Could Vyvanse® Be the Boost We Need for Treatment of Depression? 
A STIMULATING Discussion on Augmentation.

Pharmacotherapy Rounds – Friday, November 2nd, 2018

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Objectives

By the end of the presentation, the audience should be able to:

1. Describe the diagnosis and pathophysiology of depression
2. Identify depression treatment algorithm, as well as, augmentation options
3. Compare the history and research behind various psychostimulants
4. Evaluate psychostimulant augmentation in depression and its place in therapy
Depression

I. Epidemiology
   a. Common mental disorder in the United States (U.S.)
   b. In 2016, ~16.2 million U.S. adults had at least 1 major depressive episode (6.7% of all U.S. adults)
   c. In 2016, ~10.3 million U.S. adults had at least 1 major depressive episode causing severe impairment (4.3% of all U.S. adults)

II. Definition of Major Depressive Disorder (MDD)
   a. Diagnosed per 2013 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)
   b. ≥ 5 symptoms for at least 2 consecutive weeks which represent a change from previous functioning – (at least one must be depressed mood or anhedonia):
      - Depressed mood and/or anhedonia
      - Weight loss or gain
      - Decreased or increased appetite
      - Insomnia or hypersomnia
      - Psychomotor agitation or retardation
      - Fatigue or loss of energy
      - Feelings of worthlessness or excessive or inappropriate guilt
      - Diminished ability to think, poor concentration, or indecisiveness
      - Suicidal ideation (SI)
   c. Symptoms cause significant impairment in social, occupational, and other areas of functioning
   d. Can have specifiers of anxious distress, mixed features, melancholic features, atypical features, psychotic features (mood-congruent and mood incongruent), catatonia, peripartum onset, seasonal pattern
   e. Not attributed to substances, or another medical/mental health condition (see Figure 2)

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**Figure 1. U.S. Adults Major Depressive Episode Severity (2016) per Substance Abuse and Mental Health Services Administration**

**Figure 2. Differential Diagnosis of MDD**
III. Assessments (see Appendix A)\textsuperscript{3,5}
   a. Hamilton Depression Rating Scale (HDRS or HAM-D)
   b. Montgomery-Asberg Depression Rating Scale (MADRS)
   c. Patient Health Questionnaire (PHQ-9)
   d. Beck Depression Inventory (BDI)
   e. Quick Inventory of Depressive Symptomatology (QIDS-SR, QIDS-C)

IV. Pathophysiology\textsuperscript{3}
   a. Monoamine hypothesis
      - Decreased levels norepinephrine (NE), serotonin (5-HT), and dopamine (DA)
   b. Dysregulation hypothesis
      - Delayed time for full antidepressant (AD) effect accounted for by adaptive changes in homeostatic regulation of receptor sensitization over several weeks
      - Effective ADs restore adequate regulation in the dysregulated neurotransmitter system
   c. Chronic stress model
      - Stress affects the hypothalamic-pituitary-adrenal axis causing inflammation and release of cortisol and glucocorticoids, ultimately decreasing hippocampal neurogenesis
      - ADs are thought to increase hippocampal neural cell proliferation
   d. Anatomical structure abnormalities

V. Management/treatment\textsuperscript{4,6,9}
   a. Psychotherapy
      - Interpersonal treatment focusing on behaviors and thought processes
      - Examples include: cognitive behavioral therapy (CBT), interpersonal psychotherapy, behavioral activation
   b. Pharmacotherapy
      - Used to bring neurotransmitter regulation back to a new-normal homeostasis
      - Measurable improvement in depressive symptoms is usually delayed (~4-6 weeks)
   c. There is no “one-size-fits all” treatment – various AD classes and agents (see Appendix B)
   d. Treatment goal is remission, but patients may exhibit partial response during therapy
      - From the STAR\textsuperscript{*} D Trial, research definitions:\textsuperscript{9}
        ▪ Response = \(\geq 50\%\) reduction in symptoms
        ▪ Remission = near-absence of depressive symptoms (i.e. HAM-D \(\leq 7\), QIDS-SR \(\leq 5\))
      - From DSM-5, Frank et al. (1991), & de Zwart et al. (2018) consensus clinical practice definitions (see Figure 3):\textsuperscript{2,4,7}
        ▪ Symptomatic & asymptomatic
          a. Symptomatic = \(\geq 1\) of 2 core symptoms and \(\geq 5\) of 9 total symptoms
          b. Asymptomatic = \(\leq 2\) mild symptoms
        ▪ Remission = asymptomatic for \(\geq 2\) months
        ▪ Recovery = absence of symptoms after onset of remission; sustained remission
        ▪ Relapse = full return of depressive symptoms after remission, prior to recovery; return of symptoms from ongoing episode
        ▪ Recurrence = another depressive episode after recovery; entirely new depressive episode
Therapeutic phases\textsuperscript{5-7}

\begin{itemize}
  \item **Acute Phase**
  \begin{itemize}
    \item Initiate antidepressant trial for a minimum 4-8 weeks - allowing for
time-to-effect
    \item Encourage adherence and provide appropriate counseling
  \end{itemize}
  \item **Continuation Phase**
  \begin{itemize}
    \item Recommended for patients who have a full response/remission
    \item Continue therapy for ~4-9 months
  \end{itemize}
  \item **Maintenance Phase**
  \begin{itemize}
    \item Recommended for patients with ≥ 3 prior major depressive episodes
    \item Continue therapy for extended period of time (potentially indefinite)
to prevent recurrence
  \end{itemize}
\end{itemize}

Figure 4. Treatment phases per 2010 American Psychiatric Association Guidelines (APA)

VI. Lack of remission\textsuperscript{5,6,9}

\begin{itemize}
  \item a. Remission with an initial, single AD is achieved in only ~30% of patients
  \item b. If remission is not achieved, clinician may choose to augment with another agent or switch to
another AD
    \begin{itemize}
      \item Based on APA guidelines and STAR*D Trial, evidence-based augmentation options could
include psychotherapy, second AD (different class/mechanism/target), second-
generation antipsychotic, lithium, or triiodothyronine
    \end{itemize}
  \item c. Treatment-resistant depression (TRD) is usually defined by lack of remission despite ≥2 AD trials
at therapeutic doses for at least 8 weeks
    \begin{itemize}
      \item Other definitions of TRD may be based on single criterion of failure, variably defined
lack of response to ADs, or need for electroconvulsive therapy (ECT)
      \item Inconsistency in defining TRD across trials has resulted in wide variation in TRD
estimates
        \begin{itemize}
          \item Ranging anywhere from 10-30% of all MDD patients
        \end{itemize}
    \end{itemize}
  \item d. In patients who fail to respond or remit to adequate AD trials, providers face the difficulty of
choosing between therapeutic options with less robust evidence
    \begin{itemize}
      \item Providers may draw on anecdotal experience or other less evidence-based therapies
      \item This is where the use of psychostimulants has come into play
    \end{itemize}
\end{itemize}

