Facing Three of the Greatest Unmet Needs in

MAJOR DEPRESSION MANAGEMENT:

A Focus on Cognitive Dysfunction, Sexual Dysfunction and Weight Gain

This activity is supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc. and Lundbeck.

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Faculty Disclosure

- **Dr. Clayton**: Advisory Board—Alkermes, Inc., AMAG Pharmaceuticals, Inc., Ivix, Palatin Technologies, S1 Biopharma, Sage Therapeutics, Sprout Pharmaceuticals, Takeda, Valeant Pharmaceuticals; Consultant—Alkermes, Inc., AMAG Pharmaceuticals, Inc., Ivix, Palatin Technologies, S1 Biopharma, Sage Therapeutics, Sprout Pharmaceuticals, Takeda, Valeant Pharmaceuticals; Grants—Axsome, Endoceutics, Inc., Janssen, Palatin Technologies, Sage Therapeutics, Takeda; Royalties/Copyright—Ballantine Books/Random House, Changes in Sexual Functioning Questionnaire, Guilford Publications; Shares/Restricted Stock Units—Euthymics, S1 Biopharma.

- **Dr. Maletic**: Consultant—Alkermes, Inc., Allergan, Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Shire, Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., Takeda Pharmaceutical Company Limited, Teva Pharmaceutical Industries Ltd.; Speakers Bureau—Alkermes, Inc., Allergan, H. Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion Pharmaceuticals Inc., Takeda Pharmaceutical Company Limited, Teva; Speakers Bureau (spouse)—Otsuka.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

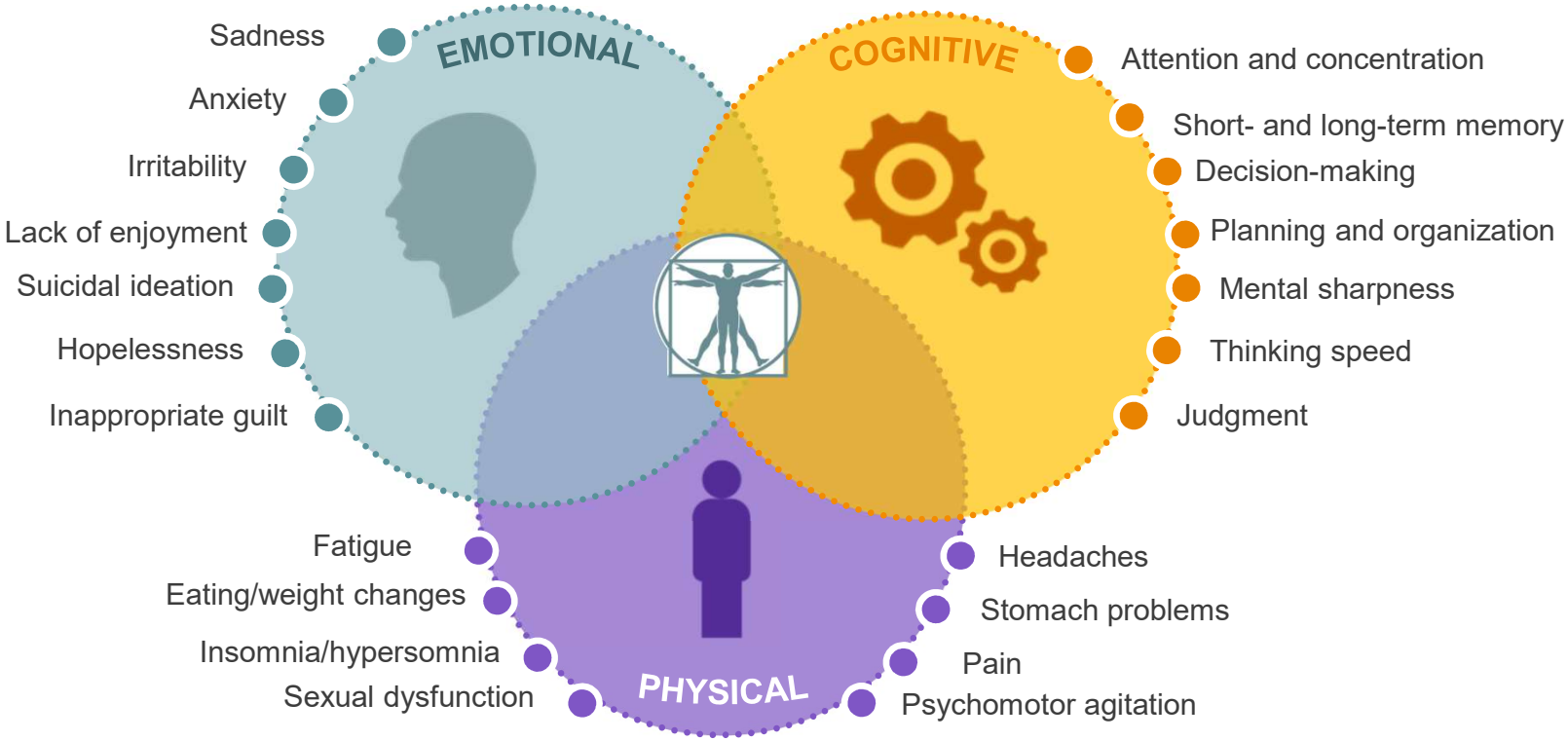
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Outline the impact of cognitive symptoms and treatment-emergent sexual dysfunction and weight gain on major depressive disorder (MDD) patient quality of life, clinical outcomes, and medication adherence
- Integrate assessment tools for the monitoring of cognitive and sexual dysfunction in MDD patients into routine clinical practice
- Describe the mechanisms of action and clinical data surrounding available and emerging MDD pharmacotherapies with respect to their associated adverse effect profiles and efficacy across MDD symptom domains
- Develop individualized MDD therapeutic strategies that consider newer antidepressants to manage the full array of MDD symptoms while mitigating adverse effects

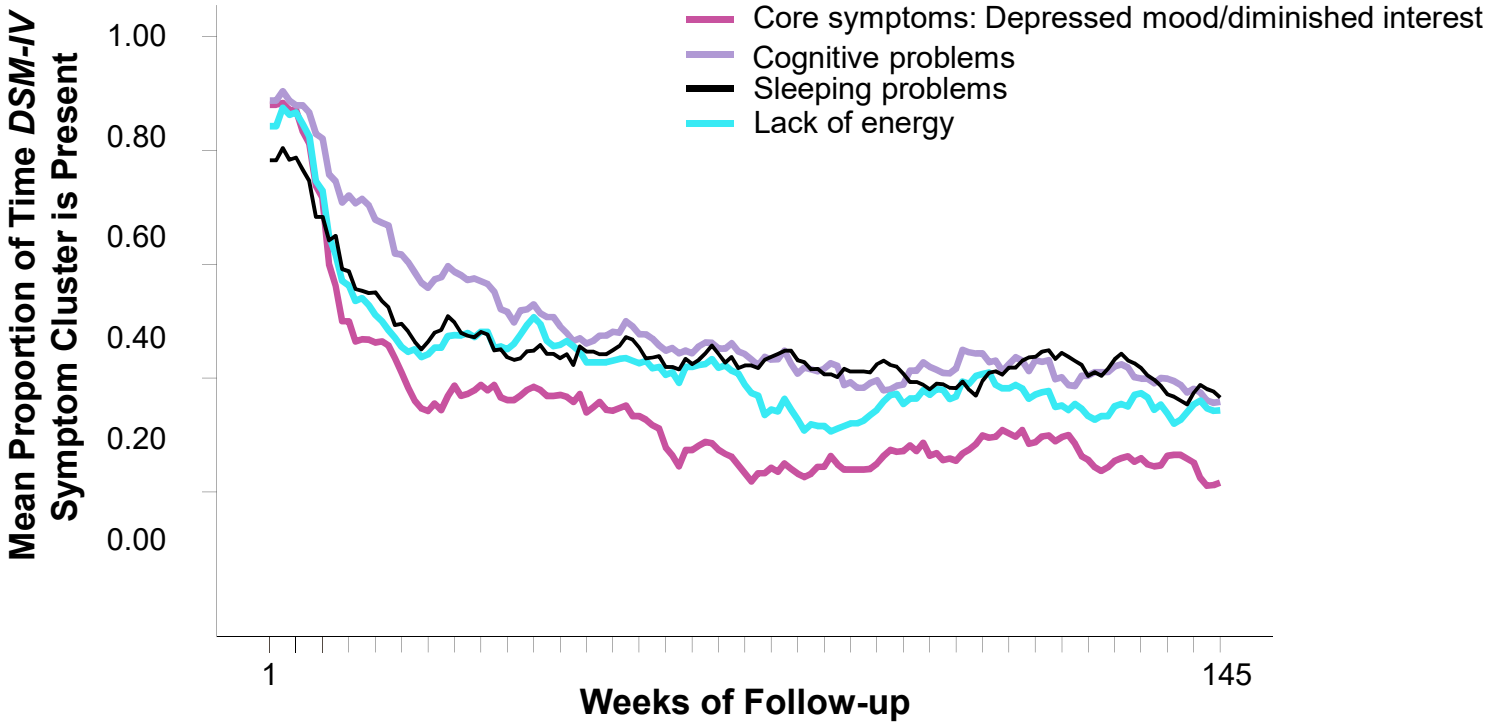
Unmet Needs in Major Depression

Depression is a Clinically Heterogeneous 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.

Not All Symptoms of MDD Respond Equally Well to Treatment



The presence of *DSM-IV* depressive symptom clusters during the 3-year follow-up of 267 initially depressed primary care patients.

MDD = major depressive disorder.

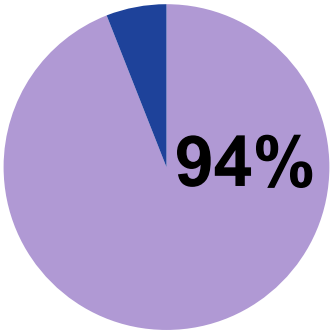
Conradi HJ, et al. *Psychol Med*. 2011;41(6):1165-1174.

Cognitive Symptoms in Depression

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

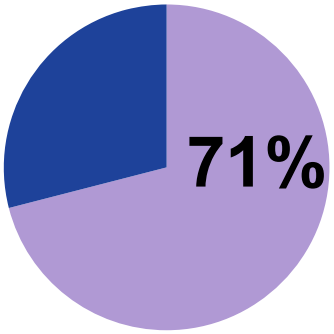
ACUTE

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



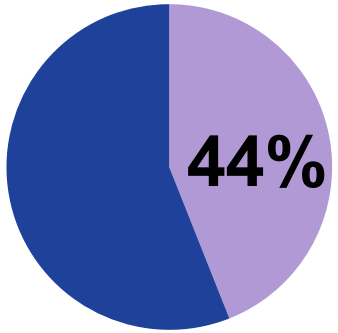
RESPONSE

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

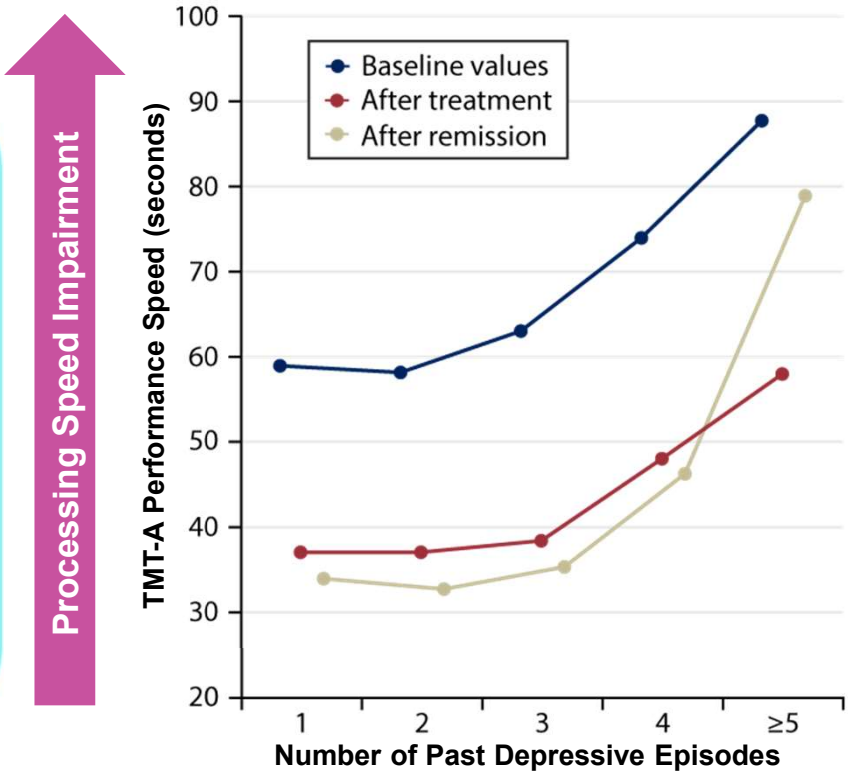


Conradi HJ, et al. *Psychol Med*. 2011;41(6):1165-1174. McClintock SM, et al. *J Clin Psychopharmacol*. 2011;31(2):180-186.

