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New and Emerging Antidepressant Strategies in MDD

Alan F. Schatzberg, MD
Stanford University School of Medicine
Stanford, CA
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Other Financial Interest: American Psychiatric Association (Royalties); Stanford University (Royalties)
Initiate a treatment plan that includes the latest pharmacotherapeutic options for the treatment of MDD.
New Antidepressant Strategies in MDD: Outline

- Levomilnacipran
- Vilazodone
- Adjunctive second generation antipsychotics
- Ketamine and other glutamatergic agents
- Onabotulinumtoxin (OBA)
Levomilnacipran ER Treatment in Adult MDD Patients with First-Episode, Highly Recurrent, and Chronic MDD

Do outcomes differ based on prior history or chronicity?

Pool data from 5 RCTs

8 or 10 wk levomilnacipran ER (40-120 mg/d; n = 1566) or placebo (n = 1032)

Mean changes from baseline to end of treatment (MADRS, HAMD, and Sheehan Disability Scale)

Compared first-episode MDD (n = 494); highly recurrent MDD (≥ 3 episodes; n = 1954); chronic MDD (current episode ≥ 2 yr (n = 218)

Serotonin-norepinephrine reuptake inhibitor. In vitro studies a >10-fold greater selectivity for norepinephrine reuptake inhibition than it does for serotonin reuptake inhibition, compared to other SNRI’s

Levomilnacipran ER Treatment in Adult MDD Patients with First-Episode, Highly Recurrent, and Chronic MDD

- Greater improvement with levomilnacipran ER vs placebo in all 3 subgroups (MADRS, HAMD)
- SDS: Greater improvement with levomilnacipran ER vs. placebo for first-episode and highly recurrent MDD; results of similar magnitude for chronic MDD, but not significant
- MADRS response rate levomilnacipran ER vs. placebo
  - First-episode MDD: 44.5% vs. 35.0%
  - Highly recurrent MDD: 44.3% vs. 33.5%
  - Chronic MDD: 36.8% vs. 22.0%; all p < 0.05

Vilazodone: SSRI and 5-HT1A Receptor Partial Partial Agonist

- Response and remission rates at the end of treatment. Pooled ITT population; LOCF. *p < .05, **p < .01, ***p < .001.
- Response defined as a decrease of 50% or greater from baseline to end of treatment in MADRS or HAMD17 total score.

Vilazodone: Sexual Functioning

- Sexual dysfunction is common adverse effect from SSRIs
- Vilazodone, a novel serotonin (5-HT) reuptake inhibitor and 5-HT1A partial agonist approved for MDD, exerts its effects at the 5-HT transporter and at both presynaptic and postsynaptic 5-HT1A receptors. This mechanism may limit sexual dysfunction.
- Three Phase III studies: two 8-week, placebo-controlled (N = 869 patients (vilazodone, 436; placebo, 433)) and a 52-week open-label study (N = 433). Sexual function was assessed by analyzing changes from baseline to end of treatment (EOT) using Arizona Sexual Experience Scale or Changes in Sexual Functioning Questionnaire.
- In the placebo-controlled studies, 8.0% of vilazodone-treated patients and 0.9% of placebo-treated patients reported ≥1 sexual-function-related treatment-emergent adverse event (p < .001).
- Sexual dysfunction prevalence was high (50%, men; 68%, women) before treatment and declined during treatment in vilazodone and placebo groups.
- At EOT, stable/improved sexual function was observed in ≥91% of patients in placebo-controlled studies;

Investigational Second Generation Antipsychotics As Adjunctive Treatment for MDD
Adjunctive Brexpiprazole in MDD: Results from MADRS vs. Placebo at 6-week Endpoint.

- Brexpiprazole
  - Approved July 2015 by US FDA as an adjunctive therapy in MDD
  - Partial agonist at dopamine D\textsubscript{2} receptor; partial agonist at 5-HT\textsubscript{1A} receptor; antagonist at 5-HT\textsubscript{2A} receptor; antagonist at noradrenergic α1B; antagonist at noradrenergic α2C

- Patients with historical inadequate response to 1-3 ADTs entered a prospective 8-week phase on physician-determined, open-label ADT.

