Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

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Disclosures

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Learning Objectives

● Evaluate patients at frequent intervals for the presence of residual symptoms or treatment resistance.

● Initiate a treatment plan that includes the latest pharmacotherapeutic options for the management of treatment resistant depression.
How many weeks constitutes an adequate trial of an antidepressant?

A. 2 weeks
B. > 4 weeks
C. < 6 weeks
D. 8 weeks
Audience Response

Remission is defined as what percent reduction in symptomatology?

A. 60%
B. 70%
C. 80%
D. 90%
Understanding Antidepressant Nonresponse

- Diagnosis
- Drug selection
- Dosage/adherence
- Duration of therapy
- Disabilities/complexity/comorbidities
Antidepressant Nonresponse is Often Explained By…

- Nonadherence
- Unrecognized bipolarity
- Unrecognized psychosis
- Unrecognized comorbidities
Response and Remission

- **Response** – usually defined as 50% improvement in symptoms
  - Allows for the presence of significant residual symptoms, which may predispose patients to recurrence, chronicity, and suicidality

- **Remission** – often defined as 80% reduction in symptomatology using one of the accepted rating scales, or as an absolute cutoff score, such as <7 on the 17-item Hamilton Rating Scale for Depression (HAM-D) or <5 on the PHQ-9

What Constitutes an Adequate Trial of an Antidepressant?

- Longer (duration) is generally better (>4 weeks at a full therapeutic dose)
- Whenever possible, the dose should be increased above the minimum
- Intolerance does not equal nonresponse
- Residual symptoms (nonremission) do not equal nonresponse
STAR-D Remission Rates Across All 4 Levels

Remission Definition: HAMD-17 ≤7

<table>
<thead>
<tr>
<th>Level</th>
<th>Duration</th>
<th>Treatment Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.9 weeks</td>
<td>Low</td>
</tr>
<tr>
<td>2,3</td>
<td>8-10 weeks</td>
<td>Treatment Resistance</td>
</tr>
<tr>
<td>4,5</td>
<td>≤14 weeks</td>
<td>Treatment Resistance</td>
</tr>
<tr>
<td>6</td>
<td>≤14 weeks</td>
<td>High</td>
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</tbody>
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Mono, single medication regimen; Augm, combination medication treatment.

References:
Should We Switch or Use Adjunctive Strategies?

- Parsimony favors switching
- Adjunctive therapies often easier to implement (i.e., avoids washout and cross-titration)
- STAR*D disappointingly did not answer this question aside from demonstrating that adjunctive strategies preferred for partial responders and switching preferred for nonresponders
New and Emerging Antidepressant Strategies in MDD
Mechanisms of Action of Known or Putative Antidepressants

- Enhanced NE and 5-HT Monoaminergic Synaptic Activity
- Second Generation Antipsychotics
- Glutamatergic Transmission
- Hormone/Peptide Regulators
- Opioid Modulators
- Onabotulinumtoxin-A (OBA)
- Deep Brain Stimulation (DBS)
Vortioxetine

- 5HT1A agonist; 5HT reuptake blocker; 5HT1b partial agonist; 5HT3 and 5HT7 antagonist
- Positive trials reported in severe and nonsevere MDD; dose is 10-20 mg per day
- Improves cognition in MDD

Vilazodone

- SSRI and 5-HT1A Receptor Partial Agonist
- Positive trials reported in severe and nonsevere MDD; dose is 10-20 mg per day
- Improves sexual function in MDD

Levomilnacipran

- Serotonin and norepinephrine reuptake inhibitor (SNRI)
- Extended release
- Improves functional impairment in MDD

Second Generation Antipsychotics

- $D_2$ and $5-HT_2$ antagonists (e.g., quetiapine, olanzapine, etc.)
- $D_2$ partial agonists with serotonin receptor properties (aripripralzole and brexpiprazole)
- $D_2$ antagonism and mixed 5HT receptor effects (lurasidone)
- Efficacy primarily in bipolar mania, bipolar depression, and MDD augmentation
Lurasidone in MDD with Mixed Features*

- *DSM-5 MDD “Mixed” requires 3 manic features
- Two or three mixed features in trial
- Lurasidone 20-60 mg/day vs. placebo x 6 weeks
- NNT = 3; highly effective
- Lurasidone was well tolerated; nausea 6.4% vs. 2% for placebo