Although Cognitive Symptoms Can Improve with Treatment, Patients with More Past Depressive Episodes May Still Have Worse Cognitive Function

Processing speed is impaired as a function of the number of previous depressive episodes (N=1140)

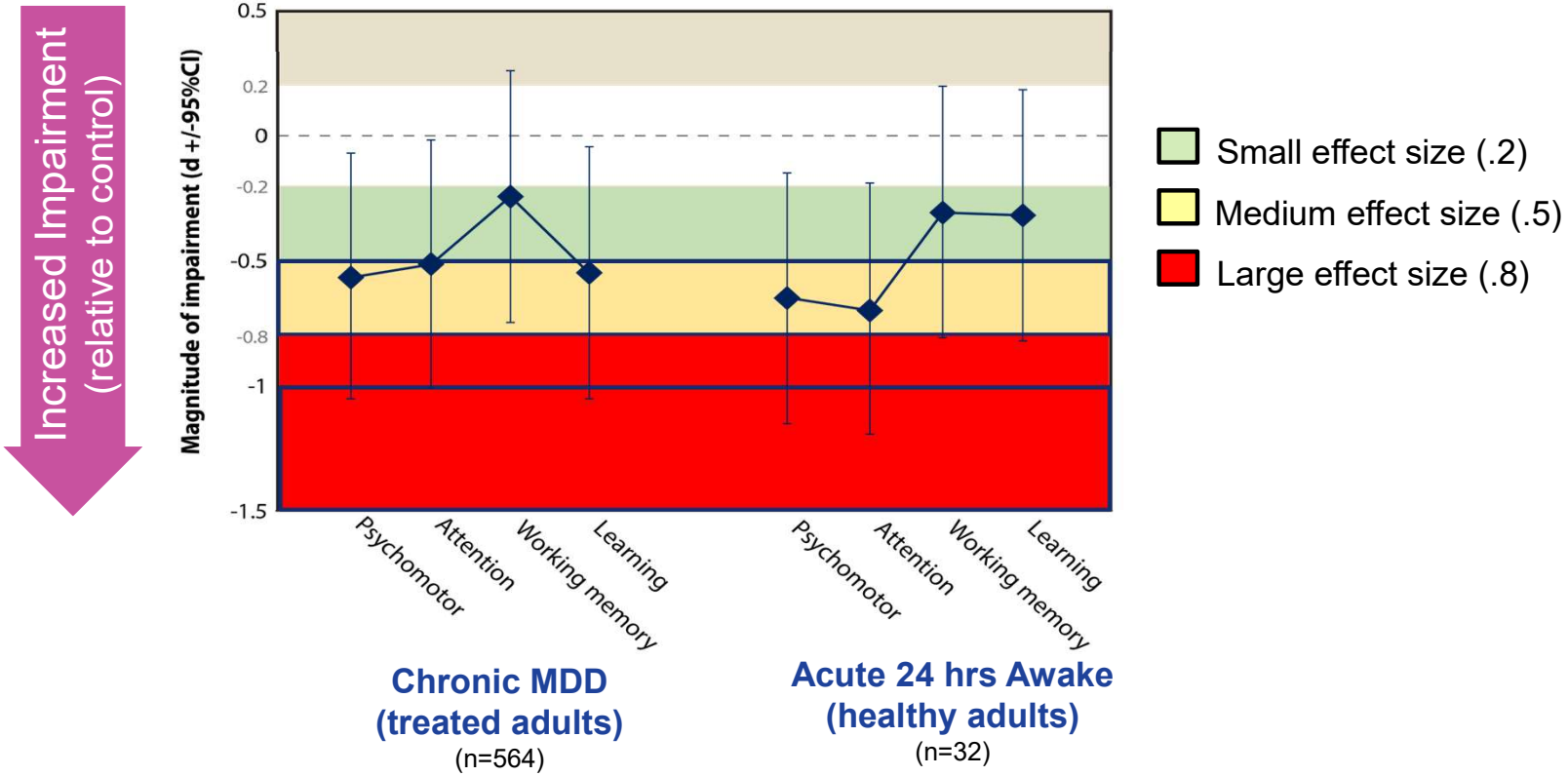
- 1140 outpatients with depression were assessed on the TMT-A (a frequently used neurocognitive drawing test that measures processing speed) at baseline, after 6 to 8 weeks of treatment, and after remission
- The study found that TMT-A performance was reduced with the number of past depressive episodes, ***regardless of whether the patients were treated or in remission***



***Remission defined as a QIDS-SR score of ≤ 5. TMT-A = Trail Making Test A; QIDS-SR = Quick Inventory of Depressive Symptomatology (Self-Report).**

Gorwood P, et al. *Eur Neuropsychopharmacol*. 2014;24(10):1630-1640.

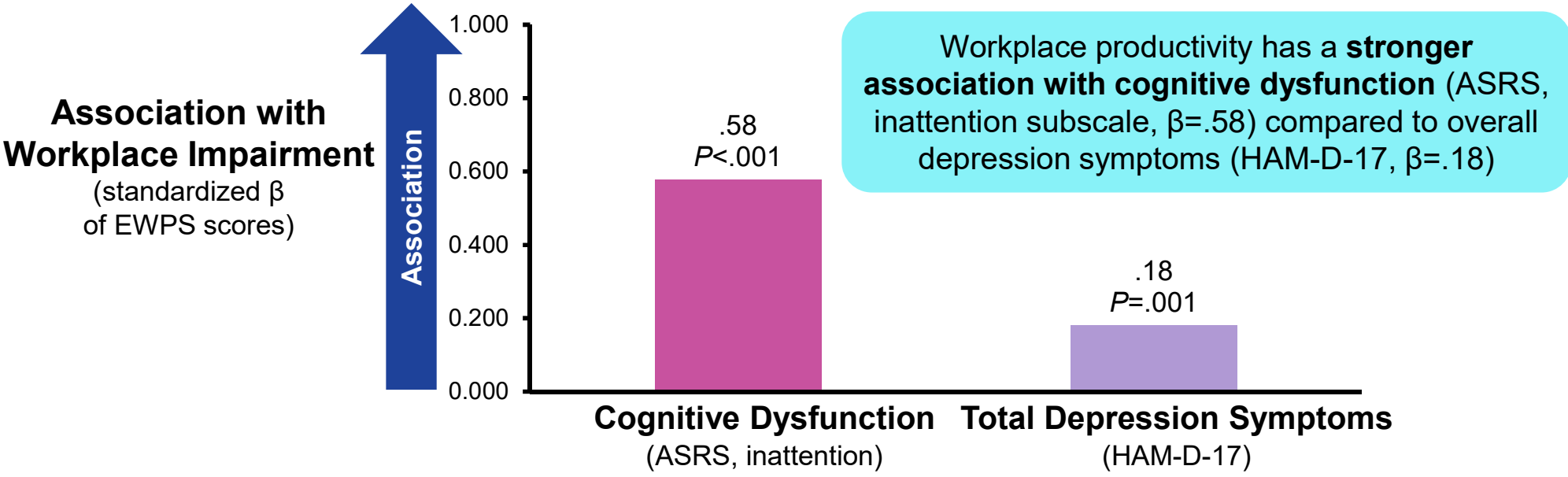
The Effect Size of Cognitive Impairment in MDD is Significant



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.

Cognitive Symptoms Contribute More to Workplace Impairment Than Mood Symptoms

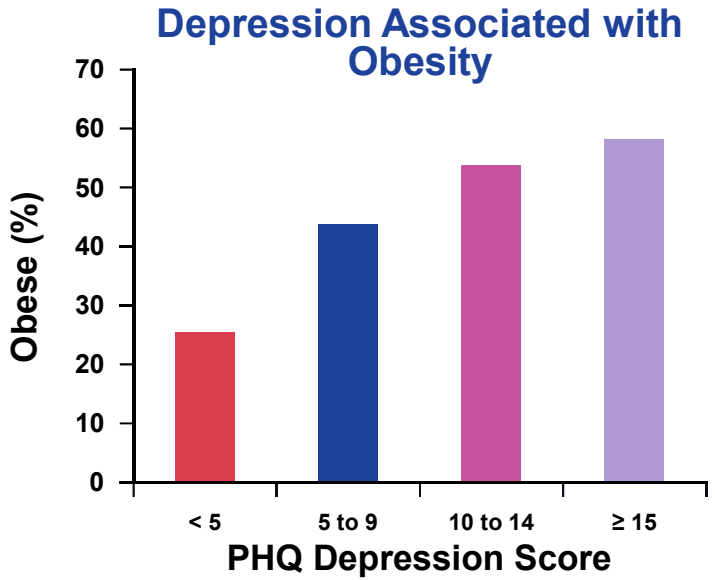
Cognitive symptoms account for more variability in workplace impairment than total depression severity in a post hoc analysis of patients with MDD (N=260)

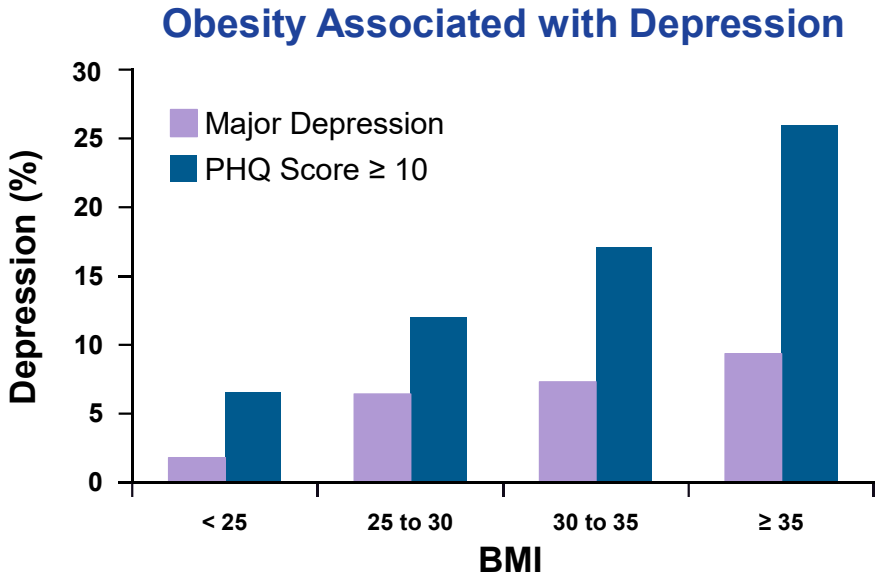


Workplace productivity has a **stronger association with cognitive dysfunction** (ASRS, inattention subscale, β=.58) compared to overall depression symptoms (HAM-D-17, β=.18)

ASRS = Adult ADHD Self-Report Scale; EWPS = Endicott Workplace Productivity Scale; HAM-D-17 = 17-item Hamilton Depression Rating Scale.
McIntyre RS, et al. *Compr Psychiatry*. 2015;56:279-282.

Bidirectional Relationships between Obesity and Depression



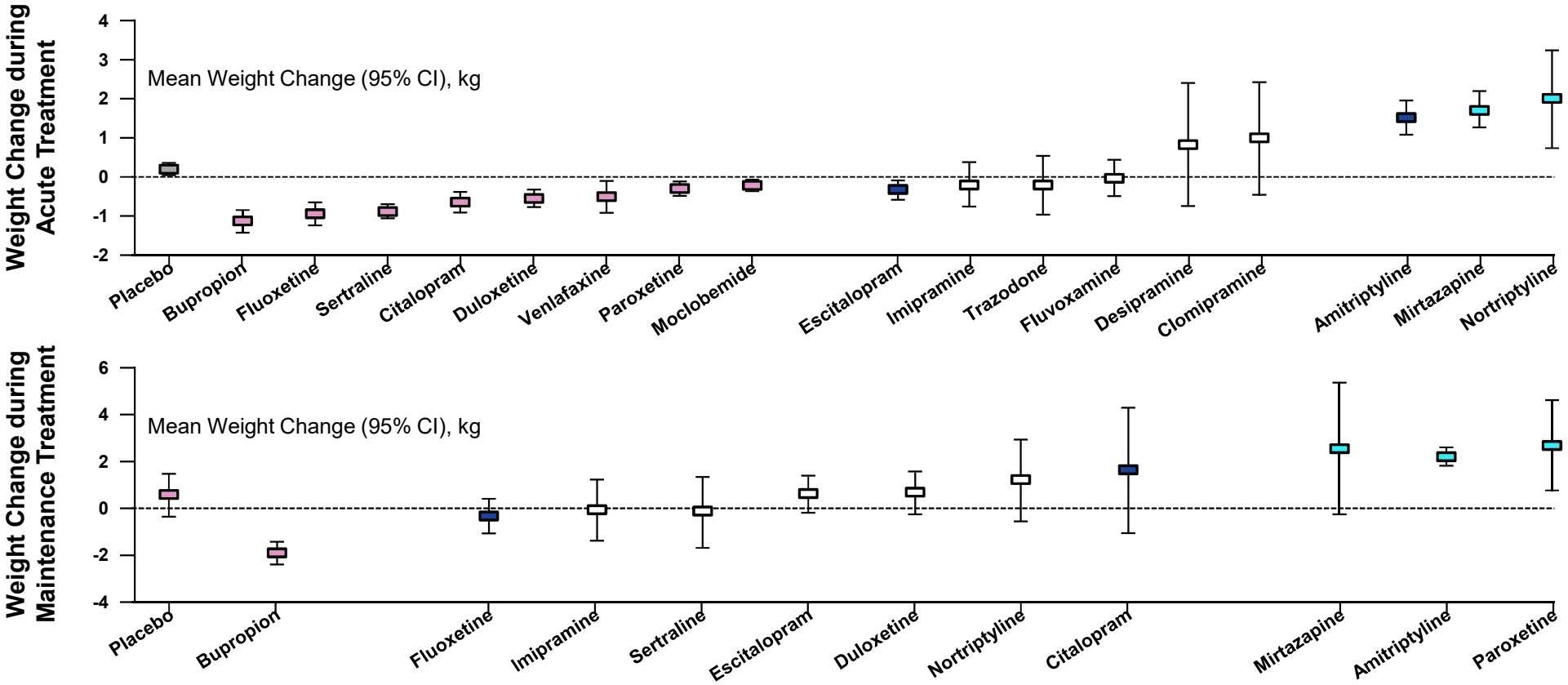


In a sample of 4641 female health plan enrollees aged 40 to 65, depression was associated with obesity and obesity was associated with depression. Prevalence of moderate or severe depression increased from 6.5% among those with BMI < 25 to 25.9% among those with BMI >35. Prevalence of obesity increased 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.

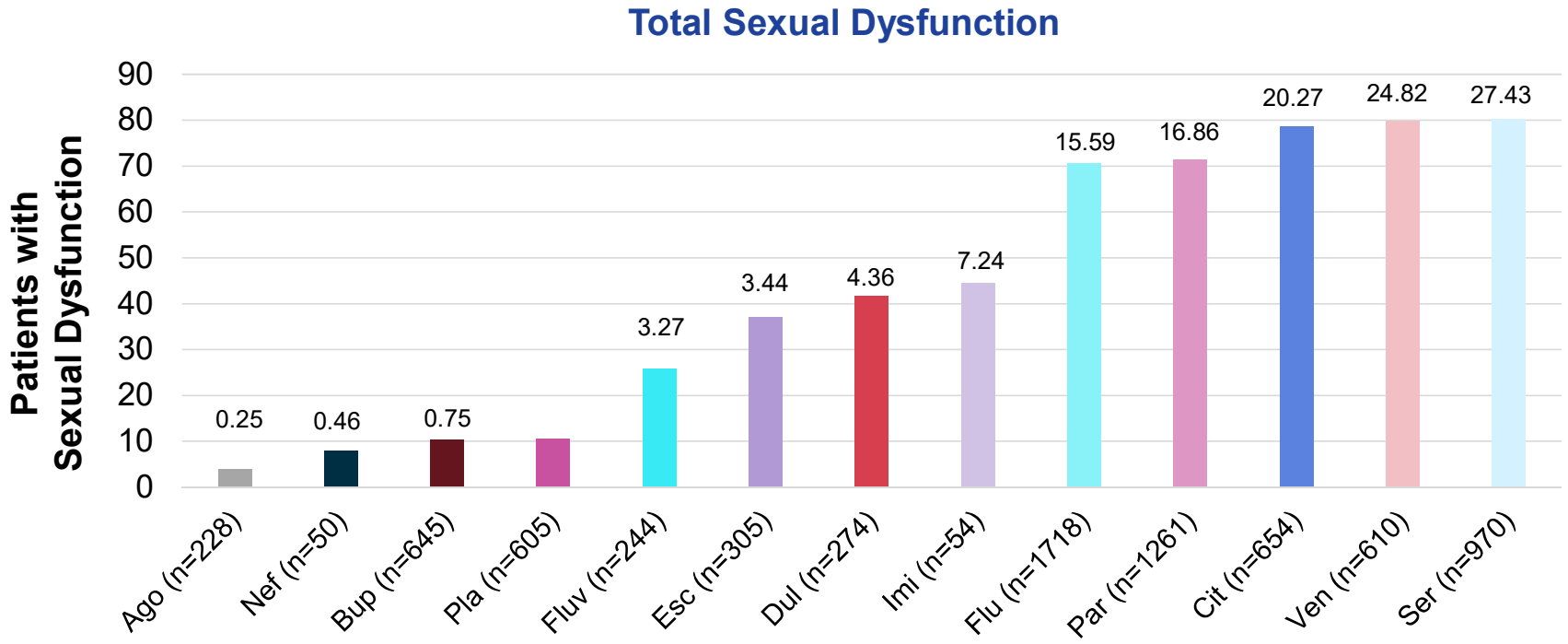
Simon GE, et al. *Gen Hosp Psychiatry*. 2008;30(1):32-39. Pan A, et al. *Int J Obes*. 2012:36(4):595-602.

