Facing Three of the Greatest Unmet Needs in Major Depression Management:

A Focus on Cognitive Dysfunction, Sexual Dysfunction and Weight Gain

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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.

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

Sadness  Anxiety  Irritability  Lack of enjoyment  Suicidal ideation  Hopelessness  Inappropriate guilt  Fatigue  Eating/weight changes  Insomnia/hypersomnia  Sexual dysfunction  Attention and concentration  Short- and long-term memory  Decision-making  Planning and organization  Mental sharpness  Thinking speed  Judgment  Headaches  Stomach problems  Pain  Psychomotor agitation

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.
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

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).

The Effect Size of Cognitive Impairment in MDD is Significant

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.
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.

Weight Change during Antidepressant Treatment

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.

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

Assessment and Monitoring of Cognitive and Sexual Dysfunction
The Perceived Deficits Questionnaire (PDQ) provides a subjective assessment of cognitive function.

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

Massachusetts General Hospital
Cognitive and Physical Functioning Questionnaire (CPFQ)

1. How has your motivation/interest/enthusiasm been over the past month?
   - 1: greater than normal
   - 2: normal
   - 3: minimally diminished
   - 4: moderately diminished
   - 5: markedly diminished
   - 6: totally absent

2. How has your wakefulness/alertness been over the past month?
   - 1: greater than normal
   - 2: normal
   - 3: minimally diminished
   - 4: moderately diminished
   - 5: markedly diminished
   - 6: totally absent

3. How has your energy been over the past month?
   - 1: greater than normal
   - 2: normal
   - 3: minimally diminished
   - 4: moderately diminished
   - 5: markedly diminished
   - 6: totally absent

4. How has your ability to focus/sustain attention been over the past month?
   - 1: greater than normal
   - 2: normal
   - 3: minimally diminished
   - 4: moderately diminished
   - 5: markedly diminished
   - 6: totally absent

5. How has your ability to remember/recall information been over the past month?
   - 1: greater than normal
   - 2: normal
   - 3: minimally diminished
   - 4: moderately diminished
   - 5: markedly diminished
   - 6: totally absent

6. How has your ability to find words been over the past month?
   - 1: greater than normal
   - 2: normal
   - 3: minimally diminished
   - 4: moderately diminished
   - 5: markedly diminished
   - 6: totally absent

7. How has your sharpness/mental acuity been over the past month?
   - 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

Digit symbol substitution test

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<td>≠</td>
<td>☐</td>
<td>☛</td>
<td>⇓</td>
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</tr>
</tbody>
</table>

2 9 2 9 4 9 4 9 1 8 9 3 1 7 2 3 6 4 8 3 1 7 8 2 5
4 7 1 7 5 8 4 1 5 2 6 9 9 5 6 7 6 2 9 4 8 7 2 8 6

The cognitive domains affected by MDD measured by the DSST

- **Executive Function**
- **Psychomotor Speed**
- **Attention**
- **Working Memory**

THINC-it
Integrated Computerized Cognitive Assessment Tool

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

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

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?

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

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.

Neurotransmitters Involved in Regulating Mood

Monoamine Dysregulation in MDD

ΔGH = growth hormone response; ΔPRL = prolactin response.
Functional Connectivity across the “Big Three” Monoamine Systems: Serotonin, Norepinephrine, and Dopamine

Mechanism of Action of Various Antidepressants

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

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.

<table>
<thead>
<tr>
<th>GPRS of Obesity-Related Trait</th>
<th>OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.18 (1.12–1.25)</td>
<td>1.6 × 10^{-10}a</td>
</tr>
<tr>
<td>CRP</td>
<td>1.08 (1.02–1.13)</td>
<td>7.3 × 10^{-3}a</td>
</tr>
<tr>
<td>Leptin</td>
<td>1.09 (1.06–1.12)</td>
<td>1.7 × 10^{-3}a</td>
</tr>
<tr>
<td>BMI-adjusted Leptin</td>
<td>1.06 (1.01–1.12)</td>
<td>2.1 × 10^{-2}a</td>
</tr>
</tbody>
</table>
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.

Appetite changes reveal 2 distinct biotypes of MDD?

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.
BMI Impacts Antidepressant Response

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

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.