\section*{Psychostimulants}

I. Also known as stimulants or “uppers”\textsuperscript{10,11}

II. Controlled substances\textsuperscript{10}

\begin{itemize}
  \item a. Ordered by abuse risk and placed in “Schedules” by the Federal Drug Enforcement Administration
(DEA) ranging from C-I to C-V, as well as, over the counter (OTC) products (see Appendix C)
\end{itemize}

III. Associated with feelings of pleasure/euphoria, decreased fatigue, increased motor activity, and mental
alertness\textsuperscript{10,11,12}

IV. Psychostimulants as a class of drugs was introduced around the 1930s\textsuperscript{10-15}
Table 1. Psychostimulant agents and pharmacology

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
<th>Pharmacology</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine-derived</td>
<td>Amphetamine (AMP), dextroamphetamine (d-AMP), and lisdexamfetamine (LDX)</td>
<td>Release DA and NE into presynaptic nerve terminal</td>
<td>AMP salts = combination of AMP and d-AMP AMP made of d-AMP (more active) and methamphetamine enantiomers</td>
</tr>
<tr>
<td>Methylphenidate-derived</td>
<td>Methylphenidate (MPH) and dexamfethamine (d-MPH)</td>
<td>Inhibit presynaptic uptake of DA and NE</td>
<td>d-MPH = more active, d-threo-enantiomer of MPH</td>
</tr>
</tbody>
</table>

Psychostimulants & Depression

I. Historical background for use in depression\textsuperscript{13-30}
   a. Research into psychostimulants and their potential utility in depression began in the 1960s
   b. Different mechanism compared to traditional SSRIs and SNRIs
      - Target DA and NE, as opposed to, 5-HT
        - Similar neurotransmitter target to bupropion
        - NE and 5-HT have traditionally been the focus of the monoamine hypothesis, but evidence suggests that DA transmission is also affected in depression
      - In recent years, first-line AD and augmentation strategies have been expanding to dopaminergic-based medications like bupropion, high-dose venlafaxine, aripiprazole, and brexipiprazole
   c. Compared to ADs, treatment effects include expediency and face validity in depression response, and patient reported euphoria and increased activity leading to improved treatment acceptance
      - Effects can be seen within days, but are often short-lived
      - Some thought in practice that a psychostimulant could be used as a short-term “facilitating” agent until AD therapy is successfully established and given adequate time-to-effect
      - Important to note that in studies, the observed quick response did not necessarily correlate to higher remission rates
   d. Appears in practice typically in patients with treatment resistant depression
      - Potential to alleviate residual symptoms
   e. Primarily studied in Unipolar Depression and as short-term duration
      - Limited research includes individuals with Bipolar Depression; most studies exclude this group
      - Longest study duration was 16 weeks (prior to 2018)

II. Randomized controlled trials (RCTs) literature\textsuperscript{17-30}

Table 2. Dextroamphetamine (d-AMP)

<table>
<thead>
<tr>
<th>RCT</th>
<th>Key Information</th>
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<tbody>
<tr>
<td>Wagner, et al. (2000)</td>
<td>d-AMP monotherapy vs. placebo (2 weeks), followed by non-responder open-label treatment d-AMP vs. d-AMP + AD in men with human immunodeficiency virus (HIV) exhibiting depression and fatigue: n=23</td>
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<tr>
<td></td>
<td>Significantly improved mood, energy, and quality of life among patients taking d-AMP (p&lt;0.05)</td>
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Table 3. Methylphenidate (MPH)

<table>
<thead>
<tr>
<th>RCT</th>
<th>Key Information</th>
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</thead>
<tbody>
<tr>
<td>Lavretsky, et al. (2006)</td>
<td>- MPH + citalopram vs. placebo + citalopram to accelerate and enhance AD response in elderly depressed patients: n=16</td>
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<td></td>
<td>- MPH + citalopram showed a significant improvement in depressive symptoms time-treatment group interaction (p=0.001)</td>
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<td></td>
<td>- Mean difference in HAM-D scores between groups at week 8 was −6.2 (p=0.05)</td>
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<tr>
<td>Patkar, et al. (2006)</td>
<td>- MPH osmotic release oral system (OROS) augmentation vs. placebo for patients TRD: n=60</td>
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<td></td>
<td>- The study did not demonstrate a statistically significant benefit for augmentation with MPH OROS in TRD</td>
</tr>
<tr>
<td>Ravindran, et al. (2008)</td>
<td>- MPH OROS augmentation vs. placebo for patients with TRD: n=145</td>
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<tr>
<td></td>
<td>- There was no statistically significant difference between the groups for depression improvement</td>
</tr>
<tr>
<td></td>
<td>- Secondary analyses found MPH OROS was superior to placebo in improving apathy and fatigue (p=0.01)</td>
</tr>
<tr>
<td>Lavretsky, et al. (2015)</td>
<td>- MPH + citalopram vs. citalopram + placebo vs. MPH + placebo for geriatric depression and assessment of cognitive outcomes: n=143</td>
</tr>
<tr>
<td></td>
<td>- MPH + citalopram showed a significant improvement in depressive symptoms rate of response compared to citalopram + placebo (p=0.03)</td>
</tr>
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<td></td>
<td>- MPH augmentation met statistical significance for depression improvement in HAM-D scores, but not clinically significant (during first 4 weeks and at 16 weeks)</td>
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<td></td>
<td>- No significant difference between groups for neuropsychological performance</td>
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Table 4. Overview of systematic review