Weight Change during Antidepressant Treatment



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

Prevalence of Antidepressant-Associated Sexual Dysfunction



Total Sexual Dysfunction Rates for Commonly Prescribed Antidepressants. (Numbers above the bars indicate odds ratios vs placebo).
Ago = agomelatine; Nef = nefazodone; Bup = bupropion; Pla = placebo; Fluv = fluvoxamine; Esc = escitalopram; Dul = duloxetine; Imi = imipramine; Flu = fluoxetine; Par = paroxetine; Cit = citalopram; Ven = venlafaxine; Ser = sertraline.
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%)

Discontinuation lifetime (60%) due to lack of efficacy

N=344; **Most wanted improvements to help adherence**

Ashton AK, et al. *Curr Ther Res Clin Exp*. 2005;66(2):96-106.

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**?					

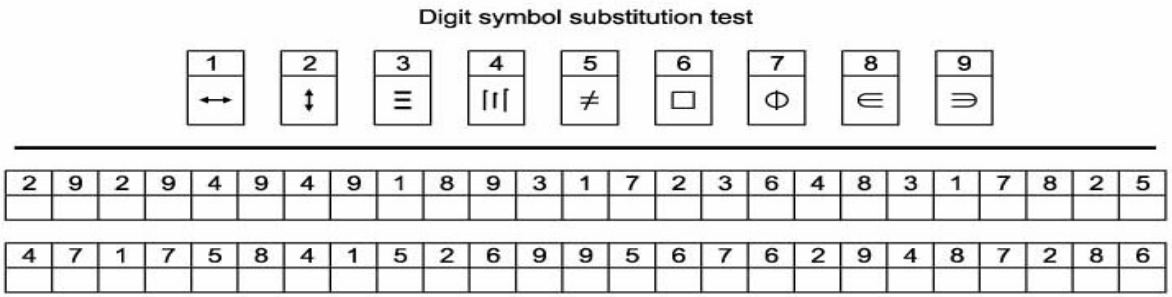
Mahableshwarkar AR, et al. *Neuropsychopharmacology*. 2015;40(8):2025-2037. The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee. MSQLI: A User's Manual. (1997). www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/MSQLI_-A-User-s-Manual.pdf. Accessed September 18, 2018.

Massachusetts General Hospital
Cognitive and Physical Functioning Questionnaire (CPFQ)

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

http://mghcme.org/academy-uploads/CPFQ_Rating_Scale.pdf. Accessed September 18, 2018.

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

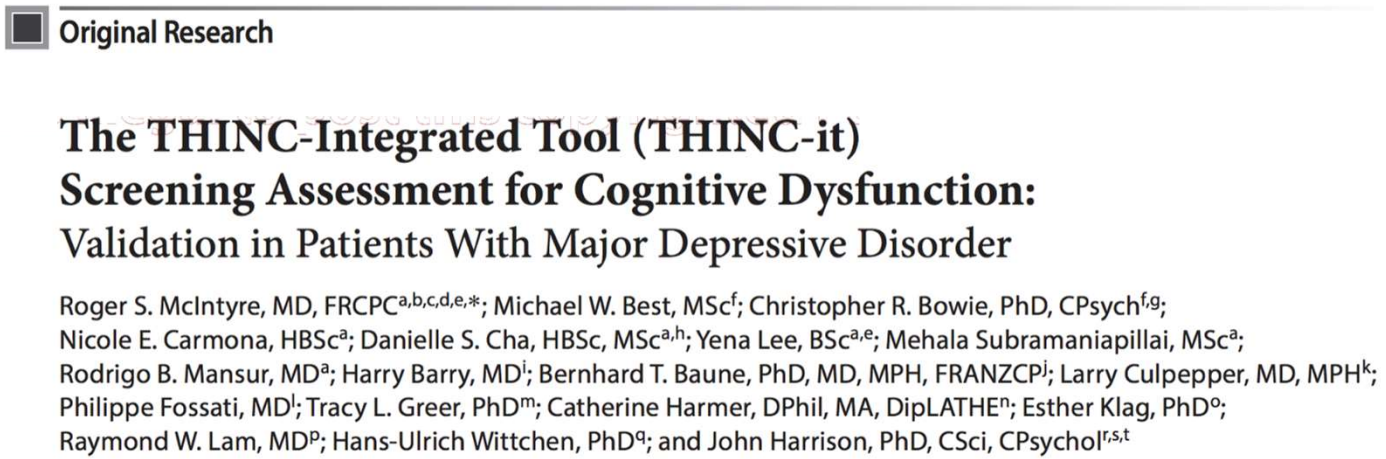


The cognitive domains affected by MDD measured by the DSST

- **EXECUTIVE FUNCTION**
- **PSYCHOMOTOR SPEED**
- **ATTENTION**
- **WORKING MEMORY**

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 September 18, 2018.

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, MD[i]; 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, DipLATHE[n]; Esther Klag, PhD[o]; Raymond W. Lam, MD[p]; Hans-Ulrich Wittchen, PhD[q]; and John Harrison, PhD, CSci, CPsychol[r,s,t]

McIntyre RS, et al. *J Clin Psychiatry*. 2017;78(7):873-881.

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?

5 Least sexual dysfunction
4
3
2
1 Greatest sexual dysfunction

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

Keller A, et al. *J Sex Marital Ther*. 2006;32(1):43-52.

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?

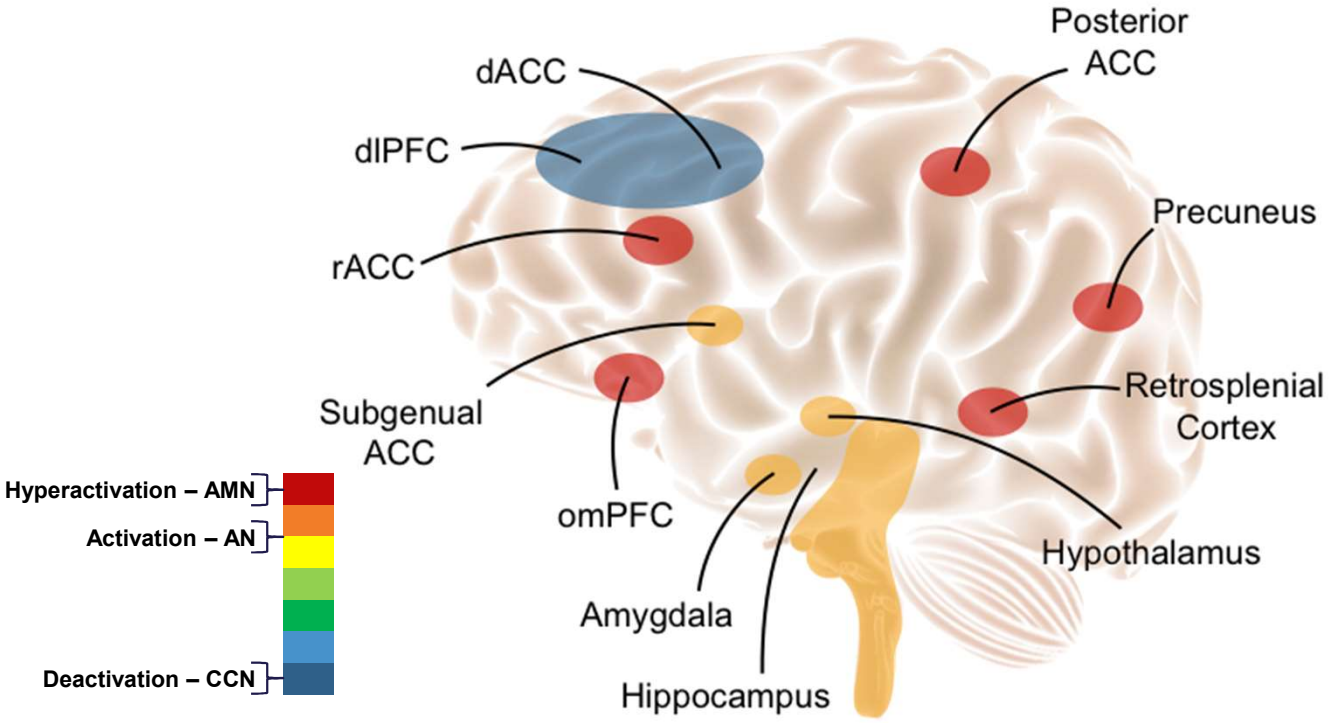
1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

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

Clinical Update:
MDD Pathophysiology and Pharmacotherapy

Inadequate Cognitive Control in Patients with MDD

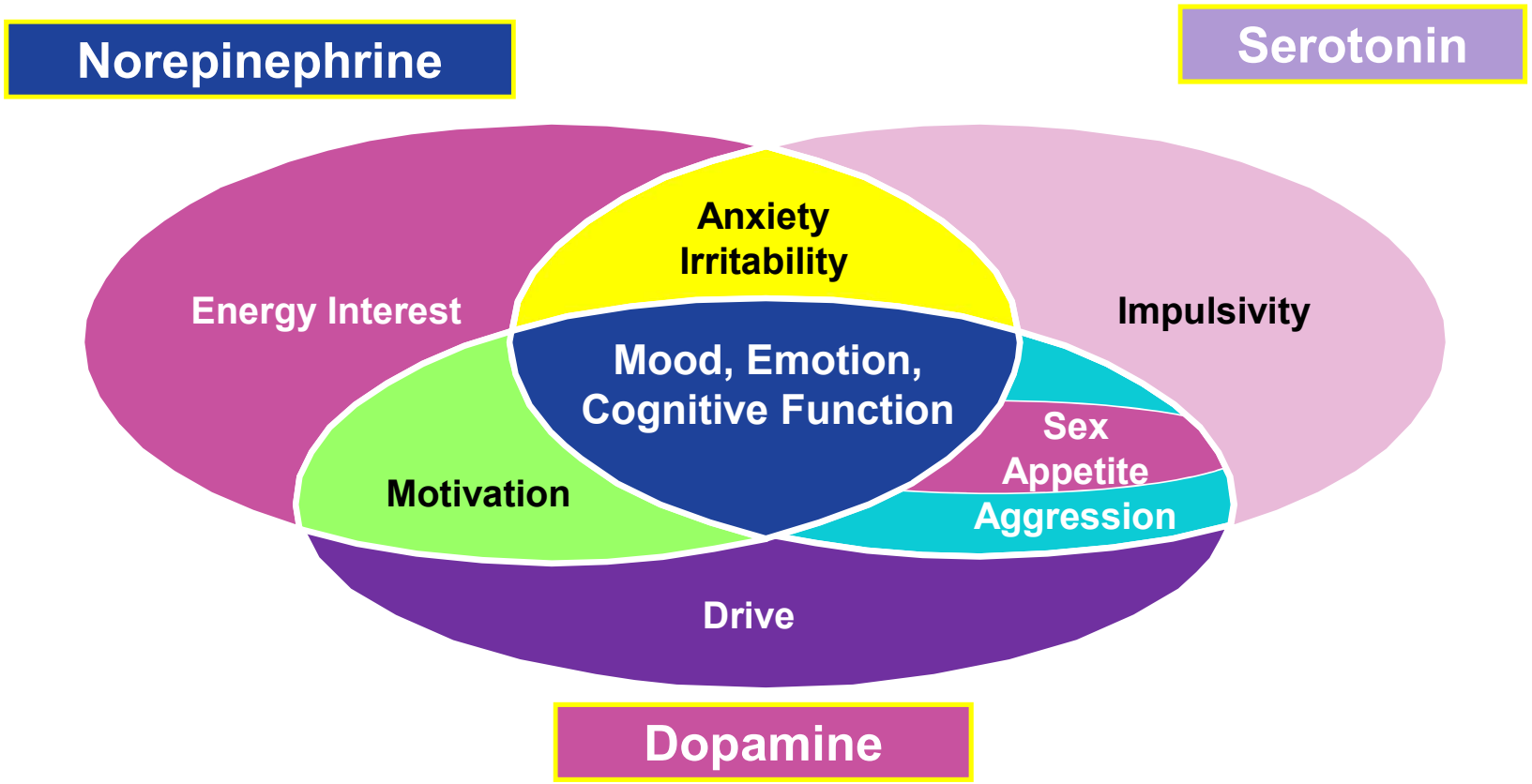
In patients with MDD, the introspective AMN is pathologically engaged (red), suppressing the activation of the CCN (blue) and leading to uninhibited activation of the AN (orange). In the context of maladaptive core beliefs about the self and the world, this gives rise to symptoms of depression such as 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 ACC; dlPFC = dorsolateral prefrontal cortex; omPFC = orbitomesial PFC; rACC = rostral ACC.

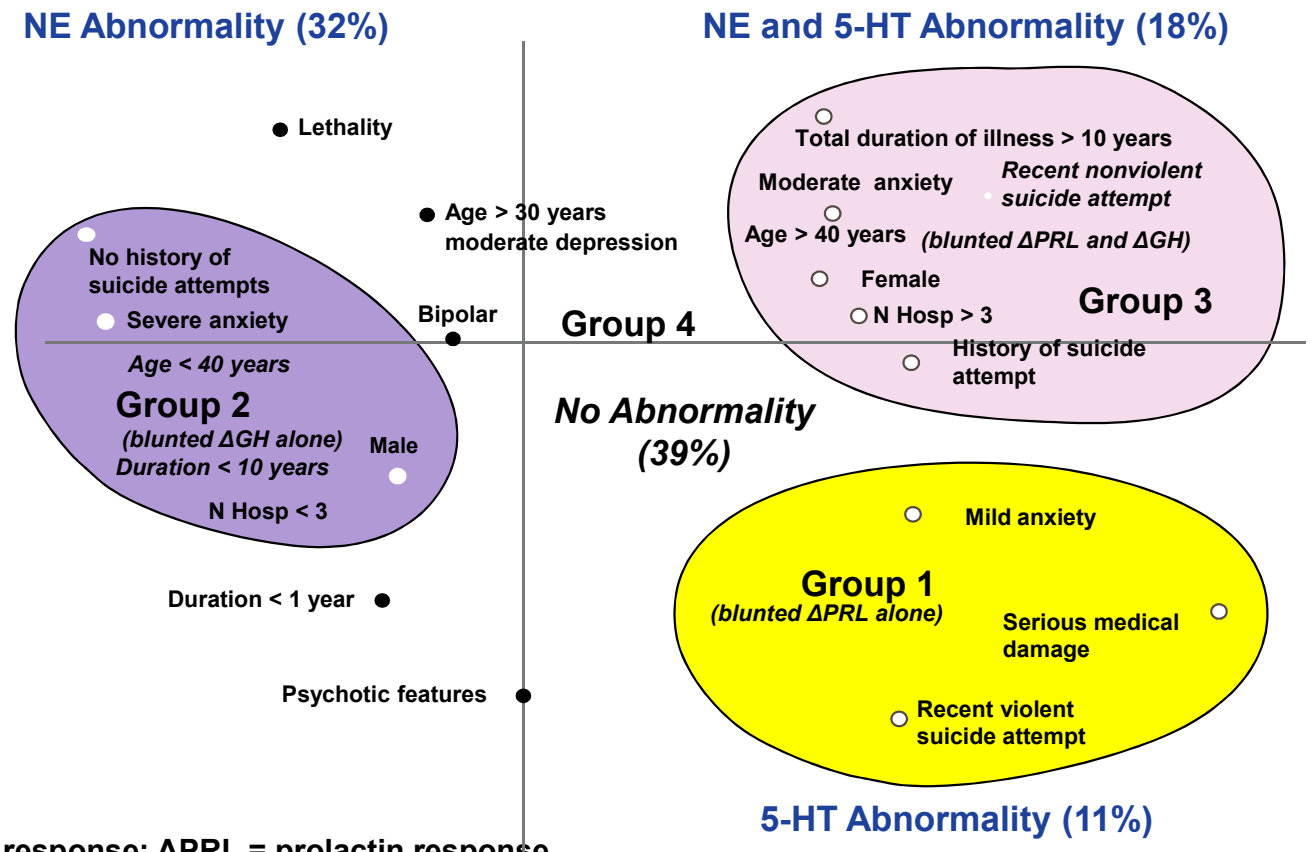
Rayner G, et al. *Neurosci Biobehav Rev*. 2015;61:53-65.

