 2 3 4 5 6
extremely easily very easily somewhat easily somewhat difficult very difficult never aroused

3a. How easily does your vagina become moist or wet during sex?

1 2 3 4 5 6
extremely easily very easily somewhat easily somewhat difficult very difficult never aroused

3b. Can you easily get and keep an erection?

1 2 3 4 5 6
extremely easily very easily somewhat easily somewhat difficult very difficult never

4. How easily can you reach an orgasm?

1 2 3 4 5 6
extremely easily very easily somewhat easily somewhat difficult very difficult never reach orgasm

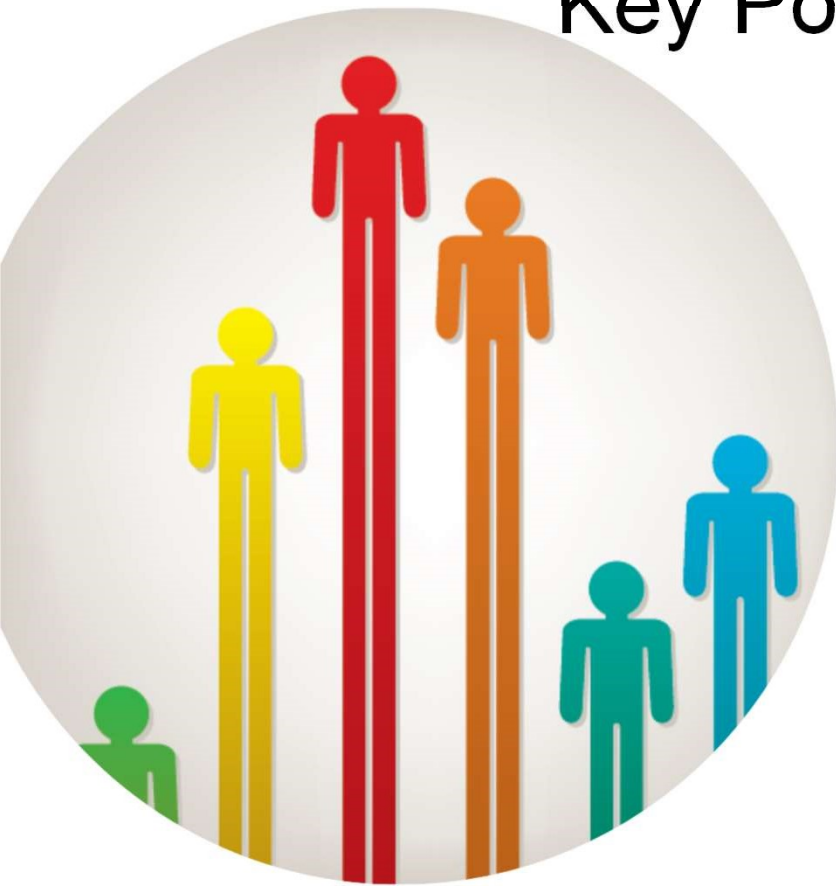
5. Are your orgasms satisfying?

1 2 3 4 5 6
extremely satisfying very satisfying somewhat satisfying somewhat unsatisfying very unsatisfying can't reach orgasm


Copyright 1997, Arizona Board of Regents, University of Arizona, All rights reserved. Scores range from 5–30. Dichotomous analysis.
<http://psychiatry.arizona.edu/research/asex-scale-information>. Accessed February 20, 2019.

McGahuey CA, et al. *J Sex Marital Ther.* 2000;26(1):25-40.

Key Points to Remember:

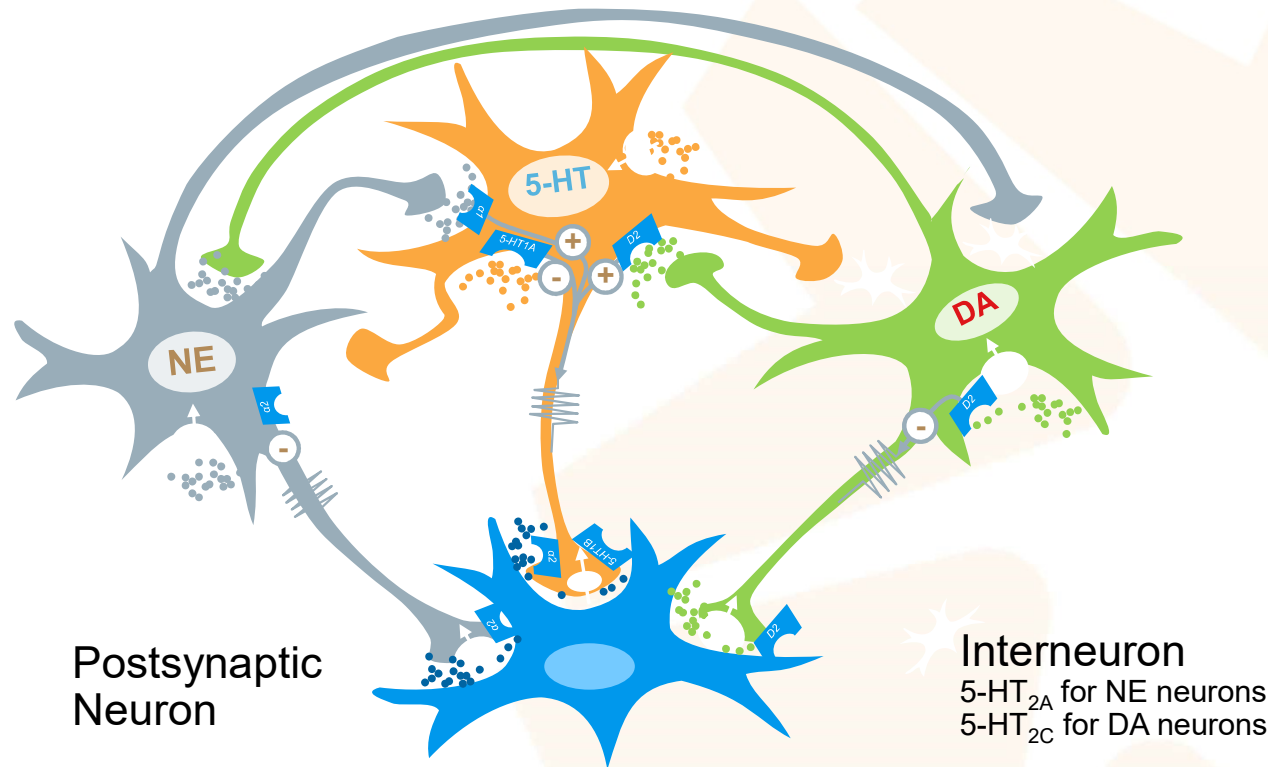


- ✓ PROACTIVELY assess for *Cognitive Dysfunction, Weight Gain, and Sexual Dysfunction*
- ✓ Use OBJECTIVE markers – such as the scales mentioned earlier