<table>
<thead>
<tr>
<th>Review Article</th>
<th>Key Information</th>
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</thead>
<tbody>
<tr>
<td>Abbasowa, et al. (2013)</td>
<td>- Reviewed 7 psychostimulant RCTs ranging from 1982 to 2011</td>
</tr>
<tr>
<td></td>
<td>- MPH (augmentation), d-AMP (monotherapy), methylamphetamine (monotherapy)</td>
</tr>
<tr>
<td></td>
<td>- Author’s conclusions: Overall poor quality of studies (small sample sizes, short duration, methodologically flawed especially older studies) with no clear evidence for effectiveness of psychostimulant MDD augmentation. Larger, better designed RCTs required to evaluate tolerance and effectiveness before psychostimulants can be recommended in routine practice.</td>
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Table 5. Overview of meta-analysis

<table>
<thead>
<tr>
<th>Review Article</th>
<th>Key Information</th>
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</thead>
<tbody>
<tr>
<td>McIntyre, et al. (2017)</td>
<td>- Reviewed 12 psychostimulant RCTs published prior to January 2016</td>
</tr>
<tr>
<td></td>
<td>- d-AMP (monotherapy/augmentation), MPH (augmentation), LDX (augmentation)</td>
</tr>
<tr>
<td></td>
<td>- Author’s conclusions: Compiled results with mixed evidence suggests possibility of some symptom mitigation with psychostimulant MDD augmentation. Less hypothesis confirming, more hypothesis generating; particularly need more research in “target-engagement” studies, i.e. targeting specific MDD psychopathology dimensions.</td>
</tr>
</tbody>
</table>
III. Focus on lisdexamfetamine (Vyvanse)\textsuperscript{14-30}
   a. LDX is the newest psychostimulant on the market – approved in 2007
   b. With mixed data from previous agents, studies in recent years have switched to trials with LDX
   c. Pharmacology
      - Stimulates the presynaptic release of NE and DA
      - Pro-drug of d-AMP
         - LDX metabolized into d-AMP
         - Not activated via cytochrome P450
         - Converted to d-AMP and L-lysine via red blood cell enzymatic hydrolysis
   d. Pharmacokinetics
      - Duration of action: ~8-14 hours
      - Time to peak: LDX ~1 hour; d-AMP ~3.5 hours
      - Half-life: LDX <1 hour; d-AMP ~10-13 hours
      - Primarily excreted in urine (96%)
      - Absorption and food effects: rapid gastrointestinal (GI) absorption; food has no effect on AUC or $C_{\text{max}}$ but does prolong the $T_{\text{max}}$ of d-AMP by ~1 hour
      - Amphetamines are bases – acidifying agents decrease blood levels and alkalinizing agents increase blood levels
   e. Dosing and indication
      - Initial: 30 mg by mouth every morning
         - Dosage increases in increments of 10-20 mg per day at weekly intervals as needed
         - MAX 70 mg/day
         - Binge-eating disorder target dose: 50-70mg/day
         - Dosage adjustments
            a. Consider lower initial dose and slower titration in elderly
            b. No dosage adjustments in hepatic impairment
            c. Renal impairment
               i. Glomerular filtration rate (GFR) >30 mL/min: no dosage adjustments
               ii. GFR 15-29 mL/min: MAX 50mg/day
               iii. GFR <15 mL/min: MAX 30mg/day
               iv. LDX and d-AMP are not dialyzable
      - Available as chewable tablet (10-60mg) or capsule (10-70mg)
   f. Adverse drug reactions
      - Common (incidence $\geq$5% and $\geq$2x rate of placebo): anorexia, anxiety, decreased appetite, weight loss, decreased body growth, diarrhea, dizziness, dry mouth, irritability, insomnia, constipation, jitteriness, upper abdominal pain, nausea, vomiting, and increase in blood pressure/heart rate
      - Serious: seizures, peripheral vasculopathy, dyspnea, chest pain, myocardial infarction, stroke palpitations, sudden cardiac death, rhabdomyolysis, dystonia, hallucinations/psychosis, and mood lability/mania
   g. Boxed warning: Abuse, misuse, diversion (high potential for abuse and dependence)
   h. Contraindications and precautions
      - Hypersensitivity to amphetamine products
      - Concurrent or within 14 days of MAOI use (including linezolid and methylene blue)
- Cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems (increased risk for sudden death)
- Peripheral vasculopathy, including Raynaud phenomenon (digital/soft tissue breakdown)
- Visual disturbances (accommodation and blurred vision)
- Pre-existing psychosis or bipolar disorder (may exacerbate thought/behavior disorder)
- Seizure disorder
- Tourette syndrome/tics (may exacerbate motor or phonic tics)
- Abrupt discontinuation after high doses for extended periods (withdrawal may cause symptoms of withdrawal, extreme fatigue)

**Clinical question:**
Does the evidence support Vyvanse® as an appropriate therapeutic option for augmentation of MDD?

**Evaluation of the Literature with LDX**

| Study design | Multicenter, randomized, double-blind, parallel-group, placebo-controlled study (USA; exploratory, proof-of-concept) |
| Objectives | To examine the efficacy, safety, and tolerability of LDX augmentation in individuals with MDD and an inadequate response to 8-weeks of escitalopram monotherapy |
| Participants | Inclusion
- 18-55 years old
- Primary diagnosis of nonpsychotic MDD
- No previous AD trial = HAM-D ≥22 or currently on AD = HAM-D ≥10 & no remission with ≥6 weeks treatment
- Nonpregnant, non lactating women on contraception
- Permitted concomitant therapy: hormonal, thyroid, antihypertensive, bronchodilator inhalers, non-sedating antihistamines, antibiotics, OTC medications not affecting BP, HR, or central nervous system (CNS) |
| | Exclusion
- Current nonresponsive MDD episode
- Lifetime history of TRD
- Comorbidities: ADHD; “confounding” psychiatric disorder (Axis I/II/other); first-degree relative with bipolar I disorder; concurrent medical illness/disability that would increase risk; history of or current suicidality; history of seizures; Tourette’s; abnormal thyroid function or glaucoma; family history of sudden cardiac death or ventricular arrhythmias; moderate to severe hypertension or resting systolic >139mmHg or diastolic >89mmHg; ≤6 months prior history of substance abuse or dependence; hypersensitivity to amphetamine, escitalopram, or citalopram |
| Methods | 4 phases:
1. Screening and washout (as needed)
2. 8-week lead-in open-label escitalopram and single-blind placebo (PBO)
3. 6-week double-blind randomized treatment with LDX vs. placebo augmentation of escitalopram
4. Safety follow-up (7-9 days after last dose) |
| | Full safety-analysis = participants prior to augmentation randomization
| | Randomized safety-analysis set = participants post-randomization |
**Intervention**
- Lead-in with escitalopram 10mg/day x 1 week, then 20mg/day + single-blind placebo
- Week 8 (augmentation baseline) with tolerable safety profile and residual symptoms (HAM-D ≥4) randomized 1:1 to double-blind LDX or placebo augmentation x 6 weeks
- Stratified by baseline escitalopram remission status
- LDX initial dose 20mg/day, then dose increased weekly to 30mg/day, then 50mg/day (dose could increase through week 2 of augmentation phase and could decrease dose once per participant at any time)
- Adverse event and concomitant med assessment during safety follow-up