Neurotransmitters Involved in Regulating Mood



Stahl SM. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Second Edition. Cambridge, UK: Cambridge University Press; 2000:152.

Monoamine Dysregulation in MDD

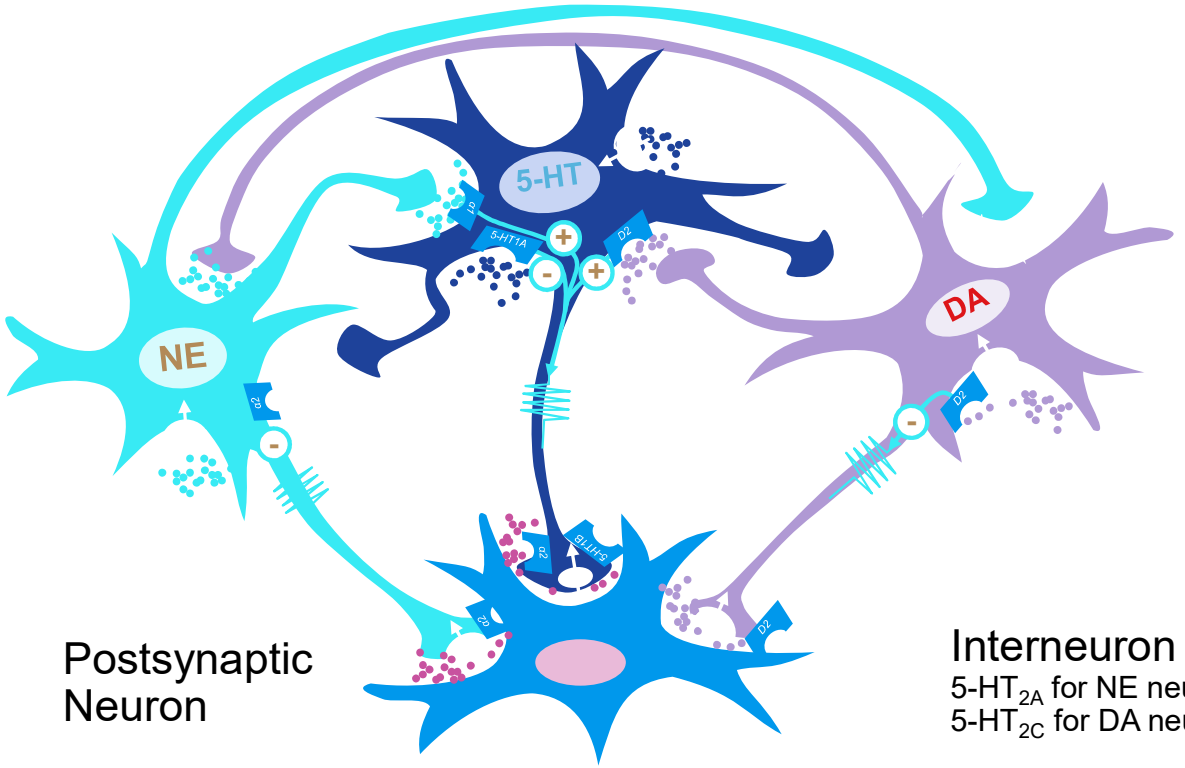


ΔGH = growth hormone response; ΔPRL = prolactin response.

Duval F, et al. *Dialogues Clin Neurosci*. 2000:2(3):299-308.

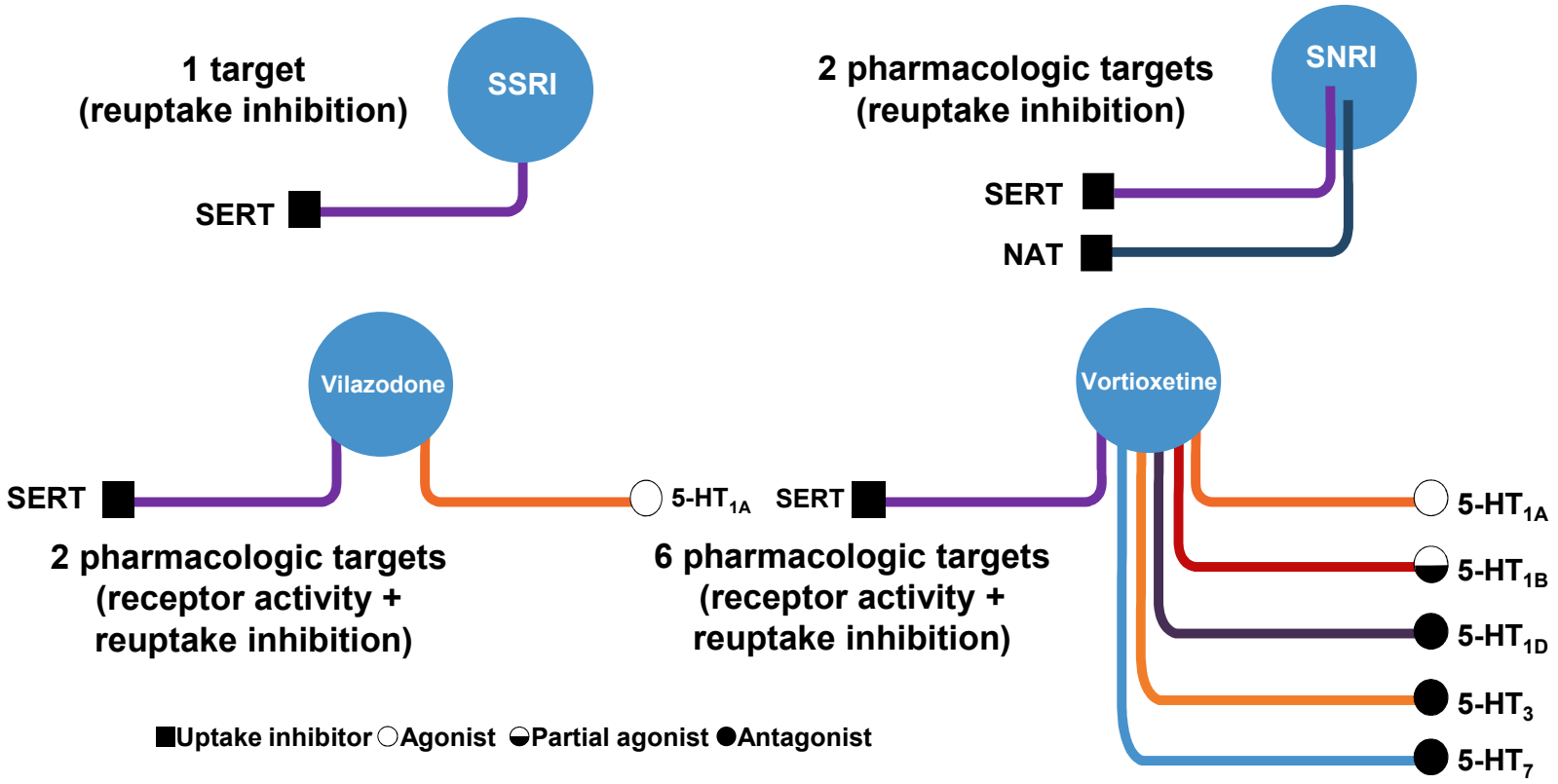
Functional Connectivity across the “Big Three” Monoamine Systems:

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.

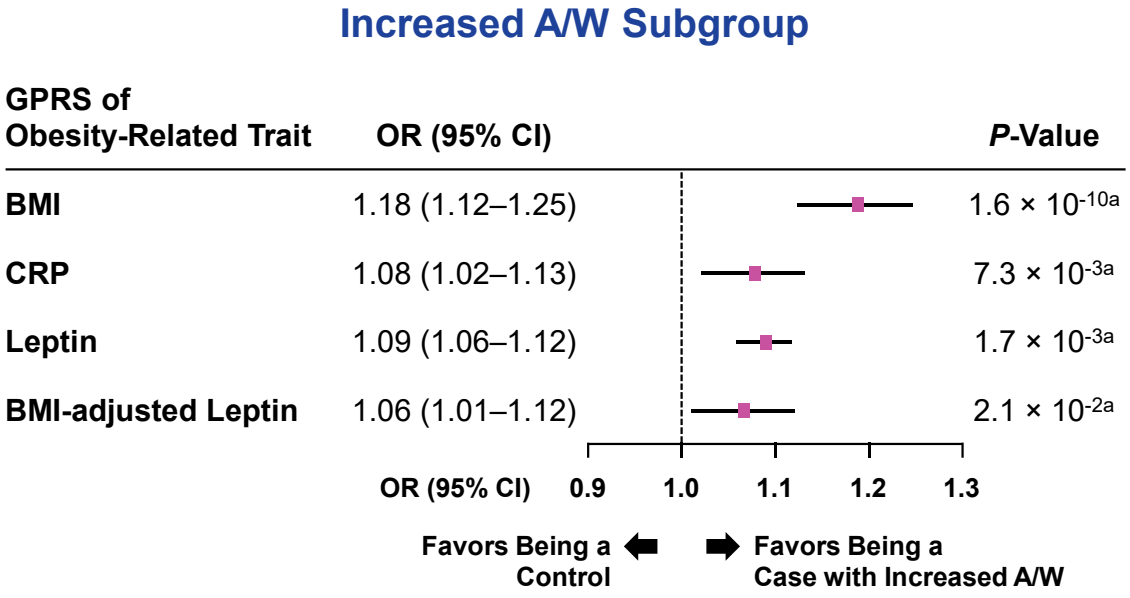
Mechanism of Action of Various Antidepressants

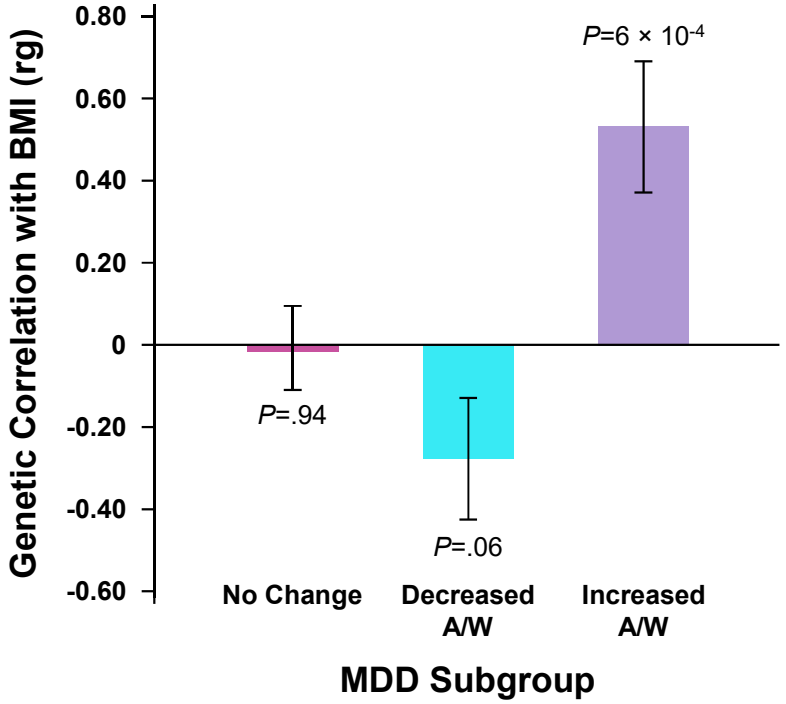


NAT = noradrenaline transporter; SERT = serotonin transporter; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

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

Is there a genetically-based MDD biotype associated with increased inflammation and appetite/weight gain?



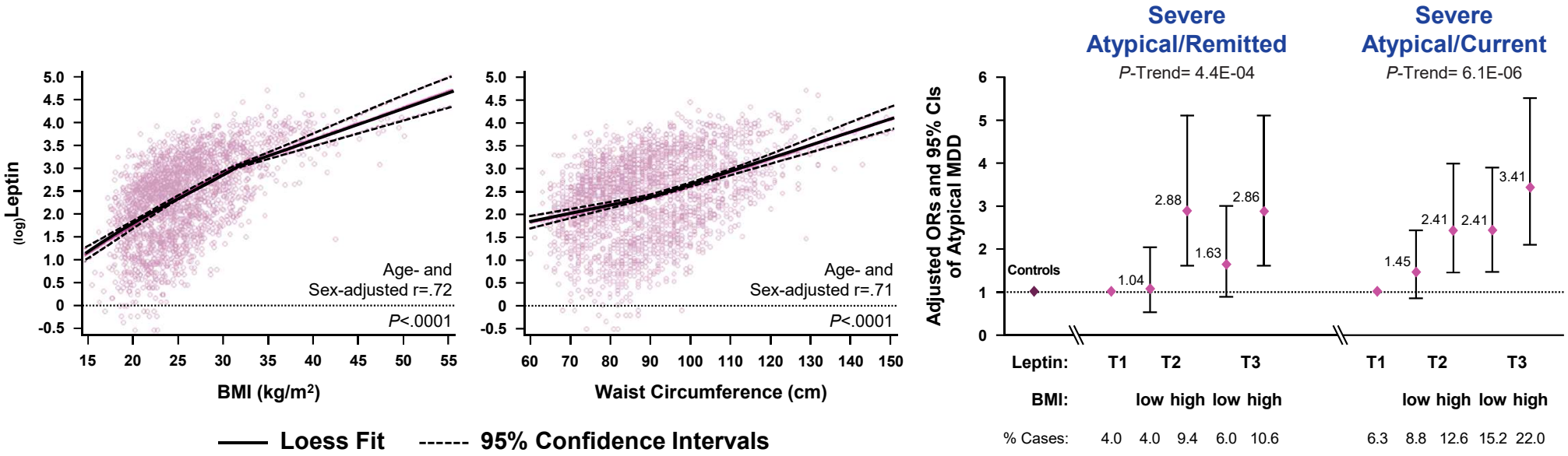


Data included 11,837 participants with MDD and 14,791 control individuals.