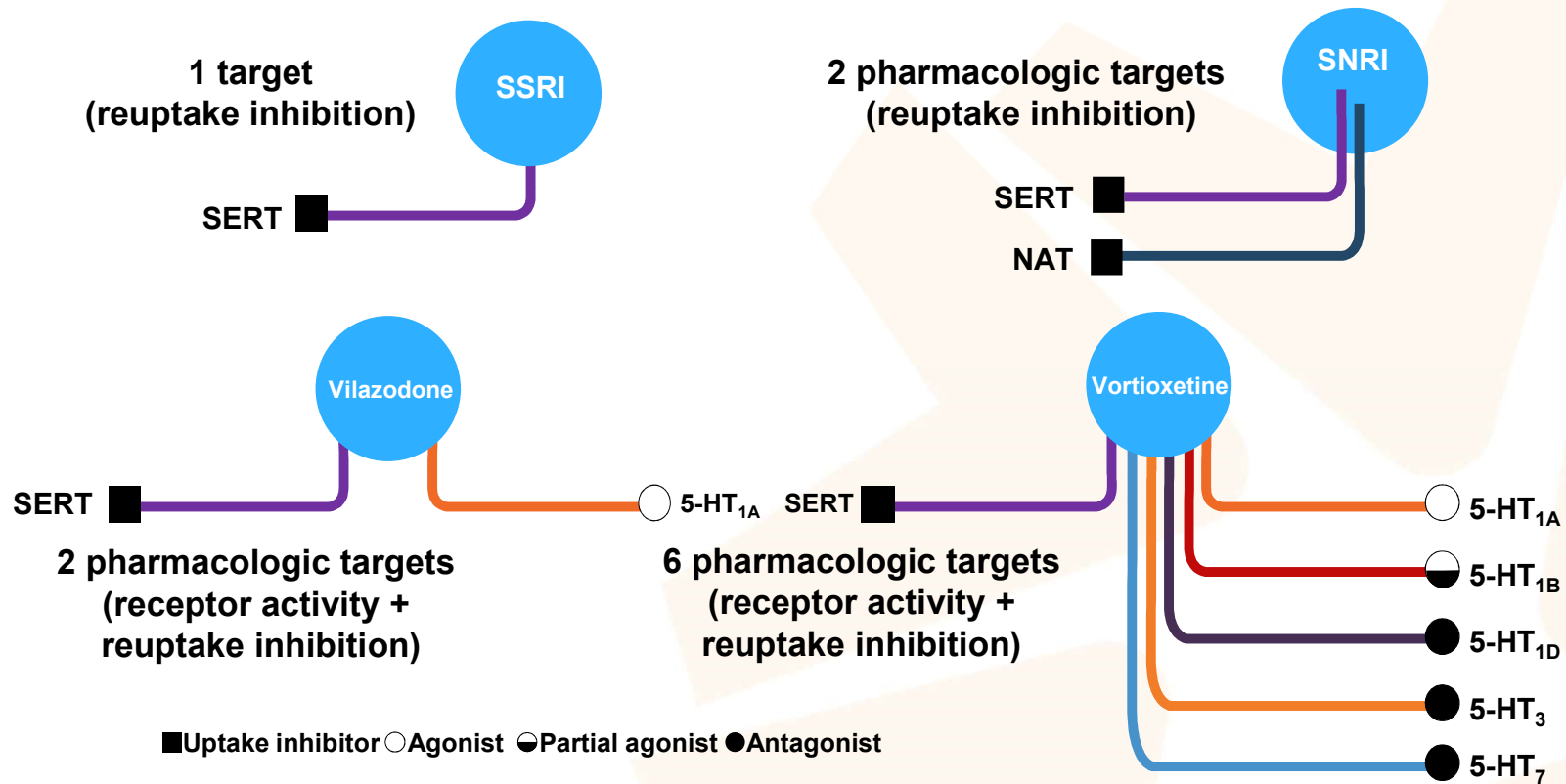
Clinical Update: MDD Pathophysiology and Pharmacotherapy

Functional Connectivity across the “Big Three” Monoamine Systems: Serotonin, Norepinephrine, and Dopamine



Kennedy SH et al. *J Affect Disord.* 2011;132(Suppl 1):S21-S23. Trivedi MH et al. *J Clin Psychiatry.* 2008;69(2):246-258.

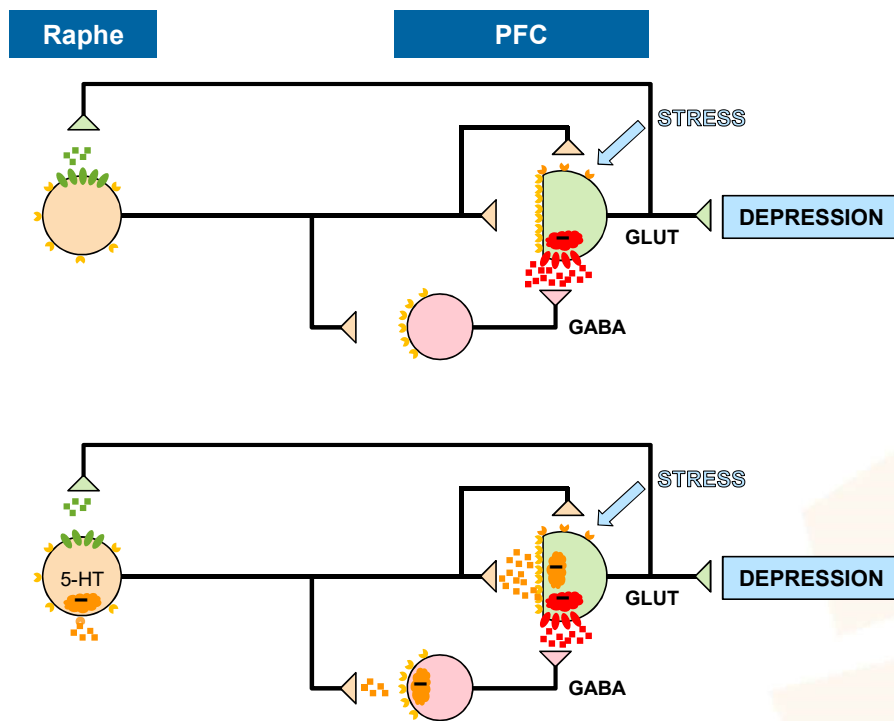
Mechanism of Action of Various Antidepressants



NAT = noradrenaline transporter; SERT = serotonin transporter.

Nutt DJ. *J Psychopharmacol.* 2009;23(4):343-345. Bang-Andersen B, et al. *J Med Chem.* 2011;54(9):3206-3221.

Serotonin Receptors and Their Interactions with Glutamate and GABA

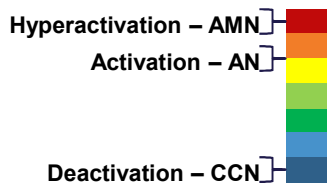
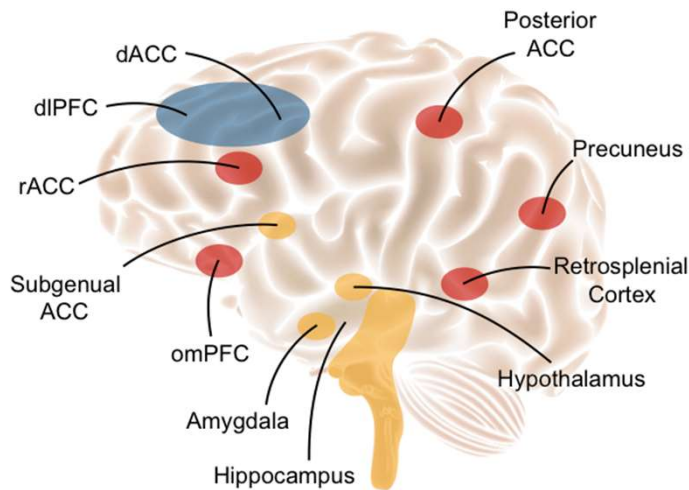


- 5-HT
- GLUT
- GABA
- 5-HT1A
- 5-HT2A
- AMPA-R
- GABA-A

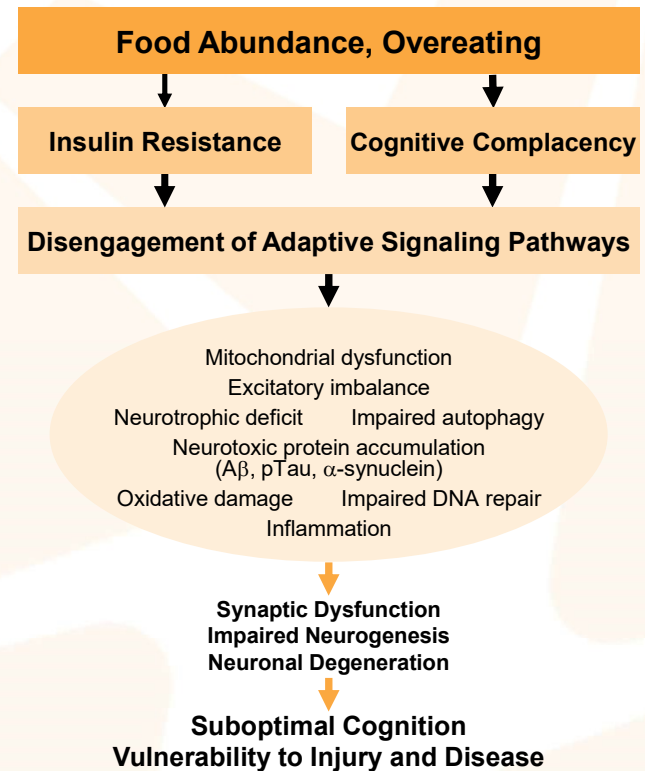
The model shows 5-HT neurons (orange) projecting to prefrontal cortex GABAergic interneurons (red) and glutamatergic pyramidal neurons (green) with transmitter release illustrated as small squares of the same colors. The presence of 5-HT1A (yellow), 5-HT2A (orange), AMPA-glutamate (green), and GABA-A receptors (red) is shown, as well as the response in the target neurons (clouds), stimulatory (+) or inhibitory (-).