**Outcomes**
- **Primary (1’):** change in MADRS total score from augmentation baseline to end of study
- **Secondary (2’):** MADRS remission (≤10) or response (50% reduction); HAM-D-17 remission (≤7) or response (50% reduction); CGI-S at weeks 0, 8, 14; CGI-I at weeks 1-14; QIDS-SR at weeks 0, 8, 14
- **Safety:** Treatment-emergent adverse events (TEAEs); vital signs at all visits; C-SSRS at all visits; labs at screening, weeks 8, 11, 14; physical exams at screening, weeks 8, 14

**Statistical analysis**
- Analysis of covariance (ANCOVA) 1’ & 2’ endpoint (MADRS & HAM-D remission, CGI-S/CGI-I); last observation carried forward (LOCF) for missing data
- 1’ endpoint reported with least squares mean (LS)
- MADRS or HAM-D evaluated for treatment effects with Cochran-Mantel-Haenszel tests
- Stratified group of escitalopram non-remitters used Fischer’s exact test
- Post hoc adjusted effect size for 1’ endpoint via ANCOVA
- Post hoc number needed to treat (NNT) for MADRS remission
- Pre-specified, 2-sided, α=0.10 for 1’ & 2’, 90% confidence interval (CI)
- Descriptive summaries of safety endpoints

**Results**
- 246 enrolled; 239 finished escitalopram lead-in treatment
- 177 randomized to augmentation; similar drop-out between placebo and LDX

<table>
<thead>
<tr>
<th>Table 7. Baseline characteristics</th>
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<tbody>
<tr>
<td>Mean age (Standard Deviation [SD])</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Race/ethnicity</td>
</tr>
<tr>
<td>MADRS baseline</td>
</tr>
<tr>
<td></td>
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<tr>
<td>HAM-D baseline</td>
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<td></td>
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</tbody>
</table>

- Mean MADRS change from escitalopram lead-in to augmentation baseline was -15.6 (+/- 9.66)
- Mean daily LDX dose 29.6mg (+/- 9.69mg); all participants received the 20mg dose, 75% dose increase to 30mg, 42% dose increase to 50mg
- Mean duration of augmentation exposure placebo 40 days (+/- 6.60 days) vs. LDX 38.3 days (+/- 9.56 days)
Table 8. Primary and secondary endpoint changes

<table>
<thead>
<tr>
<th>Score</th>
<th>Escitalopram non-remitters</th>
<th>Full analysis set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (n=64)</td>
<td>LDX (n=65)</td>
</tr>
<tr>
<td>MADRS change</td>
<td>-4.9</td>
<td>-7.1</td>
</tr>
</tbody>
</table>

Secondary endpoints

<table>
<thead>
<tr>
<th>Score</th>
<th>Escitalopram non-remitters</th>
<th>Full analysis set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (n=64)</td>
<td>LDX (n=65)</td>
</tr>
<tr>
<td>MADRS response, n (%)</td>
<td>32 (50%)</td>
<td>43 (66.2%)</td>
</tr>
<tr>
<td>MADRS remission, n (%)</td>
<td>22 (34.4%)</td>
<td>32 (49.2%)</td>
</tr>
<tr>
<td>HAM-D change</td>
<td>-4.0</td>
<td>-4.9</td>
</tr>
<tr>
<td>HAM-D response, n (%)</td>
<td>35 (54.7%)</td>
<td>41 (63.1%)</td>
</tr>
<tr>
<td>HAM-D remission, n (%)</td>
<td>17 (26.6%)</td>
<td>21 (32.3%)</td>
</tr>
<tr>
<td>QIDS-SR change</td>
<td>-1.2</td>
<td>-2.4</td>
</tr>
<tr>
<td>CGI-I change</td>
<td>2.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 9. Other secondary endpoint changes

<table>
<thead>
<tr>
<th>Week</th>
<th>PBO Mean MADRS Change (SD)</th>
<th>LDX Mean MADRS Change (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>-1.8 (3.91)</td>
<td>-2.7 (5.04)</td>
</tr>
<tr>
<td>10</td>
<td>-3.6 (5.50)</td>
<td>-4.2 (6.34)</td>
</tr>
<tr>
<td>11</td>
<td>-5.77 (6.92)</td>
<td>-5.5 (6.29)</td>
</tr>
<tr>
<td>12</td>
<td>-5.0 (7.90)</td>
<td>-5.7 (7.08)</td>
</tr>
<tr>
<td>14</td>
<td>-4.90 (7.36)</td>
<td>-7.1 (8.04)</td>
</tr>
</tbody>
</table>

- Adjusted effect size for MADRS reduction was -0.3 (CI -0.6-0) among non-remitters
- NNT=6.7 for MADRS remission with LDX augmentation for non-remitters
- 60.2% LDX (vs. 49.4% placebo) participants experienced TEAEs: 18.2% mild, 30.7% moderate, and 11.4% severe
- No participants had psychotic/manic suicidal, or aggressive adverse events
- Small mean changes in BP, pulse, and weight
- No clinically significant changes in mean lab values
- C-SSRS 1 participant in each group reported thoughts of being better off dead during augmentation – no suicidal behavior exhibited and no completed suicide

Author’s conclusions
- Among non-remitters, LDX statistically superior for total MADRS symptom reduction
- LDX numerically superior for response and remission and self-reported symptoms
- LDX augmentation was generally well-tolerated

Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>- Stratified by remission &amp; non-remission</td>
<td>- Small sample size (limited power)</td>
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<tr>
<td>- Variety of symptom assessments used</td>
<td>- Power not explicitly stated</td>
</tr>
<tr>
<td>- Suicidality assessment</td>
<td>- Proof-of-concept study</td>
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<tr>
<td>- Safety profile</td>
<td>- Defined α=0.10; 90% CI</td>
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<td>- Short LDX treatment duration (6-weeks)</td>
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<td></td>
<td>- Exclusion of severely MDD/TRD</td>
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<tr>
<td>Take home points</td>
<td>Non-significant results with LDX augmentation for primary endpoint. Single significant result for secondary endpoints in self-report (QIDS-SR) with LDX augmentation in full analysis set.</td>
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**Study design**
Multicenter, randomized, placebo-controlled, double-blind, forced-dose titration, dose-finding study (USA, Argentina, Chile, Australia, UK)

**Objectives**
To assess safety and the efficacy dose-response relationship of LDX augmentation for depression in individuals who exhibited inadequate MADRS score reduction during 8-weeks of AD monotherapy

**Participants**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>– 18-65 years</td>
<td></td>
</tr>
<tr>
<td>– Men or nonpregnant/non-nursing women</td>
<td></td>
</tr>
<tr>
<td>– 1’ diagnosis of MDD (lasted for ≥8 weeks before screening and lead-in baseline MADRS total ≥24)</td>
<td></td>
</tr>
<tr>
<td>– Nonresponse (≥6 weeks of treatment at max approved adult dose) to current MDD episode with two or more AD monotherapies or augmentation</td>
<td></td>
</tr>
<tr>
<td>– Lifetime history of TRD</td>
<td></td>
</tr>
<tr>
<td>– MDD hospitalization within last year</td>
<td></td>
</tr>
<tr>
<td>– ECT in prior 3 months</td>
<td></td>
</tr>
<tr>
<td>– Uncontrolled comorbid psychiatric disorder or controlled with prohibited medications</td>
<td></td>
</tr>
<tr>
<td>– LDX contraindication or hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>– Comorbid/history of ADHD</td>
<td></td>
</tr>
<tr>
<td>– Symptomatic cardiovascular (CV) disease</td>
<td></td>
</tr>
<tr>
<td>– First-degree relative with bipolar</td>
<td></td>
</tr>
<tr>
<td>– History of moderate to severe HTN or resting average systolic (SBP) &gt;139 or diastolic (DBP) &gt;89 at baseline screening</td>
<td></td>
</tr>
<tr>
<td>– Seizures, tic disorder, Tourette syndrome</td>
<td></td>
</tr>
<tr>
<td>– History of abuse/dependence (except nicotine)</td>
<td></td>
</tr>
<tr>
<td>– Use of CNS affecting drug within last 30 days that could affect study [ex. ADHD drug or OTC herbal]</td>
<td></td>
</tr>
</tbody>
</table>

**Methods**

<table>
<thead>
<tr>
<th>4 phases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Screening and washout (1-4 weeks)</td>
</tr>
<tr>
<td>– 8-week lead-in single-blind AD</td>
</tr>
<tr>
<td>– 6-week double-blind randomized treatment with LDX vs. PBO augmentation</td>
</tr>
<tr>
<td>– Follow-up (1 week)</td>
</tr>
<tr>
<td>– Lead-in designed to identify inadequate responders</td>
</tr>
</tbody>
</table>
Intervention
- Lead-in escitalopram or venlafaxine ER monotherapy based on clinical judgement
- If participant taking one of the lead-in ADs prior to study start, regimen maintained and titrated over 4 weeks (dose decreased or treatment discontinued as needed)
- Randomization to augmentation if met 3 criteria: MADRS ≥18, reduction in MADRS total score <50% from lead-in to augmentation baseline, and no changes in physical exam, labs, ECG or vital signs since lead-in baseline that would preclude LDX use
- 1:1:1:1:1 stratified randomization to 8-weeks of LDX 10, 30, 50, or 70mg/day (with forced dose titration) or matching placebo with maintained assigned AD therapy
- Participants with no change or worsening in MADRS score from lead-in baseline discontinued from study
- Participants requiring >1 dose reduction discontinued from study

Outcomes
1': change in MADRS total score from augmentation baseline or early termination
2': Sheehan Disability Scale (SDS) measure of functional impairment in work, family, and social life; Euro-QoL measure of general health and quality of life
Safety: adverse events, vital signs (at all visits, additional 2 collections of BP & pulse at weeks 10, 12, 16 for randomized participants; average of 3 results used to determine study continuation), lab results (at screening, week 8, 12, 16), ECG results (at screening, week 8, 16), physical exam (at screening, week 8, 16; height and weight at all visits) and C-SSRS (at all visits)

Statistical analysis
- Dose-response relationships for 1' endpoint and vital signs via multiple comparisons procedure with modeling (MCP-Mod)
- MADRS dose-response assessed in dose-response evaluable set (DRES) and verified using mixed-effects model for repeated measures (MMRM) sensitivity analysis; LOCF for missing scores during maintenance phase
- Sensitivity analysis for treatment group, sex, AD type, visit, and interaction between treatment group and visit
- MADRS score change reported with least squares mean (LS)
- Dose-response relationship for vital signs assessed
- Dose-response curves tested with appropriate contrast t statistics
- 2-sided, α=0.10, for 1' & 2' (if ≥1 candidate dose-response relationship reached this, prop of LDX dose-response established), 90% CI
- LS means for MADRS total score differences estimated with 95% CI
- Anticipated 68 participants completing each treatment arm would yield 80% power
- Safety and tolerability endpoints assessed with descriptive statistics

Results
- Lower than anticipated dropout rate led to maintained statistical power despite lower number of randomized participants – anticipated 85 participants at initiation and 68 participants/arm to complete, reality 78 participants at initiation and 68-71 participants/arm completed

<table>
<thead>
<tr>
<th>Table 11. Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Race/ethnicity</td>
</tr>
<tr>
<td>Antidepressant</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

- Mean MADRS scores at lead-in and augmentation baseline 33.9 (+/-4.89) and 25.7 (+/-5.12), respectively
- Prior to this study 52.7% of participants reported any previous AD use (fluoxetine, sertraline, escitalopram, citalopram, venlafaxine, bupropion, paroxetine, or duloxetine)
Mean MADRS changes similar regardless of baseline AD type or sex, no dose-response relationship.