A/W = appetite and/or weight symptoms; CRP = C-reactive protein; GPRS = genomic profile risk scores.

Milaneschi Y, et al. *JAMA Psychiatry*. 2017;74(12):1214-1225.

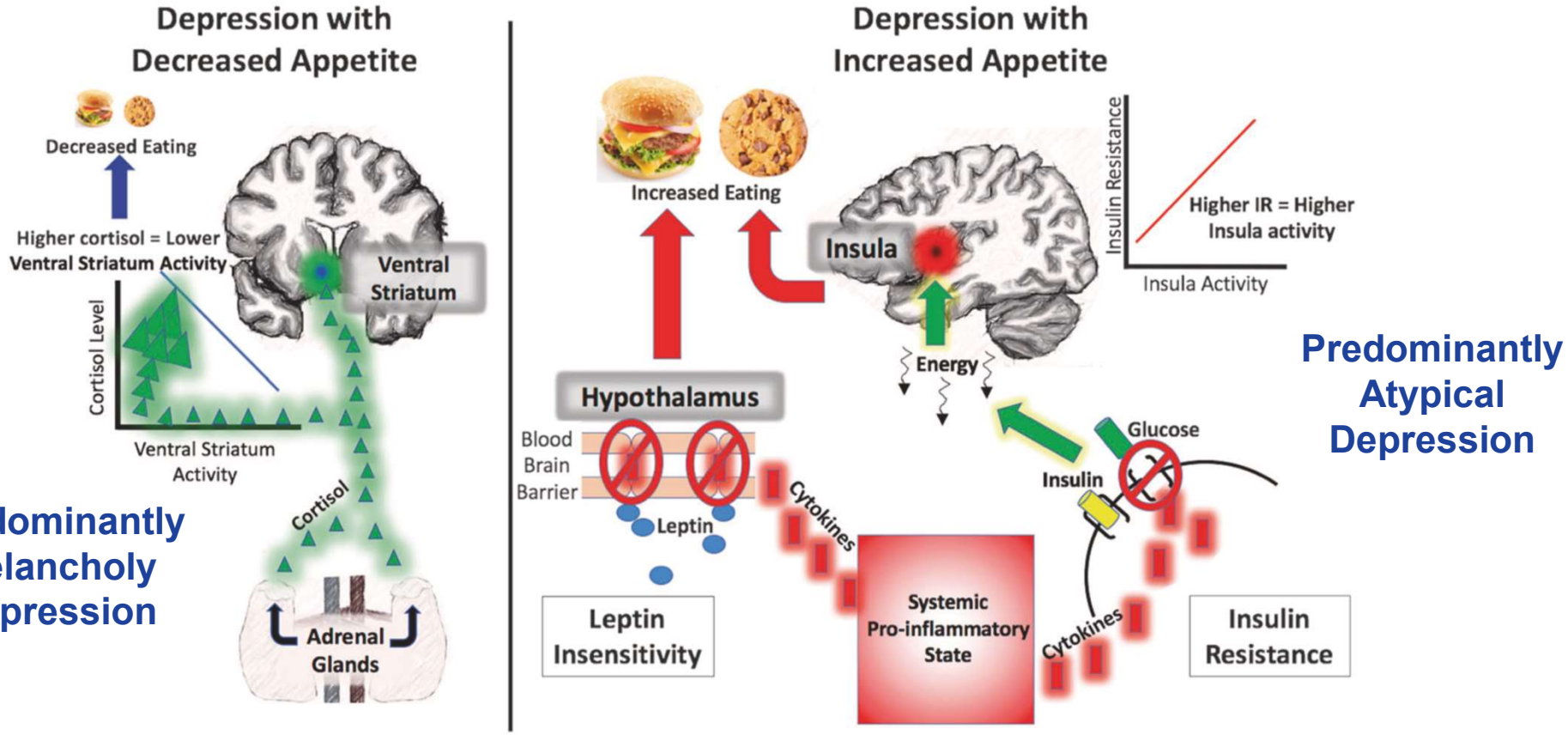
Yes! It is also known as atypical depression.



The sample consisted of participants (aged 18 to 65 years) from the Netherlands Study of Depression and Anxiety with current (n=1062) or remitted (n=711) MDD and healthy control participants (n=497). Diagnoses of MDD and subtypes were based on *DSM-IV* symptoms. Compared to control participants, higher leptin was associated with the atypical MDD subtype both for remitted (n=144, odds ratio = 1.53, 95% confidence interval = 1.16–2.03, *P*=.003) and current (n=270, odds ratio = 1.90, 95% confidence interval = 1.51–2.93, *P*=5.3e–8) cases.

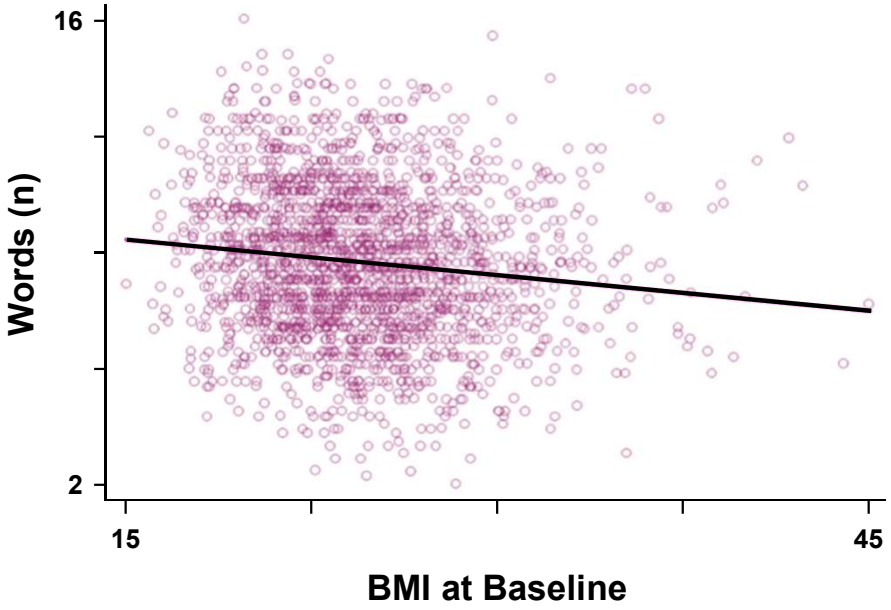
Milaneschi Y, et al. *Biol Psychiatry*. 2017;81(9):807-814.

Appetite changes reveal 2 distinct biotypes of MDD?

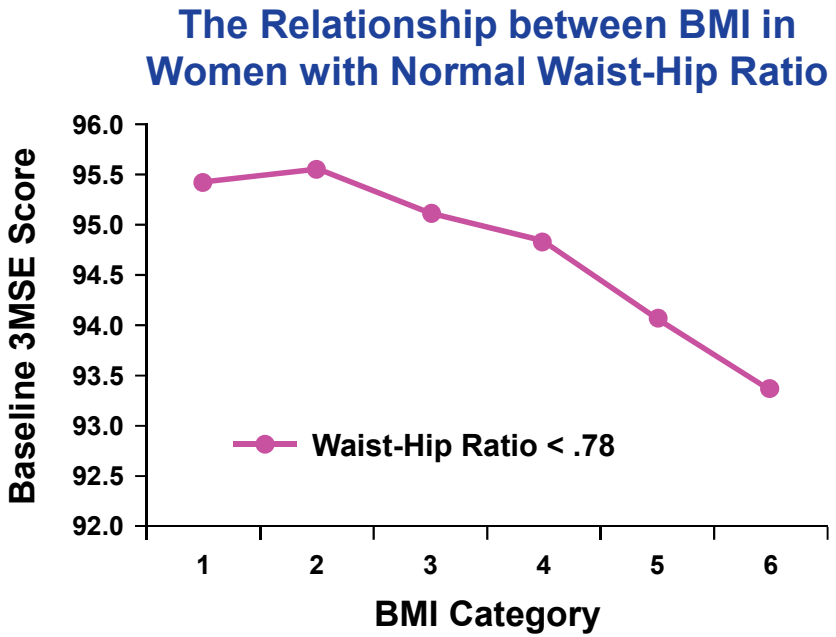


Simmons WK, et al. *Mol Psychiatry*. 2018 Jun 13;[Epub ahead of print].

Relationship between BMI and Cognition



Relationship between BMI and score at the delayed memory recall test at baseline, after adjustment for age, sex, educational level, physical activity, and region of residence.



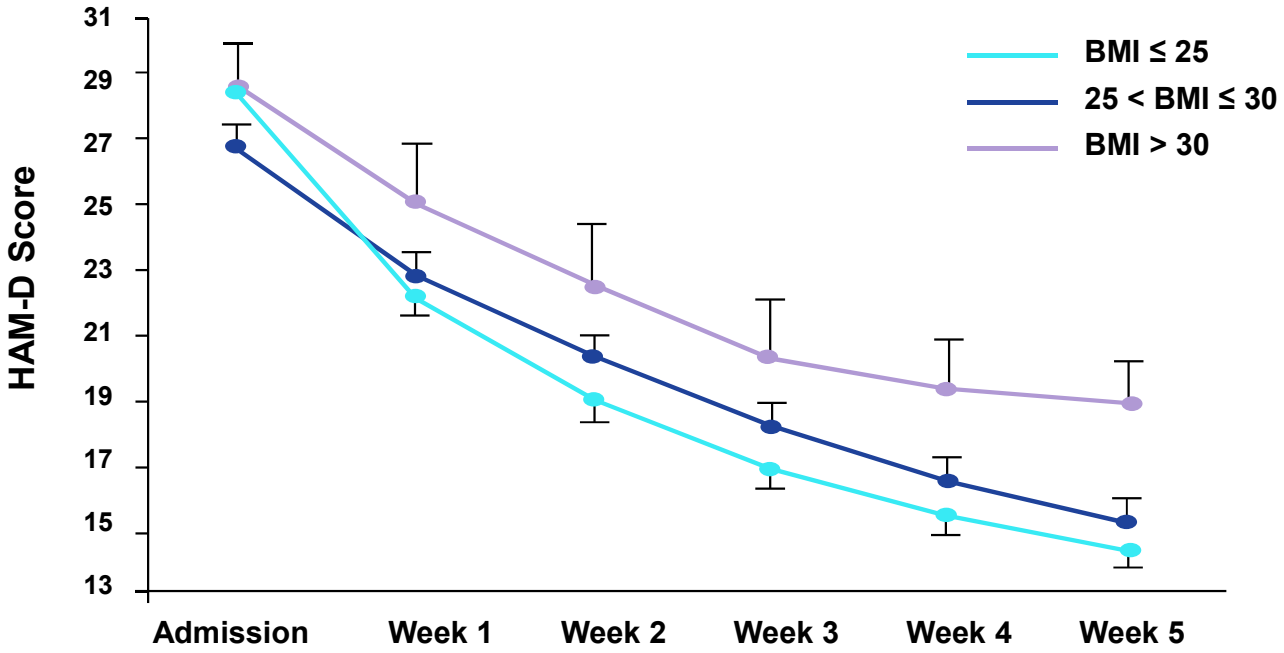
Relationship between BMI and baseline 3MSE score. BMI was inversely related to cognitive function scores after adjusting for age, education, hypertension, heart disease, stroke, and DM.

3MSE = Modified Mini-Mental State Examination; DM = diabetes mellitus.

Cournot M, et al. *Neurology*. 2006;67(7):1208-1214. Kerwin DR, et al. *J Am Geriatr Soc*. 2010;58(8):1427-1432.

BMI Impacts Antidepressant Response

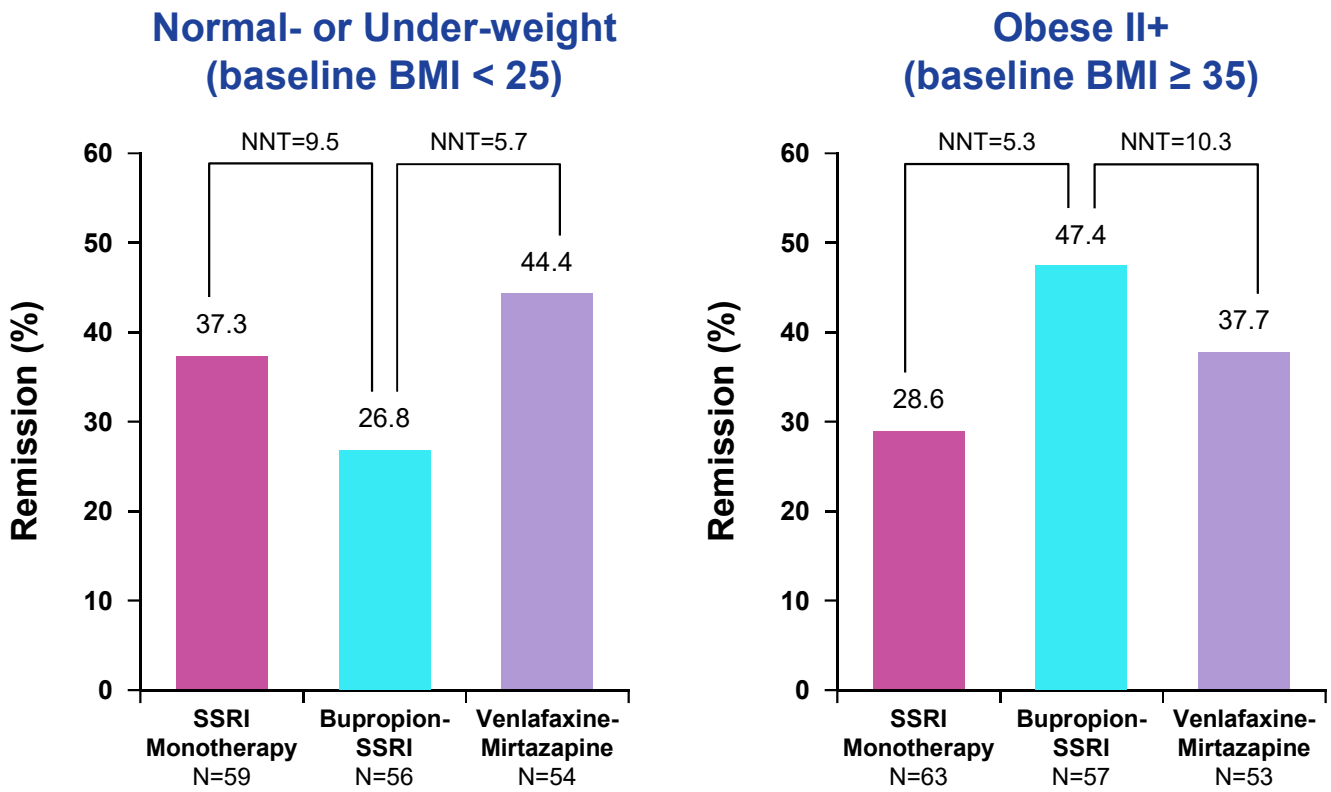
- Response to antidepressant treatment according to weight status
- Mean HAM-D rating scores and SEMs for 5 weeks after hospitalization



Kloiber S, et al. *Biol Psychiatry*. 2007;62(4):321-326.

