New Pharmacological Treatments for Resistant Depression

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### Disclosures (lifetime): Maurizio Fava, MD

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<td><strong>Stock/Other Financial Options</strong></td>
<td>Equity Holdings: Compellis; PsyTherapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to MedAvante; Methylation Sciences Inc; National Alliance for Research on Schizophrenia &amp; Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM); National Coordinating Center for Integrated Medicine (NiiCM); National Institute of Drug Abuse (NIDA); National Institute of Mental Health (NIMH); Neuralstem, Inc.; NeuroRx; Novartis AG; Organon Pharmaceuticals; Otsuka Pharmaceutical Development, Inc.; PamLab, LLC; Pfizer Inc.; Pharmacia-Upjohn; Pharmaceutical Research Associates, Inc.; Pharmavite LLC; PharmoRx Therapeutics; Photothera; Reckitt Benckiser; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Stanley Medical Research Institute (SMRI); Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceuticals; Tal Medical; VistaGen; Wyeth-Ayerst Laboratories. Copyright for the MGH Cognitive &amp; Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation–Emergent Signs &amp; Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams &amp; Wilkins; Wolters Kluwer; World Scientific Publishing Co. Pte.Ltd.</td>
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All Currently Available Antidepressants are Monoamine-Based
They are Classified Accordingly

Figure 7 | The mechanisms of action of antidepressant drugs. The selective serotonin reuptake inhibitors (SSRIs; denoted with *) have been shown to have significant binding (antagonistic) to the serotonin transporter (5-HT₁), thereby blocking serotonin reuptake. The relatively selective noradrenaline reuptake inhibitors (NRIs; denoted with **) have also shown at therapeutically relevant doses to have significant binding to the noradrenaline transporter. The tricyclic antidepressants (TCAs; denoted with *) and other cyclic antidepressants, as well as the serotonin–noradrenaline reuptake inhibitors (SNRIs; denoted with †), block the reuptake of serotonin and noradrenaline by binding to their transporter in varying ratios. TCAs, to varying degrees, are potent blockers of histamine H₁ receptors, serotonin 5-HT₁ receptors, muscarinic acetylcholine receptors, and α₁-adrenergic receptors. These effects account for the higher adverse-effect burden of the TCAs than the other classes of antidepressants. The noradrenaline–dopamine reuptake inhibitors (NDRIs; denoted with ‡) primarily block the reuptake of noradrenaline and dopamine. The α₂-adrenergic receptor antagonists (denoted with ††) seem to enhance the release of both serotonin and noradrenaline by blocking α₂-autoreceptors. More-selective dual-action serotonin receptor antagonists/agonists primarily bind to serotonin 5-HT₁ receptors. Agomelatine is a melatonin receptor (MT₁ and MT₂) agonist (not shown) and a 5-HT₁c antagonist without anticholinergic or antihistaminergic properties. Most currently used monoamine oxidase (MAO) inhibitors are irreversible inhibitors of both MAOA and MAOB, with dopamine, tyramine and tryptamine being substrates for both isoforms of MAO. Moclomibe is a selective and reversible MAOA inhibitor. In addition, other neurobiological systems (such as γ-aminobutyric acid, glutamate and opioids) are probably involved in the neurobiology of MDD and are to some extent targeted by more experimental antidepressive substances (such as ketamine). **Serotonin antagonist and reuptake inhibitor.

www.mghcme.org
Augmentation with Dopaminergic Modulators

- Atypical antipsychotics
- Dopamine agonists
- Dopamine reuptake inhibitors
Three Double-Blind Studies of Adjunctive Aripiprazole to ADT in TRD - Two Pooled Studies and a Single Study*

**FIGURE 2.** Change in mean (±SE) MADRS Total score during the randomized, double-blind treatment phase (LOCF)

TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period,
Double-Blind, Placebo-Controlled Study of Quetiapine Augmentation in TRD

Change in MADRS total score from randomization over time (LOCF; MITT population)

p value active treatment vs. placebo + antidepressant:
QUE XR 150 mg/d + AD  < 0.001  < 0.01  < 0.05  < 0.01
QUE XR 300 mg/d + AD  < 0.001  < 0.001  < 0.05  < 0.01