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = gamma-aminobutyric acid; GLUT = glutamate.
 Albert PR, et al. *Front Behav Neurosci.* 2014;8:199.

How Overeating and Resultant Weight Gain Negatively Impacts Cognition



In patients with MDD, the introspective AMN is pathologically engaged (red), suppressing the activation of the CCN (blue) and leading to uninhibited activation of the AN (orange). In the context of maladaptive core beliefs about the self and the world, this gives rise to symptoms of depression such as rumination, dysphoria, poor concentration, diminished work performance, and self critical information processing.

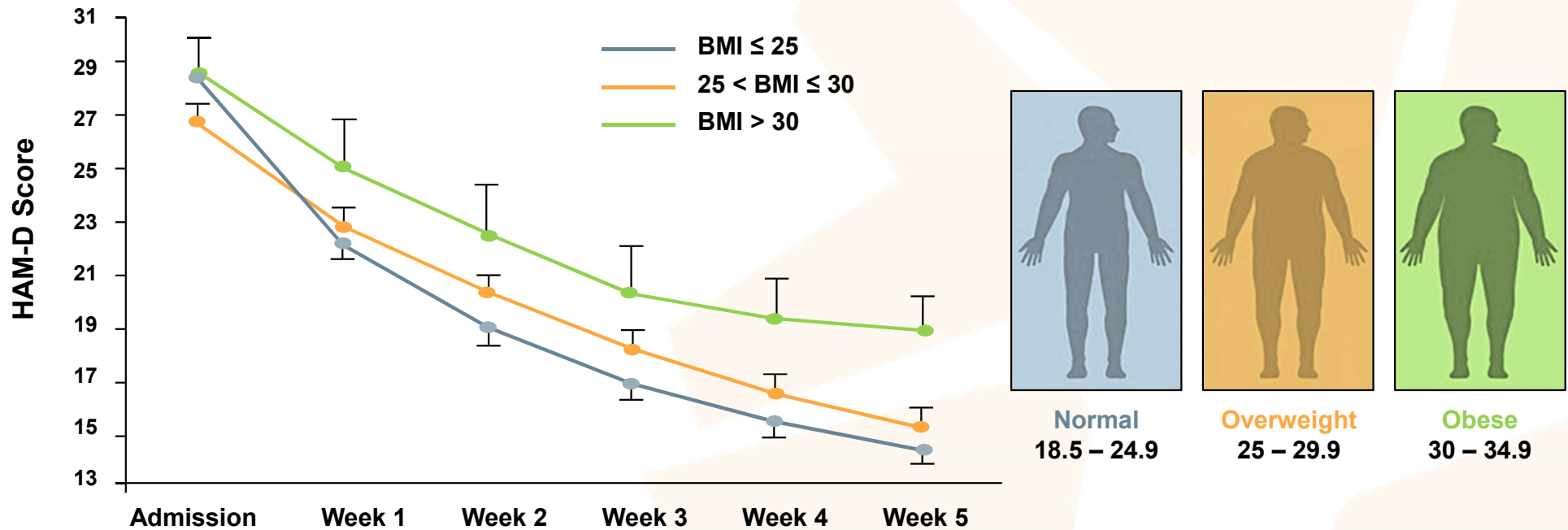


ACC = anterior cingulate cortex; AMN = autobiographic memory network; AN = affective network; CCN = cognitive control network; dACC = dorsal anterior cingulate cortex; dIPFC = dorsolateral PFC; omPFC = orbitomesial prefrontal cortex; rACC = rostral anterior cingulate cortex.

Rayner G, et al. *Neurosci Biobehav Rev.* 2016;61:53-65. Mattson MP. *Trends Cogn Sci.* 2019;23(3):200-212.

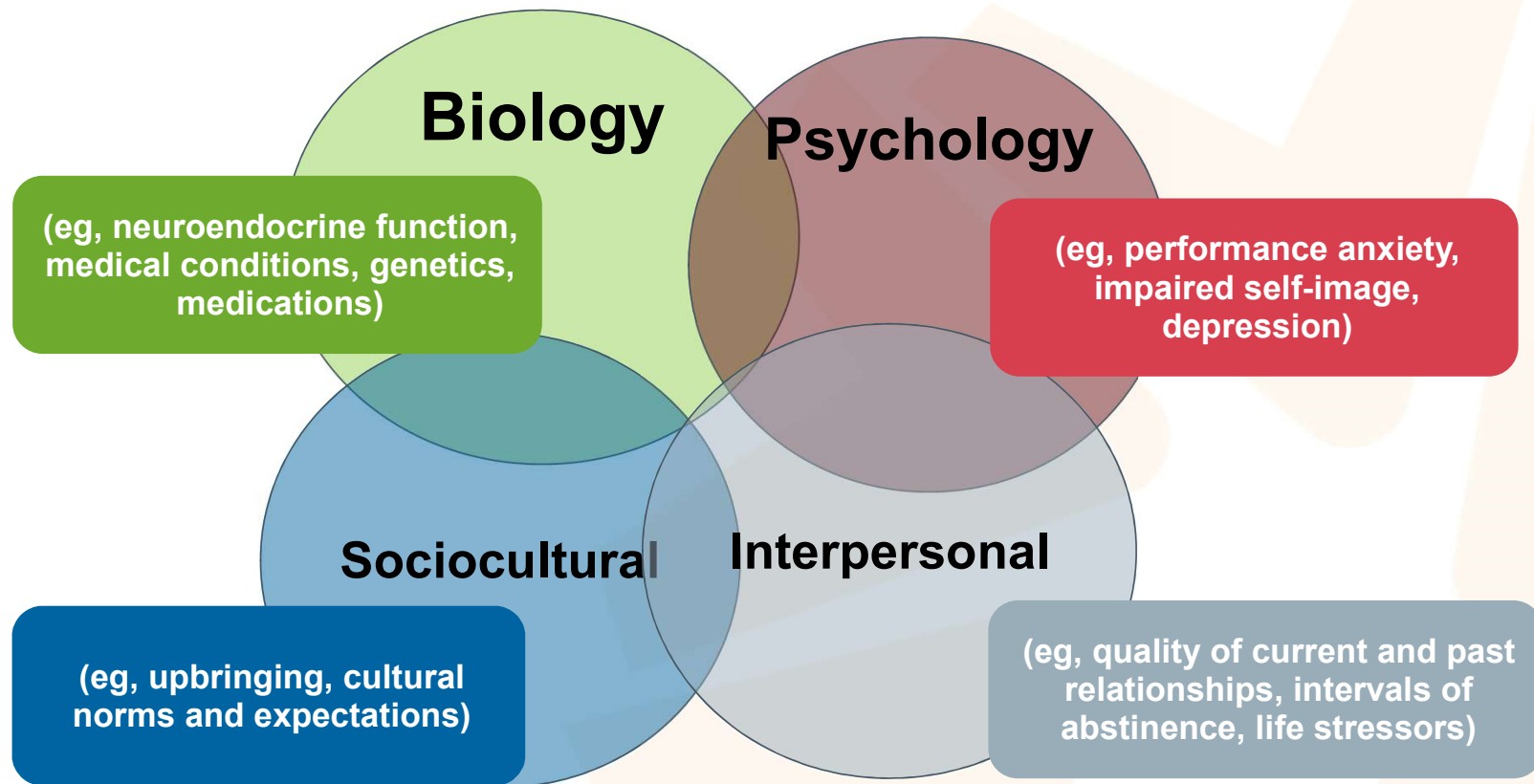
BMI Impacts Antidepressant Response

- Response to antidepressant treatment according to weight status
- Mean HAM-D rating scores and SEMs for 5 weeks after hospitalization

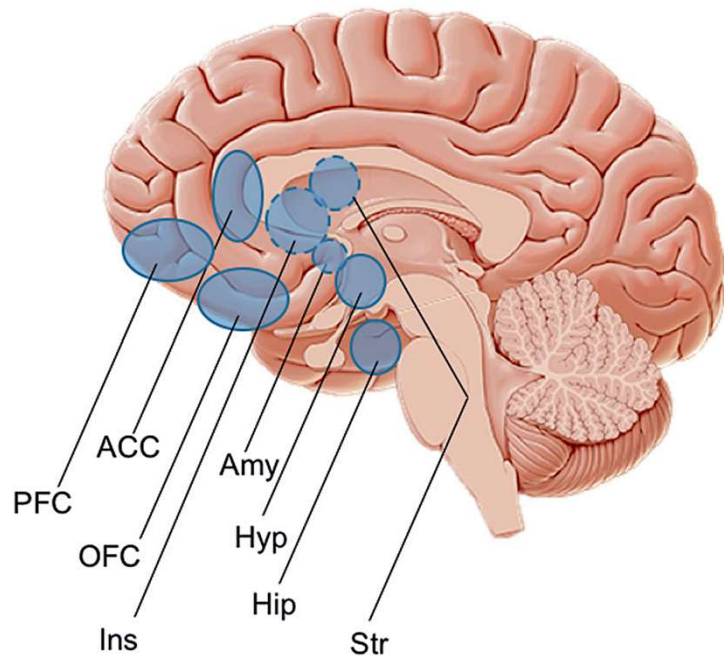


HAM-D = Hamilton Rating Scale for Depression.
Kloiber S, et al. *Biol Psychiatry*. 2007;62(4):321-326.