BMI May Influence the Response and Remission Related to Different Classes of Antidepressants

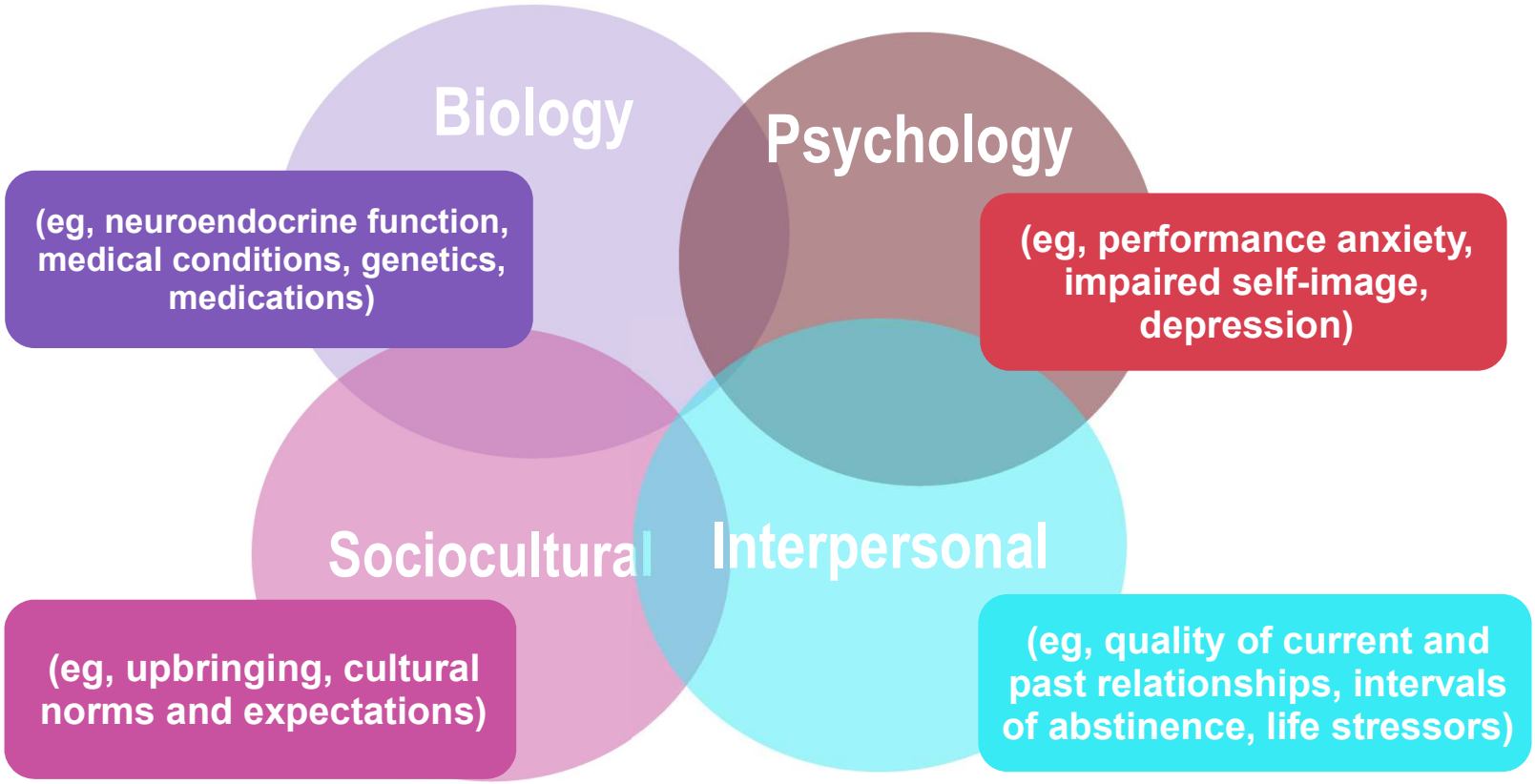
Remission rates in normal- or under-weight and obese II+ participants of CO-MED trial.



CO-MED = Combining Medications to Enhance Depression Outcomes; NNT = number needed to treat.

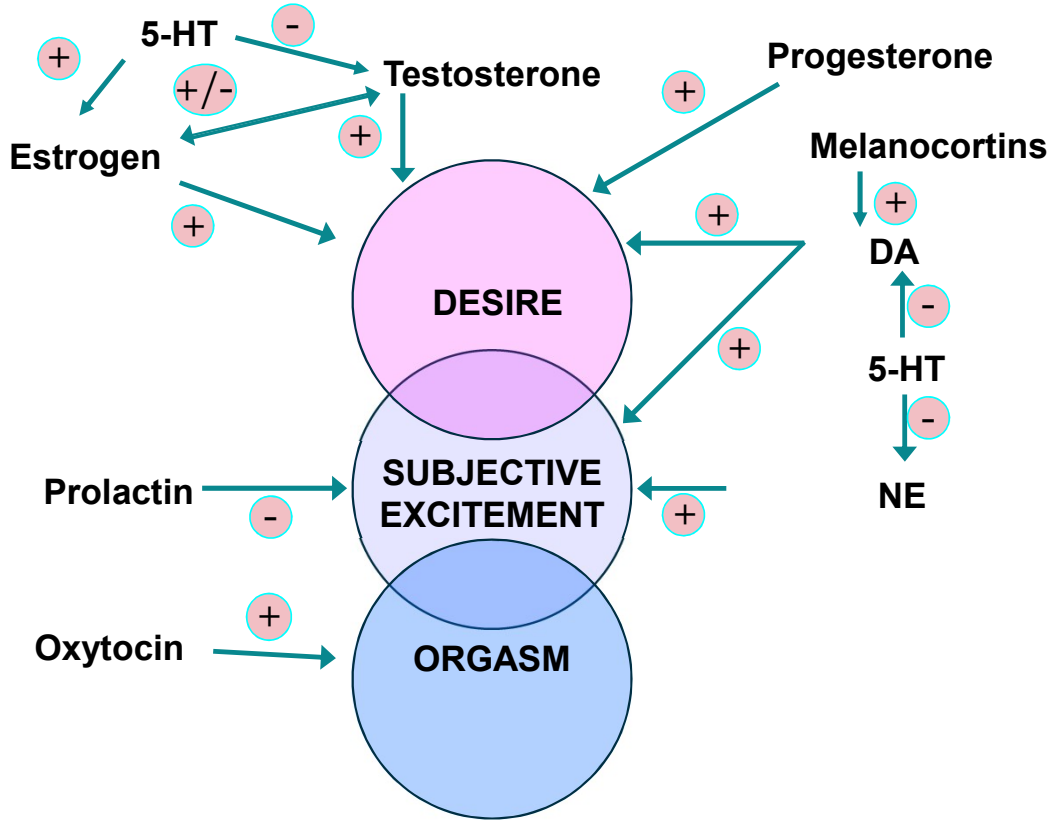
Jha MK, et al. *J Affect Disord*. 2018;234:34-37.

Biopsychosocial Model of Sexual Response



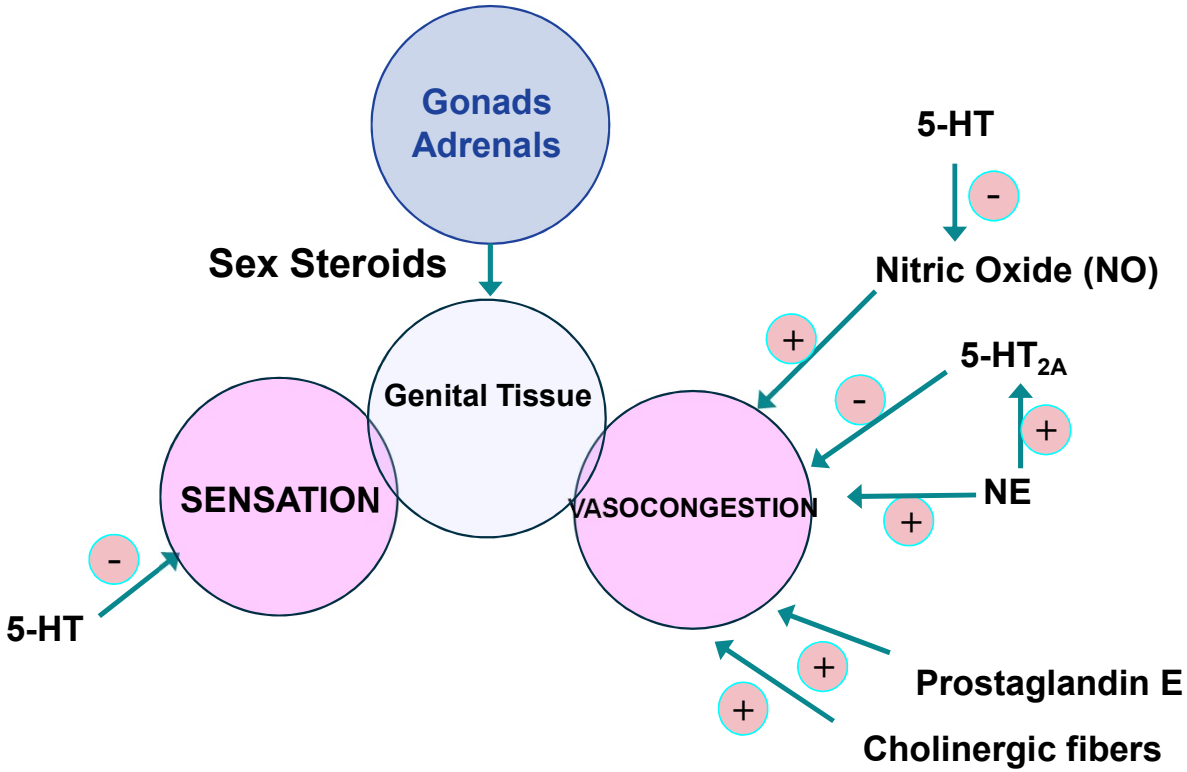
Althof SE, et al. *J Sex Med*. 2005;2(6):793-800. Rosen RC, et al. *Obstet Gynecol Clin North Am*. 2006;33(4):515-526.

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 September 7, 2018.

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
- Few negative effects on sexual function with bupropion-SR, mirtazapine, nefazodone, selegiline transdermal system, reboxetine, duloxetine, desvenlafaxine, vilazodone, vortioxetine, agomelatine
- 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

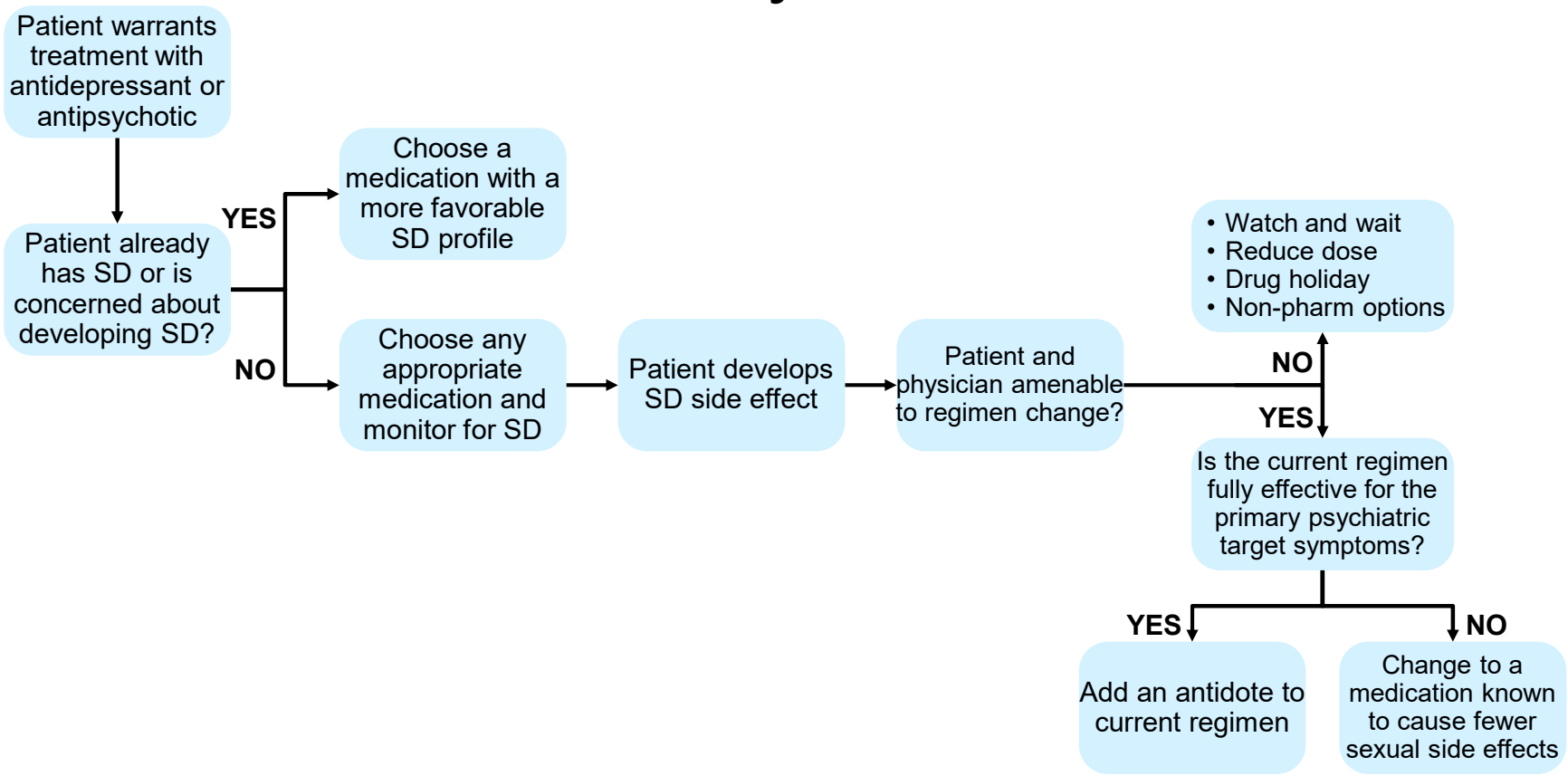
Clayton AH, et al. *Int Clin Psychopharmacol*. 2015;30(4):216-223. Jacobsen PL, et al. *CNS Spectr*. 2016;21(5):367-378. Jacobsen PL, et al. *J Sex Med*. 2015;12(10):2036-2048. Clayton AH, et al. *Int Clin Psychopharmacol*. 2017;32(1):27-35. Jacobsen PL et al. Paroxetine, but not vortioxetine, impairs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

Other Psychiatric Medications Affecting Sexual Function

- Antipsychotic medications with lower rates of sexual dysfunction:
  - D_2 antagonist-partial agonist effects and/or 5-HT_2 antagonism, eg, aripiprazole, quetiapine, brexpiprazole, ziprasidone, olanzapine, lurasidone
  - 5-HT_{1A} agonists like aripiprazole, brexpiprazole, cariprazine, lurasidone
- Other negative effects of antipsychotics related to postsynaptic dopamine blockade and elevated prolactin (eg, risperidone, paliperidone), α1 receptor antagonism (priapism), perhaps cholinergic antagonism (arousal), persistent psychosis
- Decreasing impact on sexual function: thioridazine (60%), risperidone, clozapine (?), haloperidol, olanzapine, ziprasidone, quetiapine (16%), lurasidone (?), aripiprazole

Montejo AL, et al. *J Sex Med*. 2010;7(10):3404-3413. Park YW, et al. *World J Mens Health*. 2012;30(3):153-159. Serretti A, et al. *J Clin Psychiatry*. 2010;71(10):1259-1272. Clayton A, et al. *J Clin Psychiatry*. In press. de Boer MK, et al. *Schizophr Bull*. 2015;41(3):674-686.