Double-Blind Study of Adjunctive Brexipiprazole to ADT in TRD – Studies 227* and 228*

*TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period,

*p<0.05, **p<0.01 vs placebo

MMRM analysis; MADRS baseline: ADT + placebo 26.5, ADT + Brex 1 mg 26.9, ADT + Brex 3 mg 26.5

Study 227 CSR – Thase et al, J Clin Psychiatry. 2015 Sep;76(9):1232-40


*p<0.05, **p<0.01, ***p<0.001 vs placebo

MMRM analysis; MADRS baseline: ADT + placebo 27.3, ADT + Brex 26.9
Double-Blind Study of Adjunctive Ziprasidone to Escitalopram in TRD (n=139)

A Double-Blind, Randomized, Placebo-Controlled Study of Cariprazine as Adjunctive Therapy in TRD*

Figure 1. Mean Change From Baseline to Week 8 in MADRS Total Score (ITT Population, MMRM)

*Treatment resistance assessed with the ATHF by site rater (resistance rating ≥3; ATHF global confidence score ≥3)

Double-Blind, Placebo-Controlled Study of Pramipexole (up to 1.5 mg bid) in Treatment Resistant Depression (n=60)

Pooled Analysis of Studies on Modafinil (200 mg/day) Augmentation in SSRI Partial Responders with MDD and Persistent Fatigue and Sleepiness (n=348)


Figure 4 Mean (± SEM) Changes from Baseline in 17-item Hamilton Depression Scale (17-item HAM-D) Scores between Placebo and Modafinil (All Patients).

* p = .009.
† p = .02.
Tissue Type-Specific Bioenergetic Abnormalities in Adults with Major Depression

**Figure 2** Least squares means (± SE), adjusted for total phosphorus signal in both gray matter and white matter of levels of phosphocreatine in both depressed and normal individuals. *p < 0.05 when compared with same tissue type of normal subjects. Findings were adjusted for multiple comparisons.

Harper et al, Neuropsychopharmacology (2017) 42, 876–885
Changes in Total Nucleoside Triphosphate (NTP) Levels (left) and Phosphocreatine (PCr) Levels (right) During T3 Augmentation Treatment in Two Groups of MDD Subjects (Treatment Responders and Nonresponders)

Iosifescu et al, BIOL PSYCHIATRY 2008;63:1127–1134
Double-Blind, Placebo-Controlled Creatine (5 gr/day) Augmentation of SSRIs in Women with MDD (n=52)

Lyoo et al, Am J Psych
epub
Targeting Neurogenesis: The Role of Neurogenesis—Promoting Agents for the Treatment of MDD

TNF: Tumour Necrosis Factor. BDNF: Brain Derived Neurotrophic Factor.
IL: Interleukins.
Low-Dose Combination of Buspirone and Melatonin in Novelty Suppressed Feeding (NSF) and Neurogenesis Assays

**NSF**

- **Bus** - buspirone
- **Mel** - melatonin
- **Combo** - buspirone + melatonin
- **Flu** - fluoxetine

**Neurogenesis**

- **Bus**
- **Mel**
- **Combo**
- **Flu**

**Fava et al, J Psychiatr Res. 2012 Dec;46(12):1553-63**
Low-Dose Combination of Buspirone (15 mg/day) and Melatonin (3 mg qhs) Is More Effective than Placebo and Buspirone Alone in MDD

*\( p < .05 \) combination vs placebo and buspirone alone.