- Those with inadequate response were randomized to ADT + brexpiprazole 2 mg/d or ADT + placebo for 6 weeks

- Brexpiprazole (n = 175) reduced mean MADRS total score versus placebo (n = 178) at week 6 in the efficacy population per final protocol (-8.36 vs -5.15, $p = .0002$)

ADT = antidepressant therapy.
Long-Term Safety of Adjunctive Brexpipiprazole in MDD: Results from Two 52-Week Open-Label Studies (N = 2084)

- Two phase III open-label, flexible dose, adjunctive treatment, 52-week
- Study 1: 0.25 to 3 mg/d; Study 2: 0.5 to 3 mg/d
- 40.7% completed 52 wk; mean dose 1.6 mg/d
- Safe and well tolerated; NNH = 38

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs leading to withdrawal</td>
<td>13.8</td>
</tr>
<tr>
<td>Most frequent TEAEs</td>
<td></td>
</tr>
<tr>
<td>• Weight increased, %</td>
<td>3.6</td>
</tr>
<tr>
<td>• Depression, %</td>
<td>1.3</td>
</tr>
<tr>
<td>Most common adverse events</td>
<td></td>
</tr>
<tr>
<td>• Weight increased, %</td>
<td>24.7</td>
</tr>
<tr>
<td>• Akathisia, %</td>
<td>10.0</td>
</tr>
<tr>
<td>Mean weight gain</td>
<td></td>
</tr>
<tr>
<td>• Week 26 (n = 1250), kg</td>
<td>2.9</td>
</tr>
<tr>
<td>• Week 52 (n = 829), kg</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Long-Term Safety of Adjunctive Brexipiprazole in MDD: Results from Two x 52-Week Open-Label Studies

<table>
<thead>
<tr>
<th>Rate of Akathisia</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/d brexipiprazole</td>
<td>13.5</td>
</tr>
<tr>
<td>2 mg/d brexipiprazole</td>
<td>7</td>
</tr>
<tr>
<td>1 mg/d brexipiprazole</td>
<td>4</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Most common side effects were akathisia, weight increase, tremor, and somnolence

Efficacy and Safety of Cariprazine as Adjunctive Therapy in MDD
A Double-Blind, Randomized, Placebo-Controlled Study

- Cariprazine (CAR)
  - Dopamine D₃ receptor partial agonist
  - Dopamine D₂ receptor partial agonist
  - Less potent as 5-HT₂A antagonist
- RCT, phase 2b, flexible-dose study as adjunctive treatment (n = 808)
- Patients with current episode and history of inadequate response to antidepressant randomized to adjunctive treatment
  - Cariprazine, 1-2 mg/d
  - Cariprazine, 2-4.5 mg/d
  - Placebo

Efficacy and Safety of Cariprazine as Adjunctive Therapy in MDD

A Double-Blind, Randomized, Placebo-Controlled Study

- **Efficacy**
  - CAR 2-4.5 mg/d superior to placebo: mean difference in change from baseline MADRS: -2.2 (p = 0.114)
  - CAR 1-2 mg/d not significantly superior to placebo
  - Decrease in Sheehan Disability Scale score not significant for either dose

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>CAR, 1-2 mg/d</td>
<td>38%</td>
</tr>
<tr>
<td>CAR, 2-4.5 mg/d</td>
<td>49%</td>
</tr>
</tbody>
</table>

Number needed to treat = 9

*Not currently approved by the FDA for MDD

Efficacy and Safety of Cariprazine as Adjunctive Therapy in MDD
A Double-Blind, Randomized, Placebo-Controlled Study

- Tolerability
  - Most frequent adverse events: akathisia, insomnia, nausea
  - Discontinuation rate due to adverse events: 13%
  - Discontinuation rate for placebo: 3%
  - NNH: 10

<table>
<thead>
<tr>
<th></th>
<th>Rate of Akathisia</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR, 1-2 mg/d</td>
<td>7%</td>
<td>&lt; 1 kg</td>
</tr>
<tr>
<td>CAR, 2-4.5 mg/d</td>
<td>22%</td>
<td>&lt; 1 kg</td>
</tr>
<tr>
<td>Placebo</td>
<td>2%</td>
<td>&lt; 1 kg</td>
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Lurasidone For The Treatment Of Major Depressive Disorder With Mixed Features: RDBPC 6 Week Trial

● Mixed features
  - DSM-5 introduced a "with mixed features" (subthreshold hypomanic) specifier for major depressive disorder (MDD)
  - 25%-30% of MDD patients have mixed features
  - Patients with MDD with mixed features do not respond as well to antidepressants

● First RCT of MDD with mixed features
  - Patients with MDD and MADRS score ≥ 26 with 2 or 3 symptoms of mixed features (N = 2090)
  - Randomized to lurasidone 20–60 mg/d or placebo for 6 weeks

RDBPC = randomized double blind placebo controlled

Lurasidone For The Treatment Of Major Depressive Disorder With Mixed Features: RDBPC 6 Week Trial: Results

- Mean change for lurasidone vs placebo on MADRS (-20.5 vs -13.0; p < .001; effect size, 0.80)
- Adverse event: nausea (6.4% vs. 2%)
- No worsening of anxiety
- Minimal effects on metabolic parameters