### Table 12. Primary endpoint changes from baseline

<table>
<thead>
<tr>
<th>Set</th>
<th>Dose</th>
<th>LDX 10mg</th>
<th>LDX 30mg</th>
<th>LDX 50mg</th>
<th>LDX 70mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-response evaluable set</td>
<td>Least squares (LS) mean MADRS change from baseline vs. PBO</td>
<td>-1.4 (-3.9-1.2)</td>
<td>0.1 (-2.5-2.7)</td>
<td>-0.7 (-3.4-2.0)</td>
<td>-0.9 (-3.5-1.6)</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.375</td>
<td>0.940</td>
<td>0.652</td>
<td>0.551</td>
</tr>
<tr>
<td>Full analysis set</td>
<td>LS mean MADRS change from baseline vs. PBO</td>
<td>1.6 (-4.1-0.9)</td>
<td>0.1 (-2.4-2.6)</td>
<td>-1.1 (-3.6-1.4)</td>
<td>-1.2 (-3.7-1.2)</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.288</td>
<td>0.923</td>
<td>0.468</td>
<td>0.410</td>
</tr>
</tbody>
</table>

### Table 13. Dose-response for MADRS and vitals

<table>
<thead>
<tr>
<th>Assessment</th>
<th>MADRS Total Score (SD)</th>
<th>Systolic BP, mmHg (SD)</th>
<th>Diastolic BP, mmHg (SD)</th>
<th>Pulse, bpm (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.43 (+/-1.06)</td>
<td>3.16 (+/-1.01)</td>
<td>2.16 (+/-0.75)</td>
<td>4.45 (+/-1.05)</td>
</tr>
<tr>
<td>Adjusted P-value</td>
<td>0.942</td>
<td>0.004</td>
<td>0.011</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 14. Dose-response for weight and BMI

<table>
<thead>
<tr>
<th>Dose</th>
<th>PBO</th>
<th>LDX 10mg</th>
<th>LDX 30mg</th>
<th>LDX 50mg</th>
<th>LDX 70mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg (SD)</td>
<td>0.5 (+/-1.84)</td>
<td>0.2 (+/-1.84)</td>
<td>-0.3 (+/-1.85)</td>
<td>-1.0 (+/-2.25)</td>
<td>-1.5 (+/-2.90)</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt; (SD)</td>
<td>0.2 (+/-0.61)</td>
<td>0.1 (+/-0.63)</td>
<td>-0.1 (+/-0.64)</td>
<td>-0.4 (+/-0.79)</td>
<td>-0.5 (+/-1.04)</td>
</tr>
</tbody>
</table>

- No significant difference found for 1’ endpoint in any dose-response curves
- All participants randomized to 10 or 30mg maintained maximum dose throughout study
- 4 down-titrated in 50mg (insomnia, anxiety, lethargy and nephrolithiasis, or blood pressure); 9 down-titrated in 70mg (similar, but additionally 1 for each SI and racing thoughts)
- No dose-response for specific severe TEAEs, but frequency of all TEAEs was higher in 70mg compared to all other doses
- Dose-response relationship for aggression, SI, and vitals adverse events with frequency higher in 50mg and 70mg arms
- Positive SI occurred in 14.1% participants in placebo and 9.6% LDX
- Single participant SI + attempt in LDX 70mg group (onset at 10mg)
- No instances of psychosis/mania
- Dose-response observed for LDX and decreased weight at higher LDX doses
- No clinically significant changes in mean lab values or ECG results
- Most common adverse effects (mild/moderate): dry mouth, headache, decreased appetite, nasopharyngitis

**Author’s conclusions**
- Lisdexamphetamine augmentation of escitalopram or venlafaxine ER was not statistically superior to placebo and no dose-response relationship in patients with inadequate monotherapy response
SBP, DBP, pulse, and decreased weight exhibited significant dose-response relationships with increases observed at higher LDX doses.

Lack of efficacy consistent with most previous literature of stimulant augmentation on MDD in general – limited evidence supporting clinical benefit of augmentation.

- **Strengths**
  - Assessed more severe baseline depression (MADRS ≥18) with 50% reduction in symptoms
  - Large, dose-finding study

- **Limitations**
  - Exclusion of TRD
  - Placebo-effect and 5 dose-arm split
  - Atypical depression symptoms not adequately assessed
  - Remote telephone MADRS (inter-rater variability not assessed)

**Critique**

LDX augmentation up to 70mg did not provide clinical benefit over placebo. Purpose of this study was to assess efficacy of LDX as augmentation in participants with minimal history of previous failed AD treatments ("inclusion of TRD considered to have an unfavorable risk-benefit balance"). Highlights the importance of cardiovascular monitoring/considerations with stimulant use.

**Take home points**

- LDX augmentation up to 70mg did not provide clinical benefit over placebo.
- Purpose of this study was to assess efficacy of LDX as augmentation in participants with minimal history of previous failed AD treatments ("inclusion of TRD considered to have an unfavorable risk-benefit balance"). Highlights the importance of cardiovascular monitoring/considerations with stimulant use.


<table>
<thead>
<tr>
<th>Study design</th>
<th>Multicenter, open-label, extension study (17 countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>To evaluate long-term safety, tolerability, and the clinical outcomes of LDX augmentation</td>
</tr>
</tbody>
</table>

**Participants**

- **Inclusion**
  - 18-65 years
  - Nonpsychotic MDD
  - Previously randomized to 1 of 2 antecedent studies

- **Exclusion**
  - Significant adverse event from antecedent studies
  - Physical exam, labs, ECG or vital sign abnormal preclusion criteria
  - Comorbid psychiatric disorder or uncontrolled significant symptoms
  - Lisdexamphetamine contraindications/confounders
  - Others similar to antecedent study above

**Methods**

- 3 phases:
  - 1. 4-week dose-optimization phase
  - 2. 48-week dose-maintenance phase
  - 3. Follow-up (7-9 days after final dose)

- Early termination of study due to all 3 antecedent studies failing to meet 1’ endpoint (only got up to 52-weeks total follow-up)