Biopsychosocial Model of Sexual Response



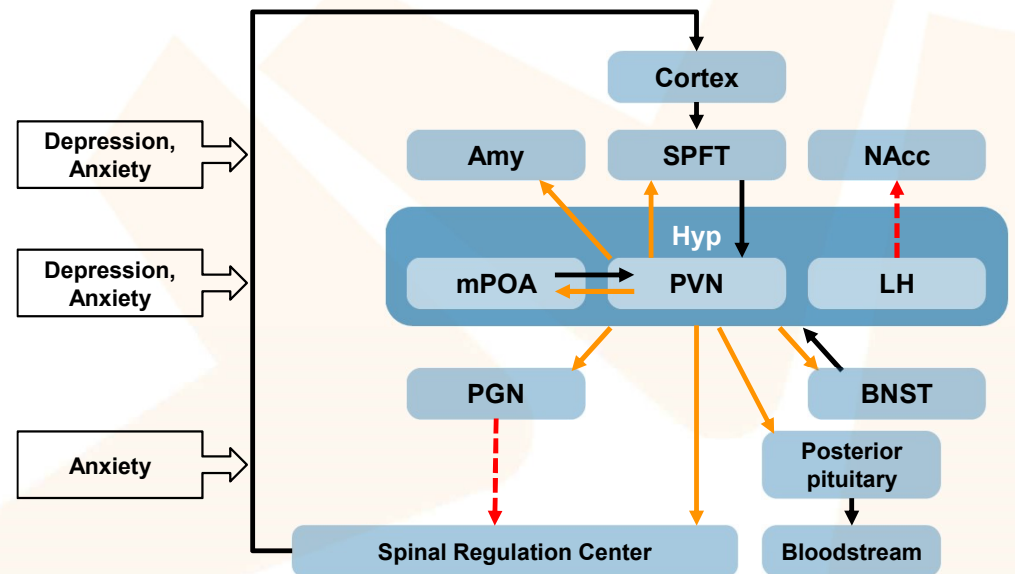
Anatomy of Sexual Desire and Its Intersection with Depression and Anxiety



Critical Cerebral Regions for Sexual Response

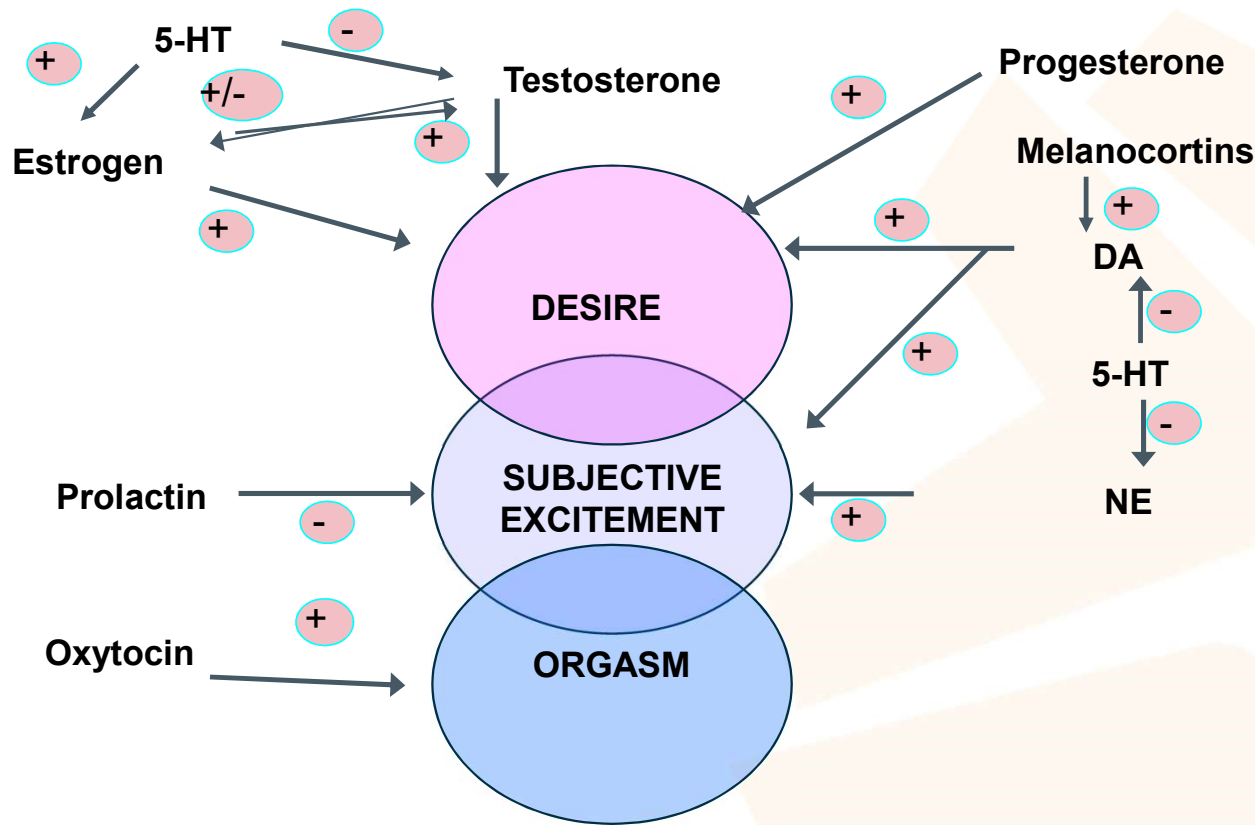
Amy = amygdala; ACC = anterior cingulate cortex; Hip = hippocampus; Hyp = hypothalamus; Ins = insula; OFC = orbitofrontal cortex; PFC = prefrontal cortex; Str = striatum; BNST = bed nucleus stria terminalis; LH = lateral hypothalamus; mPOA = medial preoptic area; NAcc = nucleus accumbens; PGN = paraventricular nucleus; PVN = paraventricular nucleus; SPFT = subparafascicular thalamus.

Trovão JN, et al. *Int J Impot Res.* 2018;30(6):279-286.