*Not FDA approved for the treatment of MDD
Lurasidone in MDD with Mixed Features


*Not FDA approved for the treatment of MDD*
Brexpiprazole: Adjunctive Treatment in MDD

- 5HT1A and D$_2$ partial agonist
- 5HT2a antagonist
- Antagonist at various NE sites
- Dose related akathisia; have lower incidence than with aripiprazole
- Long-term trial 24% had weight gain (3.1 kg mean)

Cariprazine*

- D3 and D2 partial agonist
- Less effect as 5H2a antagonist
- Superior to placebo in MDD augmentation (NNT= 9; NNH = 10)
- Dose related akathisia
- Low weight gain

*Not FDA approved for the treatment of MDD
Mechanisms of Action
Glutamatergic Agents

- NMDA antagonism – e.g., ketamine
- Other glutamate effects – e.g., GLYX-13; D-cycloserine, etc.
Ketamine*  

- Anesthetic agent  
- Used intravenously primarily  
- Used for chronic pain  
- N-methyl-D-aspartate antagonist;  
- Mu opiod agonist; stimulant (?)  
- Psychotomimetic; dissociation  
- Acute antidepressant efficacy not sustained  

*Not approved by the US FDA for MDD
Ketamine: Change in the Hamilton Depression Rating Scale

The 21-item Hamilton Depression Rating Scale (HDRS) over 1 week (n = 18)

Several single-site studies supported the rapid antidepressant efficacy of ketamine in TRD; however, uncertainties remained:
- Small sample size
- Crossover design
- Saline as control condition
- Response persistence
- Safety and tolerability

Would a single infusion of ketamine prove superior to an “active” placebo in a parallel-arm randomized controlled trial?

Ketamine (N = 47); midazolam (N = 25)

*Not approved by the US FDA for MDD
Ketamine Primary Efficacy Outcome

Study Drug

Primary Outcome

MADRS Score

Time

Baseline Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7

Midazolam Ketamine

Inpatient Outpatient

***

Memantine for Late-Life Depression and Apathy After Disabling Medical Event: HDRS Effect

*Not approved by the US FDA for MDD

AZD 6765

- Synaptic glutamate binder
- 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 at 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.
A Randomized Add-On Trial of High-Dose D-cycloserine for Treatment-Resistant Depression


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. Twenty-six treatment-resistant major depressive disorder 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 ≥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.
Mechanisms of Action
Opioid Modulators

- Mu partial or full agonists – buprenorphine; ketamine
- Mixed mu agonist – antagonist – buprenorphine/SAM
- Kappa antagonists
Buprenorphine*

- Partial mu opioid agonist
- Kappa antagonist
- Used in addiction treatment
- Open label, positive data in refractory depression
- Being developed (in combination with samidorphan, a mu antagonist) for treatment of refractory major depression¹

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Low Dose Buprenorphine Reduces Suicidal Ideation

- 88 patients with clinically significant suicidal ideation
- Buprenorphine 0.1-0.8 mg/day (mean dose 0.44 mg/day) or placebo for 4 weeks
- Buprenorphine superior to PBO for reducing suicidal ideation at 2 and 4 weeks
- No withdrawal symptoms after treatment discontinuation

RCT of ALKS 5461 (buprenorphine plus the mu antagonist ALKS 33) in SSRI non-responders

Figure 4: MADRS Change from Baseline at Week 4

Stage 1
Stage 1 baseline MADRS (all subjects): 30.6
- Placebo: -9.6
- ALKS 5461 2/2: -13.3
- ALKS 5461 8/8: -11.4

Stage 2
Stage 2 baseline MADRS (all subjects): 23.8
- Placebo: -1.8
- ALKS 5461 2/2: -5.0
- ALKS 5461 8/8: -8.7

ALKS-5461 As Adjunct in MDD

- FORWARD-3 and FORWARD-4
- 814 patients in DB, PBO controlled 11 week trials in antidepressant non-responders
- Doses of buprenorphine/samidorphan (0.5/0.5 mg and 2/2 mg)
- Both doses not superior to PBO
- FORWARD-5 (1/1 mg and 2/2 mg) continues

Mechanisms of Action
Hormone/Peptide Regulators

- Glucocorticoid receptor antagonists
  - e.g., mifepristone
- CRH-R1 antagonists
- Melatonin type 1 and 2 receptor agonist
  - e.g., agomelatine
Agomelatine*

- M1 and M2 agonist
- 5HT2c antagonist
- Several positive European studies led to European licensure
- Phase III US program – 2 positive trials published
- Elevated LFTs are a potential limiting factor for FDA approval

*Not approved by the US FDA for MDD
Agomelatine Efficacy and Acceptability Revisited: Systematic Review and Meta-Analysis of Published and Unpublished Randomized Trials*

METHOD:

- Randomised controlled trials comparing agomelatine with placebo in the treatment of unipolar major depression were systematically reviewed. Primary outcomes were (a) Hamilton Rating Scale for Depression (HRSD) score at the end of treatment (short-term studies) and (b) number of relapses (long-term studies).