**Intervention**

- All participants received LDX treatment
  - Background ADs included: escitalopram, sertraline, venlafaxine ER, or duloxetine
  - Dose adjustments to background AD could be considered, but could not change the AD
  - Dose-optimization phase participants titrated to individualized LDX dose; starting at 30mg titration by 20mg weekly increments to 50mg and 70mg
  - Previous placebo participants or those on LDX 10mg (in dose-finding study only) or LDX 20mg titrated starting at 20mg
  - Those who required down-titration and could not tolerate LDX 20mg dose were discontinued
1. Safety & tolerability: TEAEs; vital signs and weight (average of 3 readings); ECG at weeks 0, 12, 24, 36, 48, 52; lab results at weeks 0, 24, 52; C-SSRS; Amphetamine Cessation Symptom Assessment (ACSA) after week 52/discontinuation of LDX

2. Statistical analysis
   - Descriptive statistics for safety and tolerability
   - Descriptive statistics for clinical outcome assessments
   - Baseline defined from antecedent studies augmentation baseline

Results
1. 1570 enrolled, 1559 included in safety analysis set
2. 1270 did not complete the full 12-month study (771 discontinued due to study termination; 63 discontinued due to prespecified BP or pulse limits) – only 300 participants completed the 52-week study

Table 16. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>42 years (+/-12)</td>
</tr>
<tr>
<td>Sex</td>
<td>68% female</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>82% white</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>46% escitalopram, 14% sertraline, 23% venlafaxine ER, 17% duloxetine</td>
</tr>
</tbody>
</table>

- Mean and median lengths of LDX exposure >160 days, but wide range with early termination
- Mean LDX dose over study course was 49.9 +/- 16.72mg
- 10 participants reported suicidal related TEAEs – 7 with SI, 3 attempts, all resolved
- Commonly reported TEAEs: headache, dry mouth, insomnia, and decreased appetite
- TEAEs leading to discontinuation were increased BP, pulse, or QT prolongation
- Greatest mean diffs in SBP & DBP seen at week 48, 52, and pulse at week 3 – differentiated between SSRI and SNRI treatment (~10mmHg and ~6bpm difference)
- Greatest mean differences for weight and BMI seen at week 24 [-1.52 +/- 5.311kg and -0.54 +/- 1.793kg/m² respectively]

Table 17. Secondary endpoint changes from baseline

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>52 *</th>
<th>52/End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants improved on CGI-I (%)</td>
<td>762/1343 (56.7%)</td>
<td>209/244 (85.7%)</td>
<td>1021/1345 (75.9%)</td>
</tr>
<tr>
<td>Mean QIDS-SR Change from Baseline (SD)</td>
<td>-1.0 (+/-4.36)</td>
<td>-3.6 (+/-4.65)</td>
<td>-2.9 (+/-4.92)</td>
</tr>
<tr>
<td>Mean SDS Change from Baseline (SD)</td>
<td>-2.4 (+/-7.07)</td>
<td>-5.2 (+/-7.55)</td>
<td>-4.3 (+/-7.77)</td>
</tr>
</tbody>
</table>

*n for week 52 compared to combination of week 52/end is much smaller (week 52 ~ 1/5th sample)

Author’s conclusions
- Safety and tolerability findings align with other short-term MDD treatment and long-term ADHD profile seen with LDX
- LDX treatment associated with increases in BP and pulse – important to monitor

Critique
- Strengths
  - Long treatment duration (first of its kind, but terminated early)
  - Primarily assessing safety and tolerability
- Limitations
  - Early termination (small sample at end)
  - Interpretation caution, esp. for symptoms
  - Descriptive statistics
Take home points
Similar safety and tolerability findings to previous long-term ADHD studies and short-term MDD studies, but unclear interpretation/value due to early termination and slim sample size at end of study.

Table 18. Other notable literature with lisdexamfetamine (LDX)

<table>
<thead>
<tr>
<th>RCT</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madhoo, et al. (2014)</td>
<td>- Replication of Trivedi, et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>- LDX augmentation vs. placebo for patients with self-reported executive dysfunction despite full/partial remission of MDD symptoms: n=143</td>
</tr>
<tr>
<td></td>
<td>- LDX augmentation significantly improved executive dysfunction and depressive symptoms in participants with mild MDD (p=0.0009)</td>
</tr>
<tr>
<td>Richards, et al. (2016)</td>
<td>- Published 2 phase-3 studies on LDX augmentation of AD monotherapy in adults with MDD; Study 1 (placebo, n=201; LDX, n=201) and Study 2 (placebo, n=213; LDX, n=211)</td>
</tr>
<tr>
<td></td>
<td>- LDX augmentation was not superior to placebo in reducing depressive symptoms in individuals with MDD</td>
</tr>
</tbody>
</table>

Conclusions

I. Future research\textsuperscript{17,18,19,20,21}
   a. Additional RCTs warranted to evaluate psychostimulant augmentation in targeting specific depressive symptoms, such as anhedonia, anergia, executive dysfunction, concentration, and lethargy
      - Current limited data
   b. Inclusion of TRD

II. Personal recommendations based on LDX literature review
   a. Not recommended in routine clinical practice, even for TRD
      - TRD excluded from RCTs
   b. Minimal evidence-based benefit for using LDX in MDD
      - Low-level of evidence supporting augmentation
      - No LDX target-specific symptom data
   c. If provider does choose to augment MDD therapy with LDX
      - Caution/avoid in patients
        - With SI
          A. Always screen for suicidality prior to consideration of LDX addition
          B. In patients with low imminent risk for suicide and LDX initiation, recommend routine suicidality monitoring at follow-ups
        - With cardiovascular risk
          A. CV monitoring
             i. ECG at baseline and when clinically indicated
             ii. Routine BP and HR at follow-ups
        - With history of substance abuse
          - Rule out all other MDD treatment confounders (Figure 2)
- Patient-provider discussion of treatment expectations when considering adding a psychostimulant to therapeutic regimen
  - Schedule II controlled medication requires extensive provider follow-up due to restrictions on short medication supply