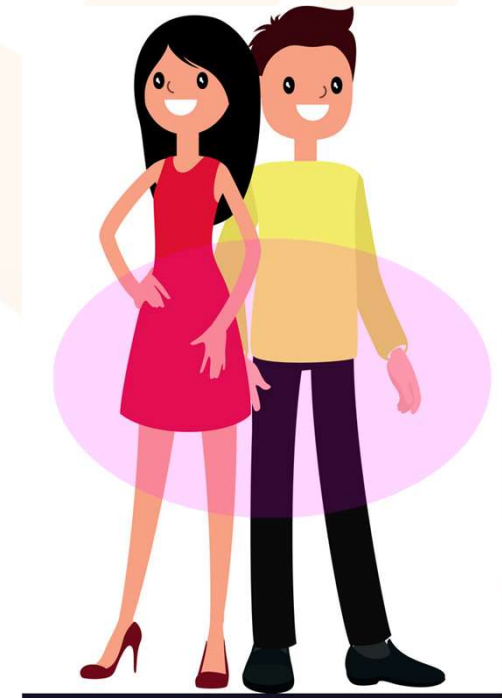
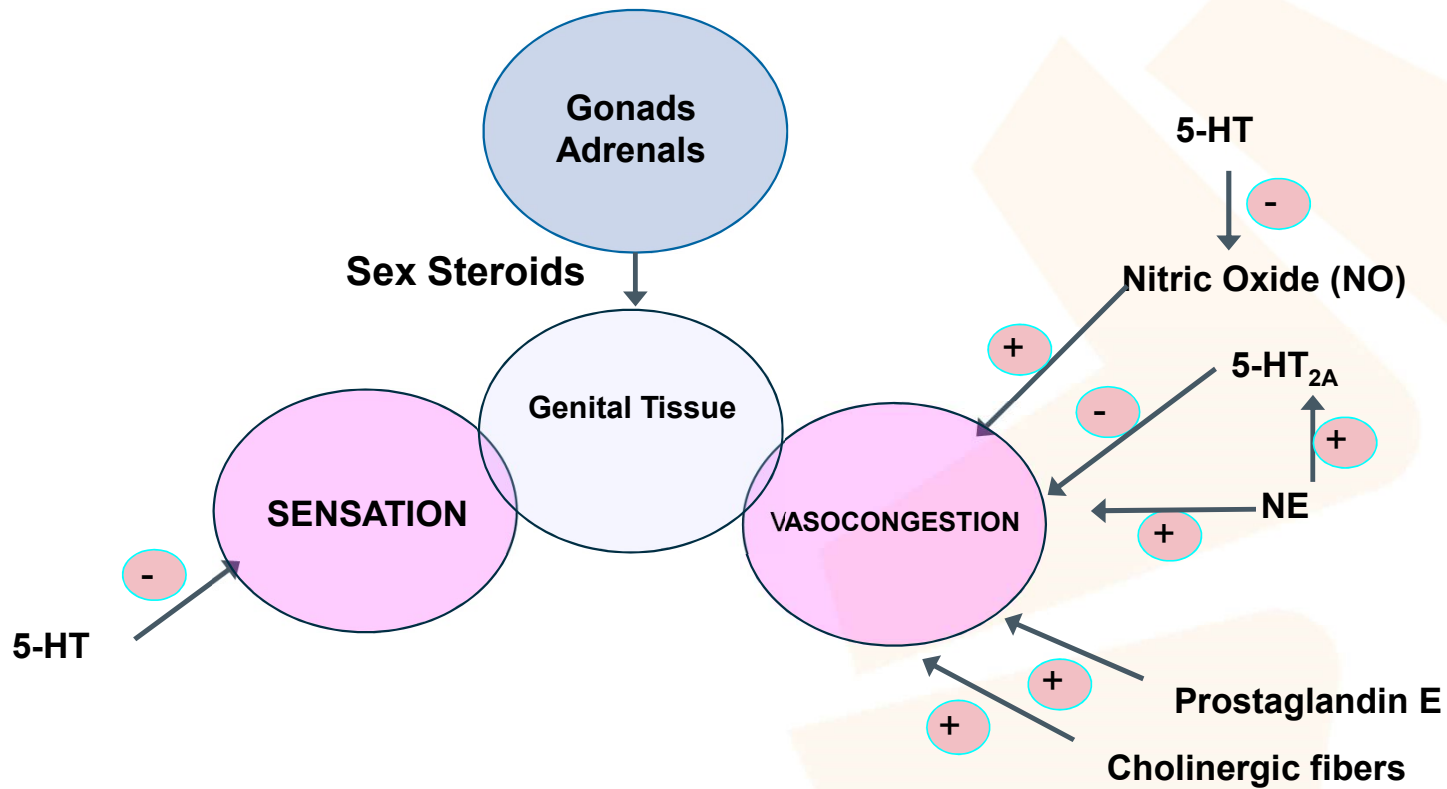
Stimulatory dopaminergic pathways are represented as black and oxytocinergic as orange arrows; and inhibitory serotonergic pathways as red arrows. Psychiatry disorders can affect the normal central sexual functioning by implying altered connectivity in certain parts of those circuits.

Central Effects on Sexual Function



Modified from: Clayton AH. *Psychiatr Clin North Am.* 2003;26(3):673-682. Cohen AJ. Antidepressant-Induced Sexual Dysfunction Associated with Low Serum Free Testosterone. 2000. www.mental-health-today.com/rx/testos.htm. Accessed February 20, 2019.

Peripheral Effects on Sexual Function



Modified from: Clayton AH. *Psychiatr Clin North Am.* 2003;26(3):673-682.

Effect of Antidepressants on Sexual Function

- Associated with sexual dysfunction: SSRIs, venlafaxine, TCAs, oral MAOIs
- Fewer negative effects on sexual function with bupropion-SR, mirtazapine, nefazodone, selegiline transdermal system, reboxetine, duloxetine, desvenlafaxine, vilazodone, vortioxetine
- FDA recommendations on study designs to characterize drug effects on sexual function in MDD trials for labeling claims
 - Study populations: MDD patients in the acute setting, MDD in maintenance setting, normal healthy volunteers with onset at steady state and sequentially by phase
 - Use ASEX (dichotomous) and CSFQ (continuous and dichotomous analyses)
 - Study drug (dose-response requires > 1 dose) vs placebo vs active control known to cause sexual dysfunction for assay sensitivity

TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor.

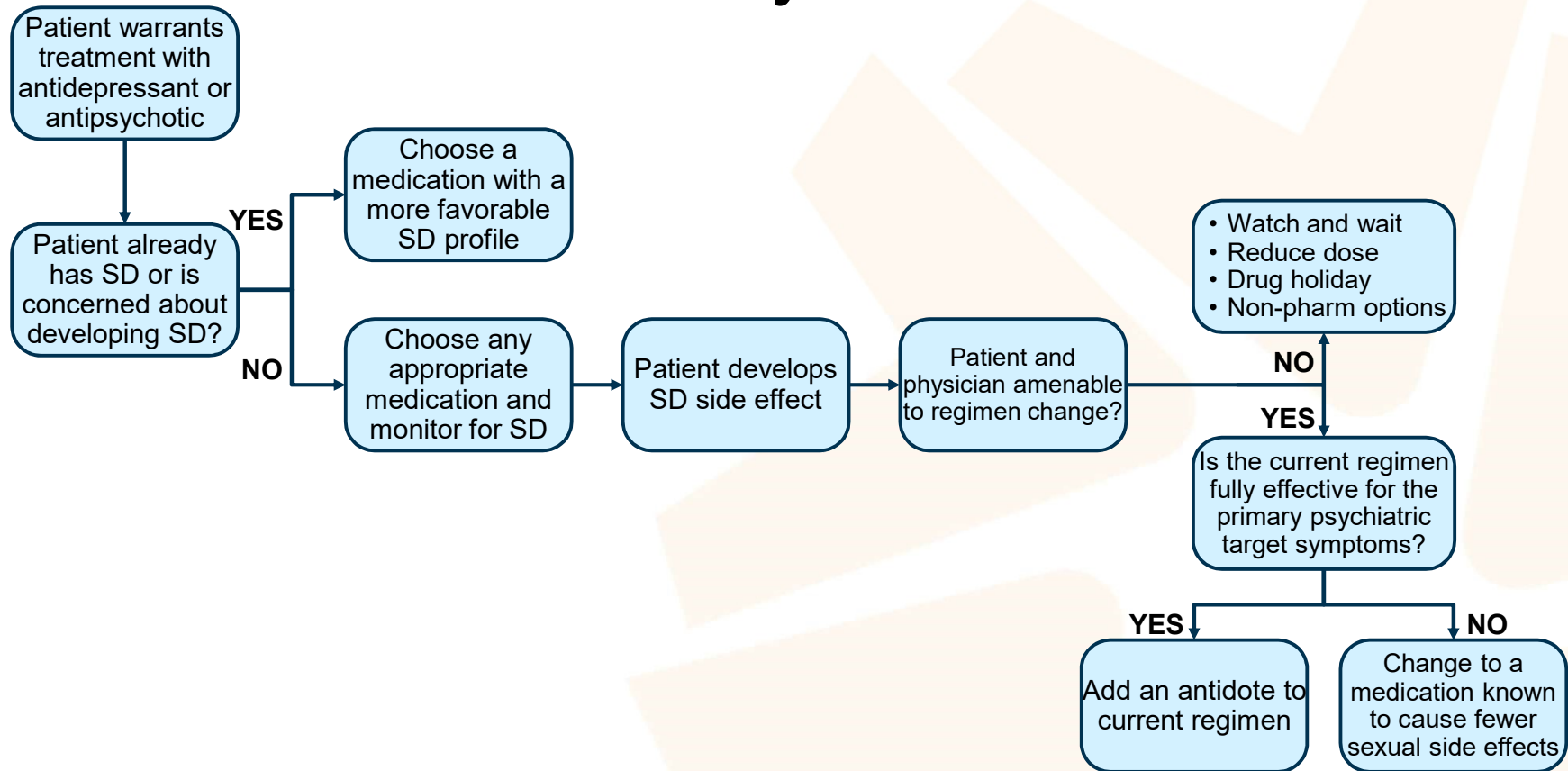
Clayton AH, et al. *J Clin Psychiatry*. 2002;63(4):357-366. Montgomery SA, et al. *J Affect Disord*. 2002;69(1-3):119-140. Boyarsky BK, et al. *Depress Anxiety*. 1999;9(4):175-179. Clayton AH, et al. *J Clin Psychiatry*. 2007;68(12):1860-1866. Clayton AH, et al. *Int Clin Psychopharmacol*. 2003;18(3):151-156. Baldwin D, et al. *J Psychopharmacol*. 2006;20(1):91-96. Clayton A, et al. *J Sex Med*. 2007;4(4 Pt 1):917-929. Clayton AH, et al. *Int Clin Psychopharmacol*. 2015;30(6):307-315. Clayton AH, et al. *J Sex Med*. 2013;10(10):2465-2476. Clayton AH, et al. *Int Clin Psychopharmacol*. 2015;30(4):216-223. Clayton AH, et al. *Int Clin Psychopharmacol*. 2017;32(1):27-35. Jacobsen PL, et al. *J Sex Med*. 2015;12(10):2036-2048. Jacobsen PL, et al. *CNS Spectr*. 2016;21(5):367-378. Montejo AL, et al. *J Psychopharmacol*. 2010;24(1):111-120. Kennedy SH, et al. *J Clin Psychopharmacol*. 2008;28(3):329-333. Khin NA, et al. *J Clin Psychiatry*. 2015;76(8):1060-1063.