This information includes a use that has not been approved by the US FDA.
Targeting Neurogenesis: The Neurogenesis-Promoting Agent NSI-189 for the Treatment of MDD

A Phase 2 Double-Blind Study of NSI-189 in MDD Patients

• 220 MDD subjects were randomized to NSI-189 40 mg daily, 80 mg daily, or placebo for 12 weeks
• The primary outcome measure was the MADRS, with secondary subject-rated measures including the SDQ, the CPFQ, and the QIDS-SR
• MADRS score reduction versus placebo did not reach significance for either dose (40 mg pooled mean difference −1.8, p = 0.22, 80 mg pooled mean difference −1.4, p = 0.34, respectively).
• However, the 40 mg dose showed greater overall reduction in SDQ (pooled mean difference −8.2; Cohen’s d for Stages 1 and 2 = −0.11 and −0.64, p = 0.04), and CPFQ scores (pooled mean difference −1.9; Cohen’s d for Stages 1 and 2 = −0.28 and −0.47, p = 0.03) versus placebo, as well as QIDS-SR scores in Stage 2 of SPCD (−2.5; Cohen’s d Stages 1 and 2 = −0.03 and −0.68, p = 0.04).
• The 40 mg dose also showed advantages on some objective cognitive measures of the CogScreen (absolute Cohen’s d ranged between 0.12 and 1.12 in favor of NSI-189, p values between 0.002 and 0.048 for those with overall significance), but not the Cogstate test.
• Both doses were well tolerated.

Depression and the Immune System

(Goldsmith DR, Rapaport MH, Miller BJ., Mol Psychiatry. 2016 Dec;21(12):1696-1709.)

Depression, Stress

Endocrine System

Inflammatory Cytokines (e.g. IFN-alpha, IL-1, IL-6, TNF-alpha)

Immune-Based Diseases

May contribute to treatment resistance in depression

Innate Immune Activation (e.g. secondary to infection, trauma, surgery, radiation, chemotherapy, psychological stress)
Double-Blind Study of SAMe (1600 mg/d) Augmentation in SSRI-Resistant Depressed Patients

FIGURE 2. HAM-D Response and Remission Rates Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo

- Placebo + Antidepressant (N=34)
- SAMe + Antidepressant (N=39)

- Data depict last observation carried forward (LOCF) for all patients randomly assigned.
- Significant difference between groups (p<0.05, Fisher’s exact test).

Papakostas G et al; Am J Psychiatry 2010; 167:942–948
Omega-3 Fatty Acid (1.2 gr/day) Augmentation of Citalopram Treatment for Patients With Major Depressive Disorder (n=42)

FIGURE 1. Hamilton Depression Rating Scale measures of depressive symptoms for subjects treated with citalopram + placebo or citalopram + omega-3 supplements over the 8 weeks of study, mean ± SD (*P < 0.05, computed via regression modeling).

Gertsik et al, J Clin Psychopharmacol 2012;32: 61-64
A Double-Blind Study of the Phosphodiesterase Inhibitor Pentoxifylline, an Inhibitor of IL-6 and TNF-α synthesis, as a Novel Adjunct to Antidepressants in MDD Patients

**Fig. 2.** Changes in Hamilton Depression Rating Scale (HAM-D) total score from baseline to week 12. Data are presented as mean and 95% confidence interval.

El-Haggar et al, Psychother Psychosom 2018;87:331–339
Minocycline (200 mg/day) (an Anti-Inflammatory and Neuroprotective Agent) as an Adjunct for Treatment-Resistant Depressive Symptoms: A Pilot, Randomized Placebo-Controlled Trial

Figure 2. Predicted means and 95% confidence intervals for Hamilton Rating Scale total scores by treatment group and week for lower socio-economic status class participants (most frequent class).

Impact of Ixekizumab^ Treatment on Depressive Symptoms in Patients with Moderate-to-Severe Psoriasis:

Griffith et al, Psychother Psychosom 2017;86:260–267

^Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A

**Fig. 2.** Proportion of patients who met remission criteria for depressive symptoms (QIDS-SR_{16} total score ≤ 5 at week 12 [last observation carried forward]) by treatment group. IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; QIDS-SR_{16}, 16-item Quick Inventory for Depressive Symptomatology – Self-Report.
Palmitoylethanolamide (600 mg bid), with Anti-Inflamatory and Endocannabinoid Effects, as Adjunctive Therapy in MDD (n=58)

Fig. 2. Repeated measure analysis for comparison of the effects of two treatments on the Hamilton depression rating scale (HDRS) scores. Values represent mean ± SEM (standard error of mean). P values show the result of the independent sample t-test for comparison of the score change from the baseline between the two groups at each time point. NS non-significant. *p ≤ .05; **p ≤ .01.
GABA and Glutamate