Algorithm to Manage Treatment-Emergent Sexual Dysfunction



Clayton AH, et al. *Psychiatr Clin North Am*. 2016;39(3):427-463.

Role of Other Neurotransmitters and Signaling Pathways

Influence of Existing Antidepressant Treatments on Cognition, Weight, and Sexual Function

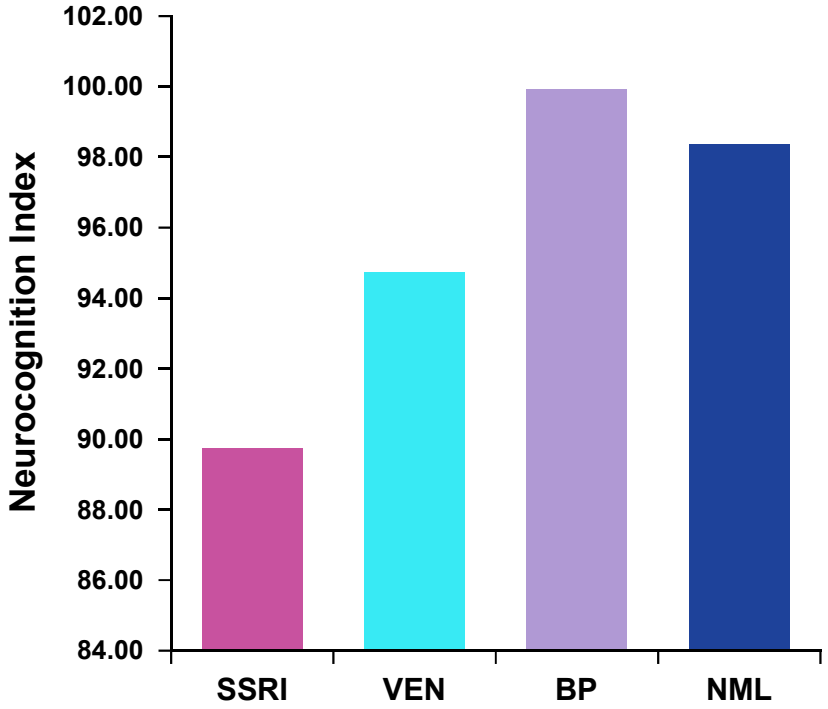
- The impact of newer medications, modulating $GABA_A$ receptors (neurosteroids), opioid receptors, glutamate receptors, glycine signaling, sigma receptors, and inflammatory signaling on cognition, weight, and sexual function has not been systematically studied using validated instruments
- MOA of medications in development suggests specific study of sexual functioning for $GABA_A$ modulators/neurosteroids (eg, brexanolone), glutamate (NMDA) antagonists (eg, [es]ketamine), κ-/μ-opioid antagonists target disrupted reward circuitry (eg, buprenorphine/samidorphan), etc.
- Most of the data available in public domain reflect short-term study outcomes and spontaneous reports of adverse reactions
- Many of the newer agents have been studied as acute adjunctive treatment (mostly combined with SSRIs and SNRIs), making it difficult to determine their specific long-term adverse reaction profile

GABA = gamma-amino butyric acid; MOA = mechanism of action; NMDA = N-methyl-D-aspartate.

Dale E, et al. *Biochem Pharmacol*. 2015;95(2):81-97.

Antidepressants Have a Differential Impact on Cognition in Patients with MDD

- N=81 patients with MDD were treated with a stable dose of medication for at least 4 weeks (bupropion=27; venlafaxine=27; SSRIs=27). N=27 controls were randomly selected from the CNS Vital Signs normal database
- Patients were tested with the CNS Vital Signs (CNSVS) battery at the North Carolina Neuropsychiatry Clinics
- CNSVS is a PC-based neurocognitive screening battery that comprises 7 familiar neuropsychological tests: verbal memory (VBM); visual memory (VIM); finger tapping (FTT); symbol-digit coding (SDC); the Stroop test (ST); the shifting attention test (SAT); and the continuous performance test (CPT)

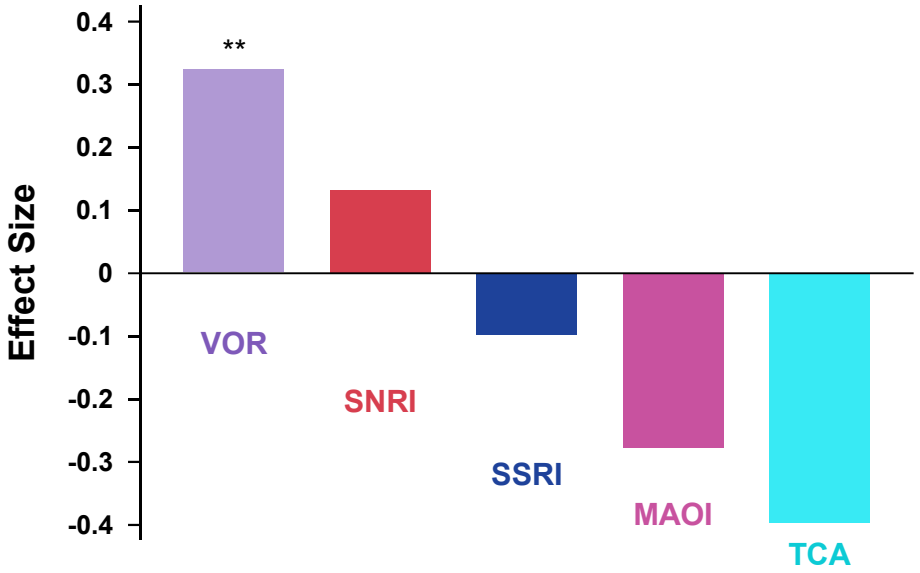


The SSRI group scored significantly below controls in tests of psychomotor speed, cognitive flexibility, and reaction time. The venlafaxine group scored more poorly than controls in reaction time, a measure of information processing speed derived from the Stroop test. The bupropion group did not differ from controls in any of the cognitive domains.

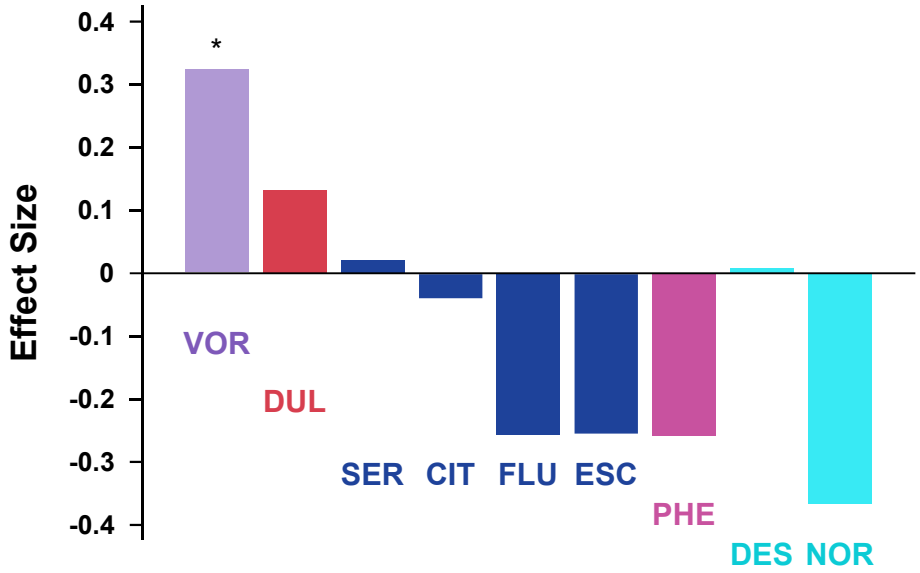
Gualtieri CT, et al. *MedGenMed*. 2007;9(1):22.

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



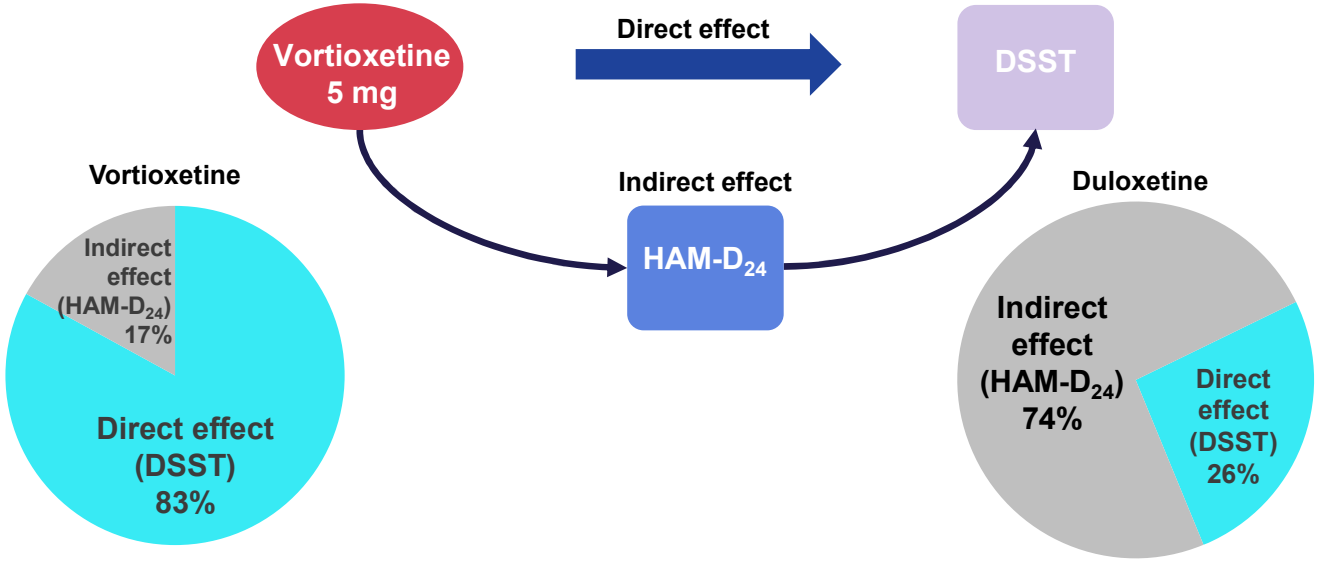
As of May 2018, US Prescribing Information for vortioxetine shows data on a positive effect on processing speed, an aspect of cognitive function that is impaired in many patients with MDD.

****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.

Effects on Cognitive Function Cannot Be Solely Explained by Improvements in Mood

Path analysis showed that in addition to improving cognitive function indirectly through the alleviation of depressive symptoms, vortioxetine exerts direct effects on depression-related cognitive impairments as measured by patient performance in relevant tests (DSST).



On RAVLT acquisition, vortioxetine had a 71% direct effect & duloxetine 65%
On RAVLT delayed recall, vortioxetine had a 72% direct effect & duloxetine 66%

Duloxetine was included as active reference for study validation, not for comparison of effect sizes. RAVLT = Rey Auditory Verbal Learning Test.

Katona C, et al. *Int Clin Psychopharmacol*. 2012;27(4):215-223.

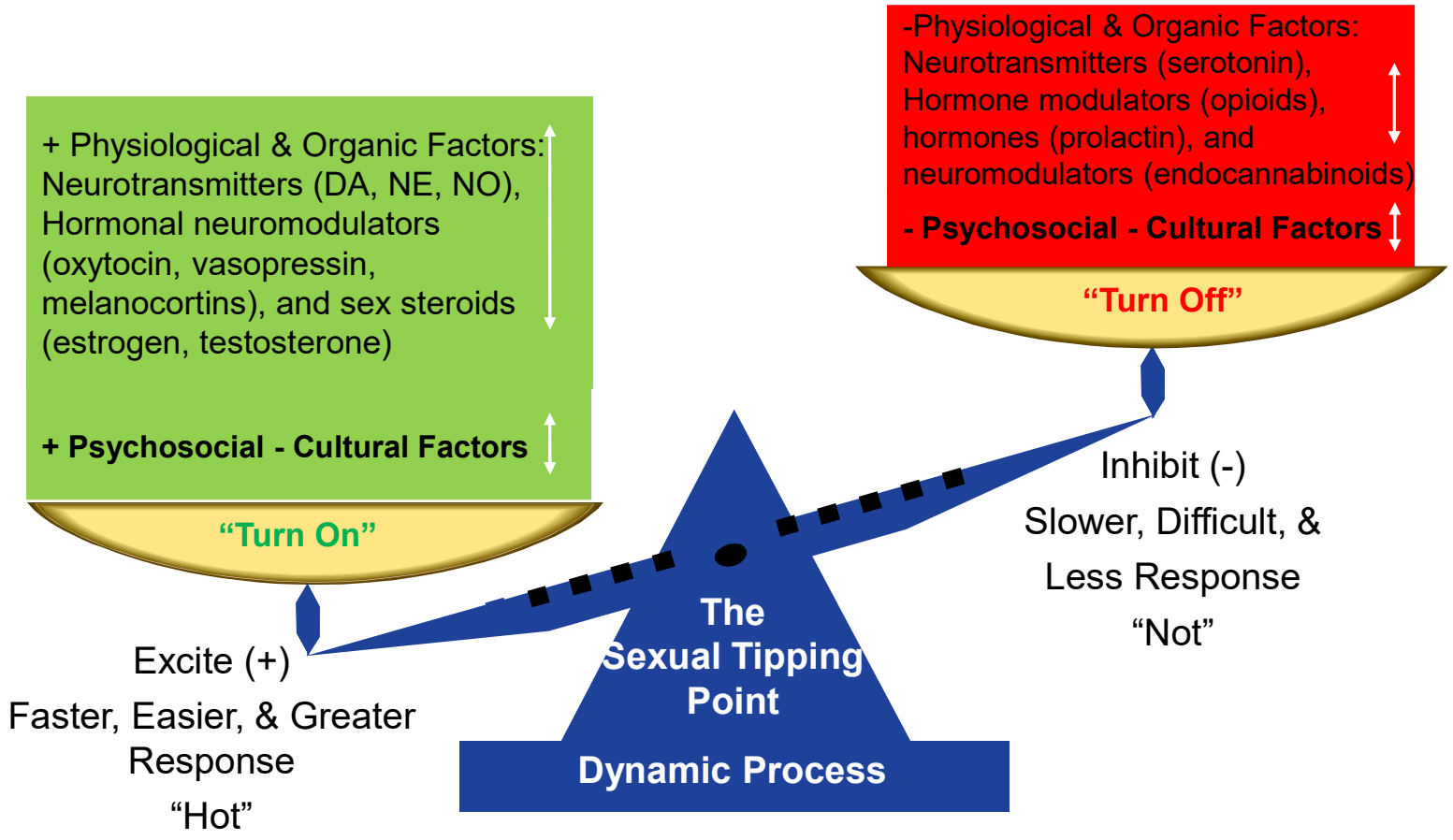
Examining the Evidence for Direct Impact on Cognitive Symptoms in MDD