Positive Systematic Antidepressant Studies

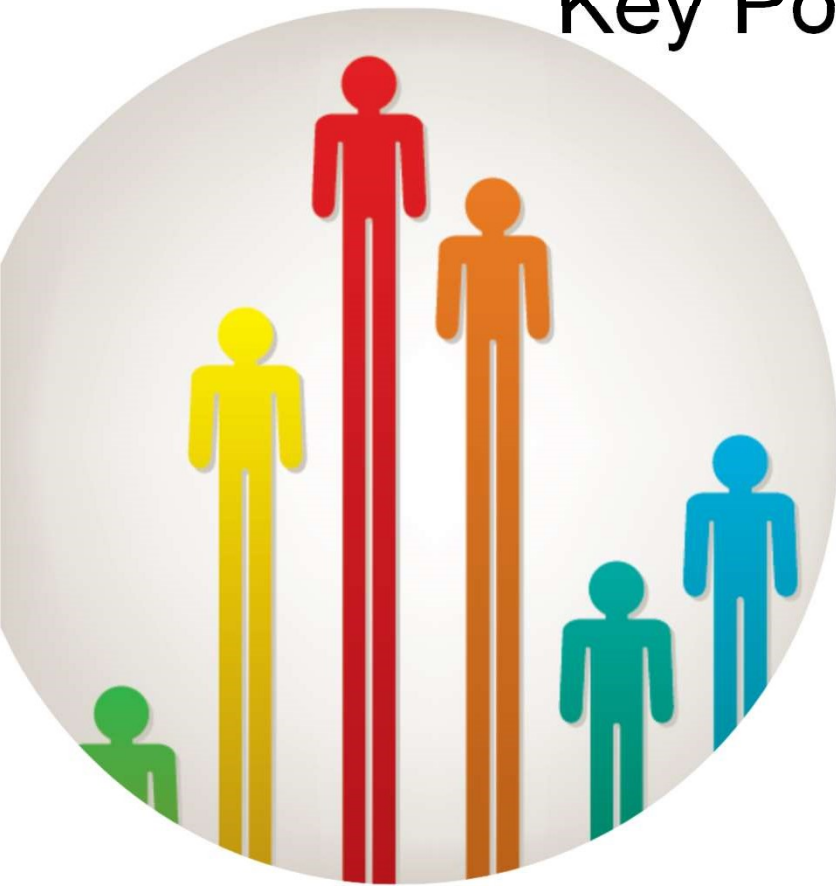
- Acute MDD treatment: vilazodone (CSFQ) and vortioxetine (ASEX)
- Maintenance MDD treatment (baseline of SD on SSRI) with switch – vortioxetine superior to escitalopram (CSFQ)
- Healthy control participants after 5 weeks:
 - Vilazodone 20 mg/day superior to paroxetine 20 mg/day only when accounted for nonadherence and did not differ from placebo (CSFQ). Probable dose response
 - Vortioxetine 10 mg/day did not differ from placebo and superior to paroxetine 20 mg/day (CSFQ). Dose response as vortioxetine 20 mg/day superior to paroxetine when accounted for nonadherence. Suggests lowering dose might be of benefit

Clayton AH, et al. *Int Clin Psychopharmacol*. 2015;30(4):216-223. Jacobsen PL, et al. *CNS Spectr*. 2016;21(5):367-378. Jacobsen PL, et al. *J Sex Med*. 2015;12(10):2036-2048. Clayton AH, et al. *Int Clin Psychopharmacol*. 2017;32(1):27-35. Jacobsen PL et al. Paroxetine, but not vortioxetine, impairs sexual functioning compared to placebo in healthy adults. Presented at: American Society for Clinical Psychopharmacology Annual Meeting; May 28–June 1, 2018; Miami, FL.


Algorithm to Manage Treatment-Emergent Sexual Dysfunction



Key Points to Remember:



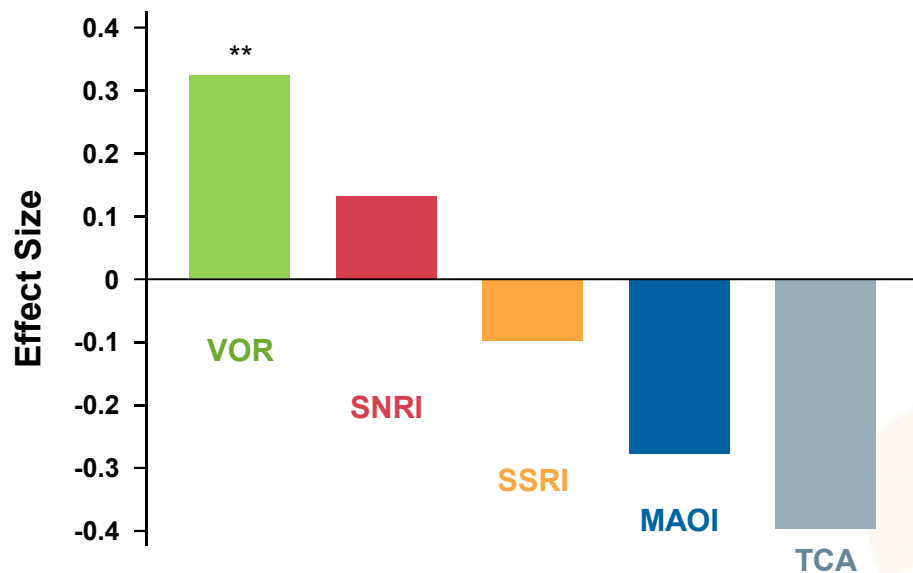
Antidepressants Have a
Differential Impact on
Sexual Function
in Patients with MDD

The background features several abstract, overlapping orange shapes of various sizes and orientations, creating a modern, geometric pattern. A solid blue horizontal band is positioned across the middle of the slide, containing the title text in white.