Figure 1 Amino acid neurotransmitter synthesis and catabolism. The synthesis and catabolism of GABA and glutamate are tightly interconnected in the brain. Abbreviations: αKGDH, α-ketoglutarate dehydrogenase; AAT, aspartate aminotransferase; CoA, coenzyme A; Cys, cysteine; GABA, γ-aminobutyric acid; GDH, glutamate dehydrogenase; GABA-T, GABA transaminase; GAD, glutamic acid dehydrogenase; GCL, γ-glutamyl cysteine ligase; Gln, glutamine; Glu, glutamate; Gly, glycine; GSH, glutathione; GHB, γ-hydroxybutyric acid; GGT, γ-glutamyl transferase; GGCT, γ-glutamyl cyclotransferase; OPLAH, 5-oxoprolinase (adenosine triphosphate-hydrolyzing); SSADH, succinic semialdehyde dehydrogenase; SSAR, succinic semialdehyde reductase.

Pehrson and Sanchez, Drug Design, Development and Therapy 2015:9 603–624
Targeting Glutamate and GABA: The Role of Glutamatergic and GABAergic Agents for the Treatment of MDD
### GABA Concentrations in MDD

**Table 1** The relationship between major depressive disorder and GABA concentration measured by magnetic resonance spectroscopy

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<th>Direction</th>
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<tr>
<td>OCC</td>
<td>14 medication-free depressed versus 18 healthy controls</td>
<td>Down</td>
<td>20</td>
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<tr>
<td>OCC</td>
<td>33 depressed subjects versus 38 healthy controls</td>
<td>Down</td>
<td>19</td>
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<tr>
<td>OCC</td>
<td>6 depressed subjects versus 12 healthy controls</td>
<td>Down</td>
<td>17</td>
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<tr>
<td>OCC</td>
<td>15 treatment-resistant depressed versus 24 healthy controls</td>
<td>Down</td>
<td>18</td>
</tr>
<tr>
<td>OCC</td>
<td>15 treatment-resistant depressed versus 18 non-treatment-resistant depressed</td>
<td>Down</td>
<td>18</td>
</tr>
<tr>
<td>OCC</td>
<td>18 non-treatment-resistant depressed versus 24 healthy controls</td>
<td>NC</td>
<td>18</td>
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<tr>
<td>OCC</td>
<td>15 recovered depressed versus 18 healthy controls</td>
<td>Down</td>
<td>27</td>
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<tr>
<td>OCC/ACC</td>
<td>12 recovered depressed versus 11 healthy controls</td>
<td>Down</td>
<td>28</td>
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<tr>
<td>OCC</td>
<td>11 depressed subjects, before and after SSRI treatment</td>
<td>Up</td>
<td>22</td>
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<td>OCC</td>
<td>8 depressed subjects, before and after ECT treatment</td>
<td>Up</td>
<td>23</td>
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<tr>
<td>OCC</td>
<td>15 medication-free depressed subjects, before and after CBT (8 subjects completed experiment)</td>
<td>Trend down</td>
<td>26</td>
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<tr>
<td>ACC</td>
<td>15 treatment-resistant depressed versus 24 healthy controls</td>
<td>Trend down</td>
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<tr>
<td>ACC</td>
<td>15 treatment-resistant depressed versus 18 non-treatment resistant depressed</td>
<td>Trend down</td>
<td>18</td>
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<tr>
<td>ACC</td>
<td>18 non-treatment-resistant depressed versus 24 healthy controls</td>
<td>NC</td>
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<td>Dorsal PFC</td>
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<td>Dorsal PFC</td>
<td>16 recovered depressed subjects versus 15 healthy controls</td>
<td>NC</td>
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<td>VM PFC</td>
<td>20 depressed patients (medication-free for 4–8 weeks) versus 20 healthy controls</td>
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<tr>
<td>VM PFC</td>
<td>16 recovered depressed subjects versus 15 healthy controls</td>
<td>NC</td>
<td>24</td>
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**Abbreviations:** ACC, anterior cingulate cortex; CBT, cognitive behavioral therapy; ECT, electroconvulsive therapy; NC, no change; OCC, occipital cortex; PFC, prefrontal cortex; SSRI, selective serotonin-reuptake inhibitor; VM, ventromedial.