Ketamine and Other Glutamatergic Agents
Ketamine (KET)

- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist
- Can cause psychotic-like symptoms
- Acute antidepressant efficacy not sustained

Change in the 21-Item Hamilton Depression Rating Scale (HDRS) Over 1 Week (n = 18)

Zarate CA, et al. *Arch Gen Psychiatry* 2006;63:856-864. PMID: 16894061
Rationale for OPT Ketamine: NIMH Trial in Treatment-Resistant Depression

- Several single-site studies supported the rapid antidepressant efficacy of KET in TRD; however, uncertainties remained:
  - Small sample size
  - Crossover design
  - Saline as control condition
  - Response persistence
  - Safety and tolerability
- Would a single infusion of KET prove superior to an “active” placebo in a parallel-arm RCT?
- KET (N = 47); midazolam (N = 25)

Primary Efficacy Outcome: MADRS at 24 hr

Memantine: Apathy Evaluation Scale

AZD6765 IV: Change in MADRS Scores


(N = 22)
Recent multicenter trials failed to demonstrate efficacy in multiple doses per week protocols over several weeks

Program reportedly canceled
GLYX-13 in Major Depression

- U shaped dose response in rat models and in Phase 2A study
- No ketamine-like side effects
- Phase 2A study – 1, 5, 10 or 30 mg or placebo; i.v.
- 5 mg and 10 mg separated from placebo at day 7 but not day 14; other doses did not
- Effect size for single dose 0.58

Burch RM: Presented at the ACNP Annual Meeting, December 2-6, 2012.
**Abstract:** Antagonism of N-methyl-d-aspartate glutamatergic receptors (NMDAR) may represent an effective antidepressant mechanism. d-cycloserine (DCS) is a partial agonist at the NMDAR-associated glycine modulatory site that at high doses acts as a functional NMDAR antagonist. 26 treatment-resistant MDD patients participated in a double blind, placebo-controlled, 6-wk parallel group trial with a gradually titrated high dose (1000 mg/d) of DCS added to their antidepressant medication. DCS treatment was well tolerated, had no psychotomimetic effects and led to improvement in depression symptoms as measured by Hamilton Depression Rating Scale (HAMD; p = 0.005) and Beck Depression Inventory (p = 0.046). Of the 13 subjects treated with DCS, 54% had a $\geq 50\%$ HAMD score reduction vs. 15% of the 13 patients randomized to placebo (p = 0.039). A significant (p = 0.043) treatment× pre-treatment glycine serum levels interaction was registered. These findings indicate that NMDAR glycine site antagonism may be a cost-effective target for development of mechanistically novel antidepressants. Larger-sized DCS trials are warranted.

Onabotulinumtoxin in (OBA)
The corrugator muscle region of the forehead has special significance in producing facial expressions associated with depression. Darwin observed in 1872 that contractions in the corrugator region produce peculiarly formed wrinkles on the forehead, referred to as "Omega Melancholium." In the present study, results from 61 right-handed, drug-free women with major depressive disorder showed a significant positive correlation between facial corrugator EMG values and psychomotor agitation. Results were not due to differences in severity of depression. These data offer preliminary evidence that agitation is reflected in corrugator muscle activity and may explain the "Omega sign" of melancholia.

OnabotulinumtoxinA (OBA) vs. Placebo in MDD: HDRS-17

N = 30 Dose : Women = 29U; Men = 40U
Amygdala-Prefrontal Coupling Underlies Individual Differences in Emotion Regulation

Abstract: Despite growing evidence on the neural bases of emotion regulation, little is known about the mechanisms underlying individual differences in cognitive regulation of negative emotion, and few studies have used objective measures to quantify regulatory success. Using a trait-like psychophysiological measure of emotion regulation, corrugator electromyography, we obtained an objective index of the ability to cognitively reappraise negative emotion in 56 healthy men (Session 1), who returned 1.3 years later to perform the same regulation task using fMRI (Session 2). Results indicated that the corrugator measure of regulatory skill predicted amygdala-prefrontal functional connectivity. Individuals with greater ability to down-regulate negative emotion as indexed by corrugator at Session 1 showed not only greater amygdala attenuation but also greater inverse connectivity between the amygdala and several sectors of the prefrontal cortex while down-regulating negative emotion at Session 2. Our results demonstrate that individual differences in emotion regulation are stable over time and underscore the important role of amygdala-prefrontal coupling for successful regulation of negative emotion.

Clinical Connections

- MDD is a heterogeneous disorder – different approaches to treatment are needed to manage symptom presentation
- Recent and emerging treatments for MDD target different mechanisms
- A personal approach to the treatment of MDD can tailor the choice of pharmacological interventions and help to prevent treatment resistance
Questions & Answers