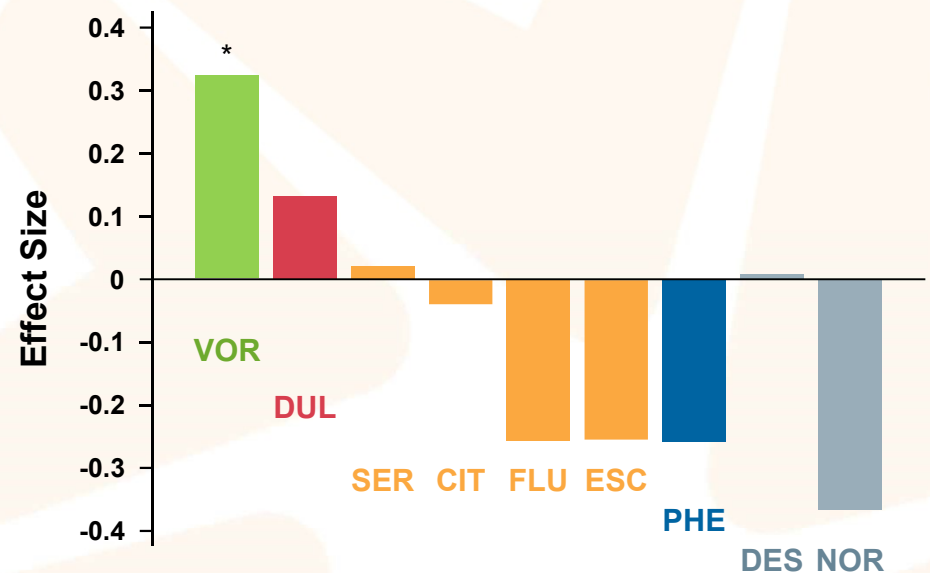
Role of Other Neurotransmitters and Signaling Pathways

Improvement in Cognitive Dysfunction in MDD as Assessed by the DSST

Standardized Effect Size Relative to Placebo by Antidepressant Therapeutic Classes



Standardized Effect Size Relative to Placebo by Individual Antidepressants



As of May 2018, US Prescribing Information for vortioxetine shows data on a positive effect on processing speed, an aspect of cognitive function that is impaired in many patients with MDD.

* $P < .05$; ** $P < .01$. CIT = citalopram; DES = desipramine; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; NOR = nortriptyline; PHE = phenelzine; SER = sertraline; VOR = vortioxetine.

Baune BT, et al. *Int J Neuropsychopharmacol*. 2018;21(2):97-107.

Examining the Evidence for Direct Impact on Cognitive Symptoms in MDD

Antidepressants and psychotropic agents that improve measures of cognition in individuals with MDD independent of improvements in measures of depressive symptom severity

	Learning/ Memory	Attention/ Concentration	Executive Function	Processing Speed
Vortioxetine	1	1	1	1
Duloxetine	1			
Lisdexamfetamine			2	
Other (eg, SSRIs, SNRIs, and bupropion)	3	3	3	3
Modafinil	3	3	3	3
Erythropoietin	2	2	2	2

Independent effect indicated by a priori specification, cognition as primary; pathoanalysis; subgroup analysis in nonresponders and nonremitters.

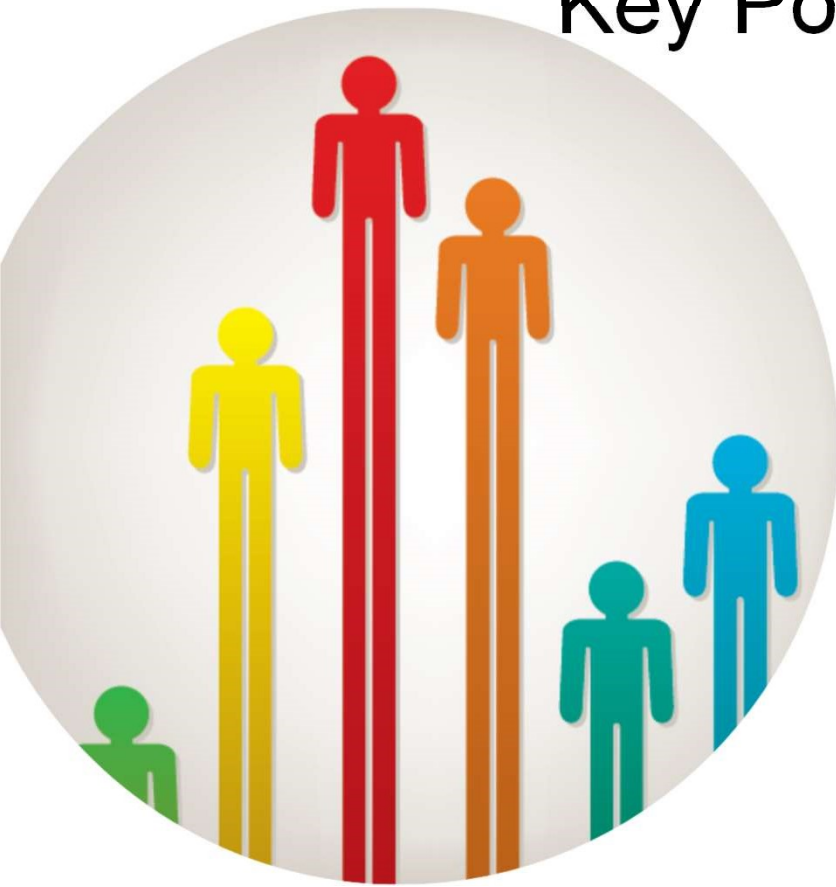
Level 1 replicated placebo-controlled trial evidence with demonstration of independent effect.

Level 2 single placebo-controlled trial evidence with demonstration of independent effect.

Level 3 uncontrolled evidence (eg, lacking placebo and case-series) with lack of demonstration of independent effect.

McIntyre RS, et al. *Curr Opin Psychiatry*. 2016;29(1):48-55. McIntyre RS, et al. *CNS Drugs*. 2015;29(7):577-589.

Key Points to Remember:

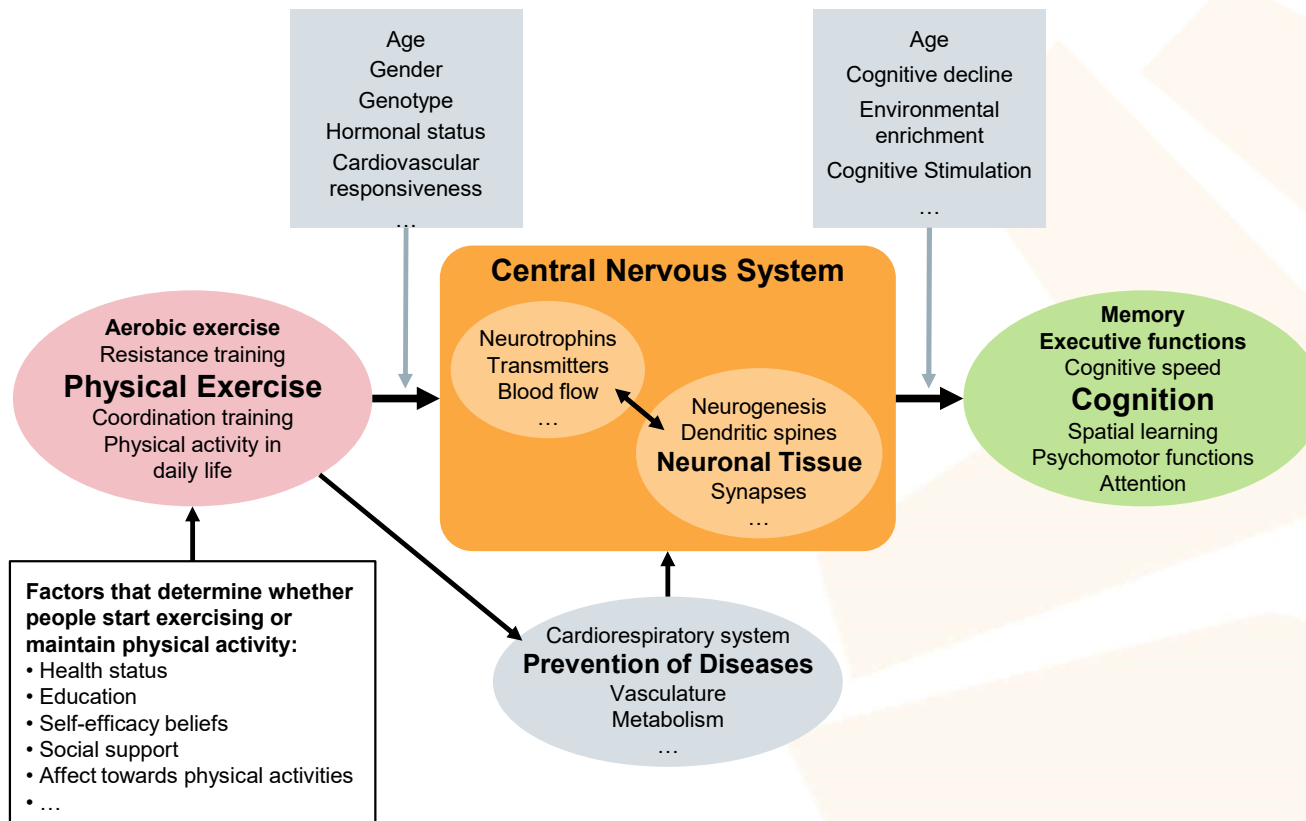


Antidepressants Have a
Differential Impact on
Cognition
in Patients with MDD

Does Physical Exercise Have a Role in Treatment?