Biopsychosocial Model of Sexual Response

(eg, neuroendocrine function, medical conditions, genetics, medications)

(eg, performance anxiety, impaired self-image, depression)

(eg, upbringing, cultural norms and expectations)

(eg, quality of current and past relationships, intervals of abstinence, life stressors)

Central Effects on Sexual Function

Peripheral Effects on Sexual Function

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.
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

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), $\alpha$1 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

Algorithm to Manage Treatment-Emergent Sexual Dysfunction

Patient warrants treatment with antidepressant or antipsychotic

Patient already has SD or is concerned about developing SD?

YES

Choose a medication with a more favorable SD profile

NO

Choose any appropriate medication and monitor for SD

Patient develops SD side effect

Patient and physician amenable to regimen change?

NO

• Watch and wait
• Reduce dose
• Drug holiday
• Non-pharm options

YES

Is the current regimen fully effective for the primary psychiatric target symptoms?

YES

Add an antidote to current regimen

NO

Change to a medication known to cause fewer sexual side effects

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_\textsubscript{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_\textsubscript{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.

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.

Improvement in Cognitive Dysfunction in MDD as Assessed by the DSST

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.

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).

Examining the Evidence for Direct Impact on Cognitive Symptoms in MDD

<table>
<thead>
<tr>
<th>Antidepressants and psychotropic agents that improve measures of cognition in individuals with MDD independent of improvements in measures of depressive symptom severity</th>
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<tbody>
<tr>
<td>Learning/ Memory</td>
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<tr>
<td>-------------------</td>
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<tr>
<td>Vortioxetine</td>
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<tr>
<td>Duloxetine</td>
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<tr>
<td>Lisdexamfetamine</td>
</tr>
<tr>
<td>Other (eg, SSRIs, SNRIs, and bupropion)</td>
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<tr>
<td>Modafinil</td>
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<tr>
<td>Erythropoietin</td>
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</table>

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.

Excitation vs Inhibition

+ Physiological & Organic Factors: Neurotransmitters (DA, NE, NO), Hormonal neuromodulators (oxytocin, vasopressin, melanocortins), and sex steroids (estrogen, testosterone)

+ Psychosocial - Cultural Factors

“Turn On”

Excite (+)
Faster, Easier, & Greater Response
“Hot”

“Turn Off”

Inhibit (-)
Slower, Difficult, & Less Response
“Not”

- Psychosocial - Cultural Factors

- Physiological & Organic Factors: Neurotransmitters (serotonin), Hormone modulators (opioids), hormones (prolactin), and neuromodulators (endocannabinoids)

Sexual Reward Circuitry

VTA = ventral tegmental area; SN = substantia nigra.
# Imaging and Antidepressant-Associated Sexual Dysfunction

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 ($P<.05$).

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

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

Mrs. Robinson

Case Presentation
Mrs. Robinson

<table>
<thead>
<tr>
<th>Presentation</th>
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<tbody>
<tr>
<td>47-year-old married female</td>
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<tr>
<td>PCP referral for treatment of depression</td>
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<tr>
<td>Patient self-reports history of several failed past treatment attempts with antidepressants</td>
</tr>
</tbody>
</table>

PCP = primary care physician.
### Mrs. Robinson

<table>
<thead>
<tr>
<th>History of Present Illness</th>
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<tbody>
<tr>
<td>• Gradual worsening depression over the past 3 months</td>
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<tr>
<td>• Chronic low mood (worse in the evening)</td>
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<tr>
<td>• Frequent bouts of crying when alone</td>
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<tr>
<td>• Moderate anxiety with occasional panic attacks when required to socialize</td>
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<tr>
<td>• Mid-nocturnal and early morning awakening</td>
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<tr>
<td>• Daytime fatigue and difficulty initiating tasks</td>
</tr>
</tbody>
</table>
Mrs. Robinson

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

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

MDE = major depressive episode.
Mrs. Robinson

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

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

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<th>Follow-Up</th>
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- **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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LIVE AUDIENCE POLLING RESULTS
### Mrs. Robinson

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

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Mrs. Robinson

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- 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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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

LIVE AUDIENCE POLLING RESULTS
Mrs. Robinson

- 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
Mrs. Robinson

- 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

- 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!

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