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

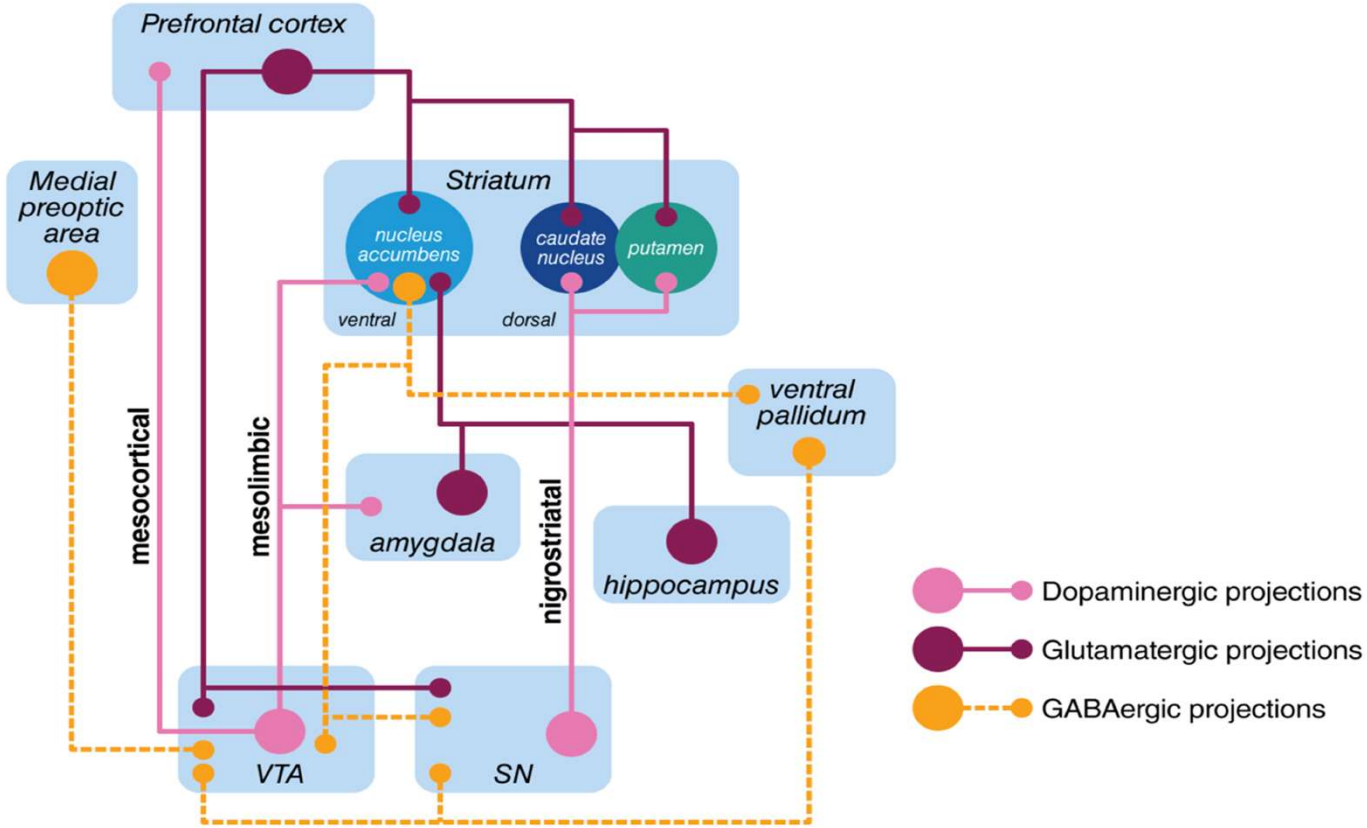
Independent effect indicated by a priori specification, cognition as primary; pathoanalysis; subgroup analysis in nonresponders and nonremitters.
Level 1 replicated placebo-controlled trial evidence with demonstration of independent effect.
Level 2 single placebo-controlled trial evidence with demonstration 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.

Excitation vs Inhibition



Adapted from: Perelman MA. In: Balon R, et al (Eds). *Handbook of Sexual Dysfunction*. Boca Raton, FL: Taylor & Francis Group; 2005.

Sexual Reward Circuitry



VTA = ventral tegmental area; SN = substantia nigra.

Kingsberg SA, et al. *CNS Drugs*. 2015;29(11):915-933. Clayton AH, et al. The neurobiology and efficacy of bremelanotide in HSDD. *J Sex Med*. 2017;14(2 Suppl):e95.

Imaging and Antidepressant-Associated Sexual Dysfunction

Brain Activation Area	Effect	PAR vs PLA	BUP vs PLA	BUP vs PAR
ACC	Emotional and autonomic components of erotic stimulation	↓		↑
Subgenual ACC	Autonomic/physiologic readiness	↓		↑
Pregenual ACC	Sexual intensity; hedonism	↓		↑
Anterior MCC	Reward processing; fear	↓	↓	
Posterior MCC	Detect complicated error	↓	↑	↑
Midbrain structures		↓		↑
Nucleus accumbens, ventral striatum	Motivational processing	↓		↑
Amygdala, thalamus, parahippocampus			↑	↑

18 men received 20 mg/day paroxetine, 150 mg/day bupropion or placebo × 7 days separated by 1 week washout in random cross-over design. Viewed erotic and non-erotic stimulus. Erotic video on placebo activated ACC, amygdala, and hypothalamus (*P*<.05).

PAR = paroxetine; PLA = placebo; BUP = bupropion; MCC = midcingulate cortex.

Abler B, et al. *Neuropsychopharmacology*. 2011;36(9):1837-1847.

Mrs. Robinson

Case Presentation

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- 47-year-old married female
- PCP referral for treatment of depression
- Patient self-reports history of several failed past treatment attempts with antidepressants

PCP = primary care physician.

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

History of Present Illness

- Gradual worsening depression over the past 3 months
- Chronic low mood (worse in the evening)
- Frequent bouts of crying when alone
- Moderate anxiety with occasional panic attacks when required to socialize
- Mid-nocturnal and early morning awakening
- Daytime fatigue and difficulty initiating tasks

Mrs. Robinson

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

PHQ-9 = Patient Health Questionnaire 9-item.

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

Past Psychiatric/Medical History

- Bulimia, 18–22 years of age, in remission
- MDD with approximately 5 episodes
  - Initial depressive episode coincided with birth of first child at age 25
  - Symptom presentation was similar to current episode
- Irregular menses with decreased duration and flow in past year
- Multiple selective SSRIs and SNRIs have been tried
  - None helped *"more than 50%"* but better than nothing
  - Escitalopram was the most effective
- Patient discontinued medications between her depressive episodes
  - She has suffered from moderate chronic anxiety between MDE
- No significant medical history

MDE = major depressive episode.

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

Social History

- Married
  - States she and her husband live separate lives and stay together only *"for convenience"*
- Couple has 2 grown children
- She has been working as an executive secretary for more than 2 decades at same company
- Reports moderate social drinking
  - 3–4 drinks per week
- Denies illicit drug use

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- After comprehensive discussion of treatment options, Mrs. Robinson expressed no interest in psychotherapy
- Escitalopram was initiated at 10 mg/day

Mrs. Robinson

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 escitalopram
  - PHQ-9 = 16

At this point, the most appropriate course of action would be to:

1. Agree to discontinue the escitalopram immediately and observe patient for worsening
2. Convince the patient to try a different antidepressant that might work better
3. Empathically explore why the patient wants to stop an antidepressant that appears to have been working prior to the last 2 weeks
4. Review in detail how the patient is taking her antidepressant
5. 3 and 4

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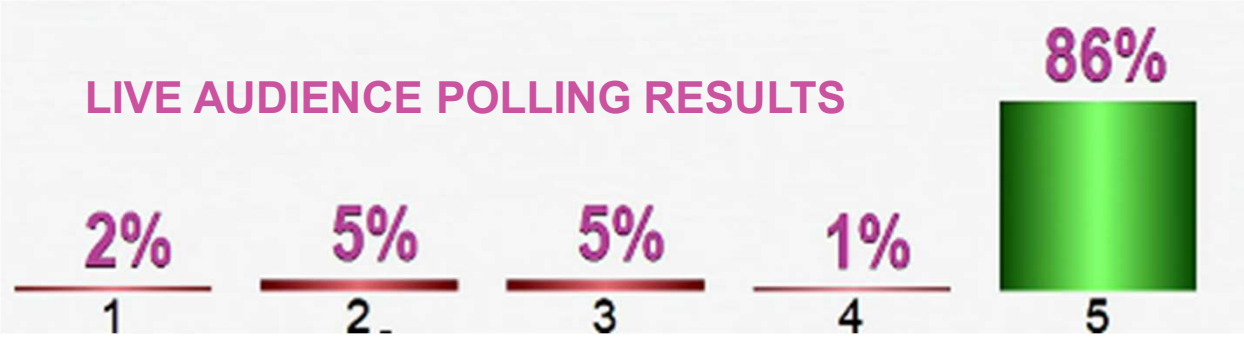

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- Is she taking her escitalopram?
  - Evasive in response
  - Admits she stopped medication 2 weeks ago
- Is she experiencing side effects?
  - She looks down and says, *"I don't know how to talk about it, but the meds take away my ability to enjoy myself. That's why I've always stopped taking them—I've just always been too embarrassed to mention this."*

At this point, the most appropriate course of action would be to:

1. Emphasize to the patient that the clinical benefits from the antidepressant more than compensate for the loss of sexual function
2. Discontinue escitalopram and switch patient to an antidepressant with fewer sexual side effects
3. Explore more deeply with the patient the nature of the sexual dysfunction she is experiencing and discuss potential treatment alternatives
4. All of the above

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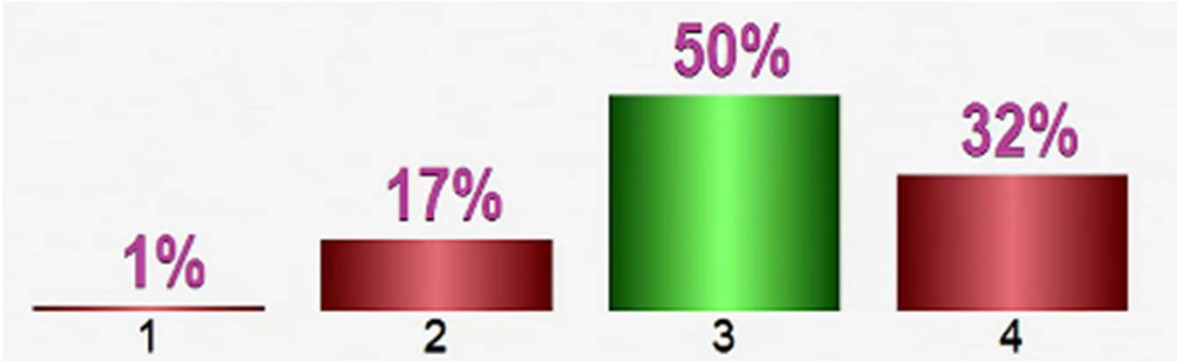
LIVE AUDIENCE POLLING RESULTS



Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- Interest in sex was already decreased from depression
  - SSRI made her unable to have an orgasm
- On a clinical hunch you make an open-ended comment about her telling you at the first meeting that she no longer had an intimate relationship with her husband
  - Places her head in her hands and sobs
  - Extramarital affair
    - A younger lover unwilling to leave his wife
  - Prompted current depressive episode
  - Fearful about him abandoning her, worried about weight gain
  - Guilt that she is not meeting his needs

At this point, the most appropriate course of action would be to:

1. Tell the patient that if she discontinues her extramarital affair her depression will resolve
2. Explore with her potential connections between her extramarital affair and her depressive relapse
3. Do not address her psychosocial situation and recommend she restart escitalopram and add bupropion to diminish sexual side effects
4. Discuss with patient what is known about options for minimizing sexual side effects during pharmacologic treatment of depression
5. 2 and 4

At this point, the most appropriate course of action would be to:

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4. Discuss with patient what is known about options for minimizing sexual side effects during pharmacologic treatment of depression
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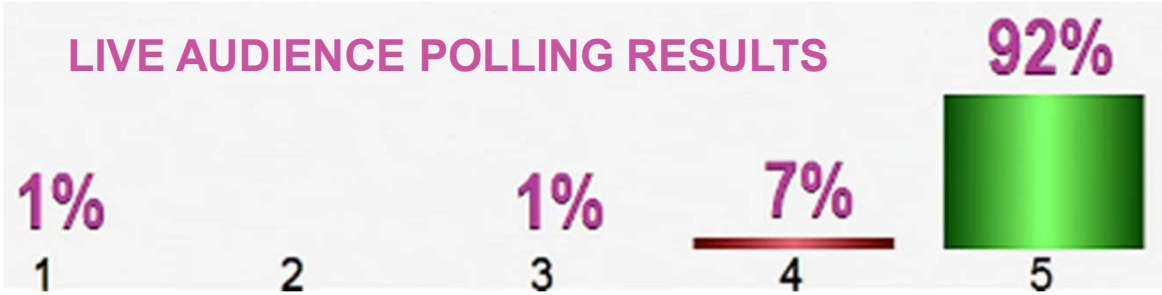

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- Upon discussion of alternative treatments, Mrs. Robinson continues to express reluctance to engage in individual psychotherapy. *"It is all too embarrassing. I don't want to unload this mess on a stranger."*
- Patient did express some interest in trying a new MMA
- *"Is it going to make me heavy or give me sexual side effects? I will tell you upfront, I would rather stay depressed than take medicine that will cause more problems in my life."*
- Based on her past history of SSRI intolerance due to gastrointestinal side effects, decision was made to initiate treatment with the lowest dose of MMA

MMA = multimodal antidepressant.

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- 2 weeks later: Mrs. Robinson called saying that she has experienced only mild nausea, which has resolved but, only minimal improvement in her depressive symptoms. She was asked to increase the dose to mid-range
- Office visit 4 weeks later: Much less crying, denied even passive thoughts of suicide. She still has little initiative and interest in life, sleep is minimally improved
- PHQ-9 = 12
- "*On the good side, I have not noticed any sexual side effects and my appetite is under control.*" "*Can I try a higher dose?*"
- Dose was increased and she was asked to schedule an appointment in 3–4 weeks

Mrs. Robinson

Presentation | History | Treatment | Follow-Up

- Affect is much brighter. Mrs. Robinson 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 changes in her personal life, Mrs. Robinson smiled, responded that it was *“OK”*, and showed no further interest in exploring this topic

That concludes this video webcast.
Thank you for watching!

Make sure you take the post-test and evaluation to claim your credit for participating.