RESULTS:

- Meta-analyses included 10 acute-phase and 3 relapse prevention studies. Seven of the included studies were unpublished. Acute treatment with agomelatine was associated with a statistically significant superiority over placebo of -1.51 HRSD points (99% CI -2.29 to -0.73, nine studies). Data extracted from three relapse prevention studies failed to show significant effects of agomelatine over placebo (relative risk 0.78, 99% CI 0.41-1.48). Secondary efficacy analyses showed a significant advantage of agomelatine over placebo in terms of response (with no effect for remission). None of the negative trials were published and conflicting results between published and unpublished studies were observed.


*Not approved by the US FDA for MDD
Psychotic Major Depression

- 15-19% of community-based subjects with major depression\(^1\)
- Marked neuropsychological impairments \(^2,3\)
- Excessive HPA axis activity\(^4\) proposed as a cause of psychosis and/or cognitive impairment and target for treatment\(^5\)
- Mifepristone – GR antagonist 7 day treatment with longer term relief out to 8 weeks\(^6\)

Mifepristone** Plasma Level: Clinical Response (Placebo N = 626; Drug N = 824)

* $p = .0004$ (in comparison to Placebo)

**Not approved by the US FDA for MDD

Schatzberg AF. *Biol Psychiatry* 2015;77(9S): Abs403.
Mifepristone Plasma Level: Serum Cortisol and ACTH, at Day 7

Schatzberg AF. *Biol Psychiatry* 2015;77(9S): Abs403

*Serum Cortisol*

- Placebo (n=461)
- <1637 ng/ml (n=321)
- ≥1637 ng/ml (n=292)

*Plasma ACTH*

- Placebo (n=515)
- <1637 ng/ml (n=349)
- ≥1637 ng/ml (n=321)

**p = .0040**

* p = <.0001 (in comparison to Placebo)

** p = .0004
Onabotulinumtoxin A*

- ACh release inhibitor and neuromuscular blocking agent
- Pain indications – chronic migraine and cervical dystonia
- 2 positive RCT’s in major depression
- Effects of one injection last up to 16 weeks

*Not approved by the US FDA for MDD
Drawing of Patient Showing Omega Sign and Veraguth’s Fold

OnabotulinumtoxinA* (OBA) and Frown Expression


Frown Expression before and after OBA treatment

(N = 30)

before
(patient went into remission)
Dose – Women 29U
    Men 40U

*Not approved by the US FDA for MDD
OnabotulinumtoxinA* (OBA) vs. Placebo in Major Depression: HDRS-17

(N = 30)

Dose – Women 29U
Men 39U

*Not approved by the US FDA for MDD
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.

Deep Brain Stimulation for Treatment-Resistant Depression

Helen S. Mayberg,1,2,* Andres M. Lozano,3,* Valerie Voon,4 Heather E. McNeely,5 David Seminowicz,6 Clement Hamani,3 Jason M. Schwalb,3 and Sidney H. Kennedy4

First published study of DBS for TRD
Hypothesis driven, safety/proof-of-concept study
Open trial of subcallosal cingulate white matter DBS in 6 pts
4/6 Responders at 6 months (HRDS=8±3)
All 4 still well at 5+ years with continued Stimulation
Recent DBS Results

- Trial using the anterior capsule canceled after interim analysis
- Trial on subgenual capsule canceled after interim analysis
- Pilot trial suggested medial forebrain bundle may be a preferred site for implantation; further study resulted in failed trial

Psychotherapy for MDD

- Cognitive Behavioral therapy (CBT)
  - How thoughts effect feelings
  - “Automatic thoughts”
  - Homework

- Interpersonal Therapy (IPT)
  - Form of CBT, emphasis on interactions

- Problem-Solving Therapy (PST)
  - Form of CBT, emphasis on identifying and solving a particular problem related to depression

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Questions & Answers