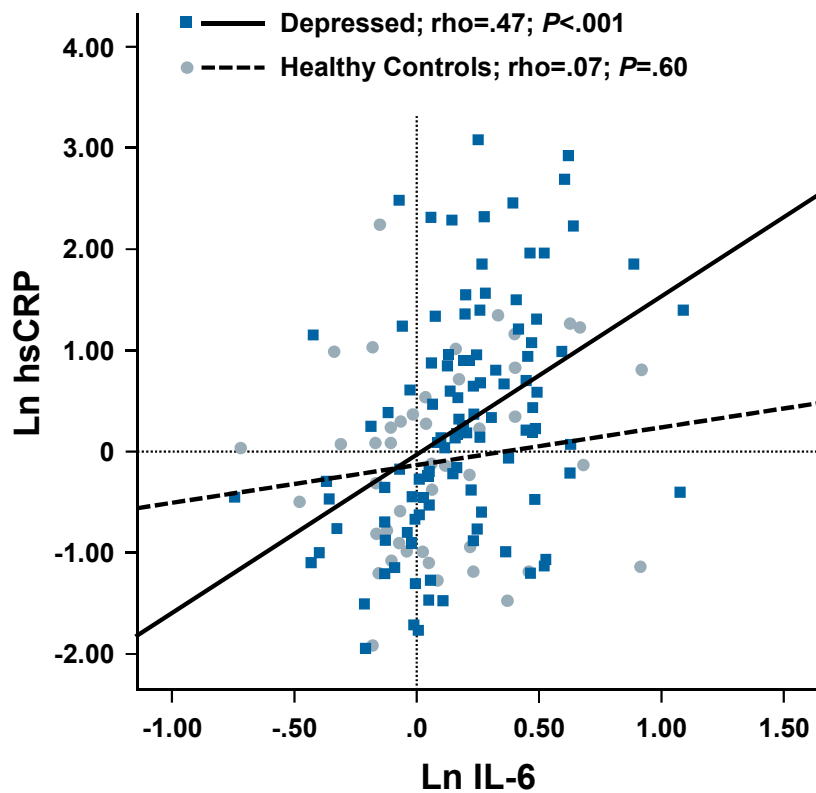
Answer Appears to be a Yes

Exercise and Cognition – A Marriage Made in Heaven



Summary of the possible relationship between physical exercise, neuroplasticity and cognition with possible moderator variables which might influence exercise behavior, the impact of exercising on the central nervous system and whether changes in the nervous system translate into measurable changes in cognitive variable.

Exercise-Related Improvement in Cognition May Be Associated with Decreased Inflammation in MDD



	IL-6	P-Value	hsCRP	P-Value
<u>Memory</u>				
Digit span, forward	0.03	.74	0.00	.95
Buschke, total score	-0.10	.37	0.07	.56
Rey complex figure	-0.06	.60	0.06	.61
<u>Attention</u>				
Digit span, backward	0.03	.74	-0.15	.18
Serial sevens	0.09	.43	-0.04	.77
Stroop test – colored crosses	0.03	.76	0.13	.27
Stroop test – congruent	-0.06	.58	0.20	.08
Stroop test – incongruent	<u>0.23</u>	<u>.03</u>	0.20	.08
<u>Visuomotor speed</u>				
Trail making A	-0.14	.17	<u>0.31</u>	<u>.005</u>
Trail making B	0.16	.11	0.05	.63
Digit symbol test	-0.15	.16	-0.13	.24
<u>Language</u>				
Verbal fluency, animals	<u>0.24</u>	<u>.02</u>	-0.04	.72
Verbal fluency, s words	-0.01	.90	-0.05	.63
<u>Executive function</u>				
Design fluency	0.01	.91	0.03	.76

Correlation between change in IL-6 and hsCRP, and change in cognitive skills during a 3-month exercise intervention follow-up period.

hsCRP = high-sensitivity CRP.

Krogh J, et al. *Brain Behav Immun.* 2014;35:70-76.



Mrs. Santos

Case Presentation

Mrs. Santos

Presentation

History

Treatment

Follow-Up

- 43-year-old married female
- PCP referral for treatment of depression
- Patient self-reports history of trying several antidepressants in past, but always stopped them early because of various side effects

PCP = primary care physician.

Mrs. Santos

Presentation

History

Treatment

Follow-Up

History of Present Illness

- Gradual worsening depression over the past 18 months
- Chronic low mood (worse in the evening)
- Frequent bouts of crying when alone
- Mid-nocturnal and early morning awakening
- Daytime fatigue and difficulty initiating tasks

Mrs. Santos

Presentation

History

Treatment

Follow-Up

History of Present Illness

- Increased appetite with episodes of binge eating
 - 15-pound weight gain in 3 months
- Markedly reduced libido and poor concentration
- Loss of interest in daily activities
- Denies active suicidal ideation
 - States she often feels that she'd be *"better off dead"*
- Denies any obvious precipitants for her symptoms
- PHQ-9 = 20

Mrs. Santos

Presentation

History

Treatment

Follow-Up

Past Psychiatric/Medical History

- MDD with approximately 3 previous episodes
- Multiple selective SSRIs and SNRIs have been tried
 - None helped “*more than 50%*” but she would stop medications within 4 to 5 weeks of starting because the medications “made me foggy, eat more, and my sex drive went out of the window”
- No significant medical history
- Tried CBT for 16 weeks. No real symptom reduction

CBT = cognitive-behavioral therapy.

Mrs. Santos

Presentation

History

Treatment

Follow-Up

- After comprehensive discussion of treatment options, Mrs. Santos expressed no interest in continuing psychotherapy
- An antidepressant with MMA mechanism of action was initiated at 10 mg/day

MMA = multimodal antidepressant.

Mrs. Santos

Presentation

History

Treatment

Follow-Up

- **2-week follow-up**
 - Patient states she feels better and appears noticeably improved
 - Mild nausea in first week of treatment, now resolved
 - PHQ-9 = 12
- **4-week follow-up**
 - Symptomatic improvement
 - Endorsing enhanced life functioning
 - PHQ-9 = 8
- **6-week follow-up**
 - Appears significantly more depressed and tearful in session
 - Desire to discontinue MMA
 - PHQ-9 = 16

Mrs. Santos

Presentation

History

Treatment

Follow-Up

- Is she taking her MMA?
 - Says, “This time I am taking it”
- Is she experiencing side effects?
 - She reports no mental fogginess, sexual dysfunction, or any appetite changes

Mrs. Santos

Presentation

History

Treatment

Follow-Up

- Dose of MMA increased to 20 mg/day
- Exercise as a lifestyle and depression treatment option discussed with her. She appears extremely interested in “giving it a try”. She is also educated on sleep hygiene, and increased social activity is recommended. Educational materials on above interventions handed to her, and she is recommended to share it with her very supportive spouse

Mrs. Santos

Presentation

History

Treatment

Follow-Up

- Affect is much brighter. Mrs. Santos is wearing makeup and appears more animated
- PHQ-9 = 6
- *“I think that we are finally on to something.” “It is easier to start and complete tasks, my concentration at work is noticeably better. I almost feel like my old self. My confidence is better and I am starting to enjoy life again.”*
- Patient denied any significant side effects aside from nocturnal sweating, but indicated that she *“can live with that”*
- When asked about her current situation, she reports *“OK, we are on the right track”*

The background of the slide features several overlapping, semi-transparent orange geometric shapes, including rectangles and trapezoids, scattered across the white background. A solid blue horizontal band is positioned in the upper middle section of the slide.

In Conclusion ...

In Conclusion ...



These 3 issues – cognitive dysfunction, weight gain, and sexual dysfunction are common, impairing, and disabling



Key Points to Remember:

- It is wise to proactively keep all issues (cognition, sexual dysfunction, weight gain) in mind as we offer a treatment option to our patients
- Also, proactively inform and educate patients about all 3 issues

1



Key Points to Remember:

- Measure, measure, measure
- Measurement-based care at baseline and throughout the course of treatment is a wise clinical action to take

2



Key Points to Remember:

- Different pharmacologic interventions have different profiles on cognition, sexual dysfunction, and weight gain. It is best to exploit these differences for a patient's benefit
- Nonpharmacologic interventions, such as exercise, sleep, nutrition, etc., all have a positive impact on the well-being of patients with MDD and should always be offered

3