References


<table>
<thead>
<tr>
<th>Scale</th>
<th>Assessment</th>
<th>Key Features</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Depression Rating Scale (HDRS or HAM-D)</td>
<td>Clinician administered</td>
<td>Gold standard for research. Used for screening, severity, and treatment outcome assessment. Assesses symptom severity, including somatic symptoms, over past week.</td>
<td>None/minimal: 0-7&lt;br&gt;Mild: 8-13&lt;br&gt;Moderate: 14-19&lt;br&gt;Severe: 20-25&lt;br&gt;Very severe: ≥26</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
<td>Clinician administered</td>
<td>Commonly used in research. Differentiates among all the intermediate grades of depression and less bias introduced for patients with other medical/somatic symptoms. May be more sensitive to drug treatment compared to HAM-D.</td>
<td>None/minimal: 0-8&lt;br&gt;Mild: 9-17&lt;br&gt;Moderate: 18-34&lt;br&gt;Severe: ≥35</td>
</tr>
<tr>
<td>Quick Inventory of Depressive Symptomatology (QIDS-SR, QIDS-C)</td>
<td>Clinician (-C) or patient self-report (-SR)</td>
<td>Used in research and clinical practice. Similar to HAM-D in symptom sensitivity/highly correlated with HAM-D. Most common is 16-item rated self-report (SR-16). Assesses 9 core DSM-5 MDD symptoms.</td>
<td>None/minimal: &lt;6&lt;br&gt;Mild: 6-10&lt;br&gt;Moderate: 11-15&lt;br&gt;Severe: 16-20&lt;br&gt;Very severe: ≥21</td>
</tr>
</tbody>
</table>

### Other rating scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Assessment</th>
<th>Key Features</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L)</td>
<td>Patient self-report</td>
<td>Descriptive measure of general health and quality of life. Assesses 5 dimensions – mobility, self-care, usual activities, pain/discomfort, anxiety/depression – with 5 levels – no problems, slight problems, moderate problems, severe problems, and extreme problems.</td>
<td>No problems = 1&lt;br&gt;Slight problems = 2&lt;br&gt;Moderate problems = 3&lt;br&gt;Severe problems = 4&lt;br&gt;Extreme problems = 5</td>
</tr>
<tr>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS)</td>
<td>Clinician administered</td>
<td>Semi-structured interview to identify presence of SI or behavior, as well, as intensity – suicide risk assessment. Lists risk and protective factors.</td>
<td>Questions 1-2 differentiate between thoughts of being dead vs. non-specific active suicidal thoughts.</td>
</tr>
<tr>
<td>Clinical Global Impression Improvement Scale (CGI-I) and Severity Scale (CGI-S)</td>
<td>Clinician subjective (compared to clinical experience)</td>
<td>Useful for depression baseline assessment and tracking treatment progress over time. Correlates well with HAM-D.</td>
<td>Improvement scale:</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Sheehan Disability Scale (SDS)</td>
<td>Patient self-report</td>
<td>Evaluates functional impairment in work/school, family, and social life.</td>
<td>Score each 0-10 Range of total score from 0 (unimpaired) to 30 (highly impaired)</td>
</tr>
<tr>
<td>Amphetamine Cessation Symptom Assessment (ACSA)</td>
<td>Patient self-report</td>
<td>Amphetamine withdrawal symptom assessment, once-daily. Discriminates between “low” and “high-dose” users. Inversely related to subjective general well-being and directly related to BDI.</td>
<td>Withdrawal symptoms: 0 = not at all 1 = a little 2 = moderately 3 = quite a lot 4 = extremely Range of scores from 0–64; higher numbers indicating greater withdrawal symptom severity</td>
</tr>
</tbody>
</table>
### Appendix B. Antidepressant classes & agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
<th>Schedule</th>
<th>DEA Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Serotonin Reuptake Inhibitors (SSRIs)</td>
<td>Citalopram, escitalopram, fluoxetine, paroxetine, sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)</td>
<td>Duloxetine, venlafaxine, levomilnacipran, desvenlafaxine, milnacipran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine/Dopamine Reuptake Inhibitor (NDRI)</td>
<td>Bupropion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclic Antidepressants (TCAs)</td>
<td>Amitriptyline, imipramine, nortripsyline, desipramine, doxepin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>amoxapine, clomipramine, maprotiline, protriptyline, trimipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td>Isocarboxazid, phenelzine, selegiline, tranylcypromine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Antidepressants</td>
<td>Vortioxetine, trazodone, nefazodone, mirtazapine, vilazodone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Appendix C. Stimulants and associated controlled substance categories

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Schedule</th>
<th>DEA Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illicit Stimulants</td>
<td>Crack cocaine (less purified, smoked)</td>
<td>C-I</td>
<td>High abuse risk with NO safe, accepted medical use in the U.S.</td>
</tr>
<tr>
<td></td>
<td>Methylenedioxymethamphetamine (“MDMA”, “Ecstasy”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cathinones (“Bath Salts”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthetic Stimulant</td>
<td>Cocaine</td>
<td>C-II</td>
<td>High abuse risk, but has safe, accepted medical uses in the U.S. Can cause severe psychological or physical dependence</td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>Methamphetamine (Desoxyn)</td>
<td>C-II</td>
<td>High abuse risk, but have safe, accepted medical uses in the U.S. Can cause severe psychological or physical dependence</td>
</tr>
<tr>
<td></td>
<td>Lisdexamfetamine (Vyvanse)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methylphenidate (Concerta, Aptensio XR, Metadate CD, Ritalin LA)</td>
<td></td>
<td></td>
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<td></td>
<td>Dexmethylphenidate (Focalin, Focalin XR)</td>
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<td></td>
<td>Dextroamphetamine (Dexedrine, Procentra, Zenzedi)</td>
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<td></td>
<td>Amphetamine salts – amphetamine/dextroamphetamine (Adderall, Adderall XR, Mydayis)</td>
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<tr>
<td>Stimulant/wake-promoting agent</td>
<td>Modafinil (Provigil)</td>
<td>C-IV</td>
<td>Abuse risk less than C-II and have safe, accepted medical uses in the U.S.</td>
</tr>
<tr>
<td></td>
<td>Armodafinil (Nuvigil)</td>
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<tr>
<td>Stimulant/appetite suppressant</td>
<td>Benzphetamine (Didrex, Regimex)</td>
<td>C-III</td>
<td>Abuse risk less than C-II and have safe, accepted medical uses in the U.S.</td>
</tr>
<tr>
<td></td>
<td>Phentermine (Adipex, Lomaira, Suprenza)</td>
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<tr>
<td></td>
<td>Diethylproprion</td>
<td>C-IV</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Caffeine</td>
<td>-</td>
<td>Non-controlled</td>
</tr>
</tbody>
</table>