Pehrson and Sanchez, Drug Design, Development and Therapy 2015:9 603–624
A Placebo-Controlled Study of SAGE-217, an Oral, Positive Allosteric Modulator of GABA type A receptors, in the Treatment of Major Depressive Disorder

Gunduz-Bruce et al
Glutamatergic Neurometabolite Levels in Major Depressive Disorder

Glutamatergic Neurotransmission: Pathway to Developing Novel Rapid-Acting Antidepressant Treatments


**Figure 1.** Proposed mechanisms of action of glutamatergic modulators and other putative rapid-acting antidepressants. Disinhibition hypothesis: Ketamine and esketamine selectively block N-methyl-D-aspartate receptors (NMDARs). These are expressed on gamma-aminobutyric acid (GABA)-ergic inhibitory interneurons, and their blockade decreases interneuron activity that, in turn, leads to disinhibition of pyramidal neurons and enhanced glutamatergic firing. Glutamate then binds to and activates post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). Inhibition of spontaneous NMDAR-mediated transmission. Alternatively, ketamine may induce rapid brain-derived neurotrophic factor (BDNF) translation in the hippocampus, reduce phosphorylation, and activate eukaryotic elongation factor 2 (eEF2). Ketamine may also preferentially bind to NMDARs and affect neuronal NMDAR-mediated spontaneous excitatory transmission, which at rest keeps eEF2 phosphorylated and inhibits BDNF synaptic translation. De-suppression of BDNF translation then contributes to changes in synaptic plasticity that mediate ketamine’s antidepressant effects. AMPAR activation is also necessary for these effects. Inhibition of extra-synaptic NMDARs: Ketamine selectively blocks extra-synaptic GluN2B-containing NMDARs, which are tonically activated by low levels of ambient glutamate regulated by the excitatory amino acid transporter 2 (EAAT2) located on astrocytes. Inhibition of the extra-synaptic GluN2B-NMDARs de-suppress the mammal target of rapamycin complex 1 (mTORC1) function, which in turn induces protein synthesis. Blockade of spontaneous NMDAR activation inhibits eEF2 kinase (eEF2K) activity, thus preventing phosphorylation of its eEF2 substrate. This effect subsequently enhances BDNF translation and, ultimately, protein synthesis. Inhibition of lateral habenula (LHb) neurons: In animal models, local neuronal firing in a single brain region known as the lateral habenula (LHb) drives significant depressive-like behaviors. Ketamine decreases burst activity in the LHb by blocking NMDAR-dependent burst activity in the LHb and disinhibiting the downstream activity of midbrain dopaminergic neurons and serotoninergic neurons, which are responsible for activating the reward centers in the brain. Local blockade of NMDARs or low-voltage-sensitive T-type voltage-sensitive calcium channels (T-VSCCs) in the LHb sufficient to induce rapid antidepressant effects. The role of ketamine metabolites: (2R,SR)-hydroxynorketamine (HNK) exerts NMDAR inhibition-independent antidepressant actions by activating AMPAR-mediated synaptic potentiation. Other glutamatergic modulators: Metabotropic glutamate receptor (mGluR) 2/3 antagonists are thought to enhance synaptic glutamate levels, thereby boosting AMPAR transmission and firing rates and extracellular monoamine levels. GLYX-13, which has partial agonist properties at NMDARs, is hypothesized to activate mTORC and subsequently induce protein synthesis. GLYX-13 requires AMPA and activity-dependent BDNF release, but unlike ketamine does not produce glutamatebursts. AMPAR activation enhances BDNF release, activates the tropomyosin receptor kinase B (TrkB) receptor, and subsequently promotes protein synthesis by activating the mTORC complex. AC, adenylyl cyclase; CAMP, cyclic adenosine monophosphate; GAD, glutamate decarboxylase; Gsa, G alpha subunits; Glu, glutamate; GLY-1, glutamate transporter 1; Glu, glutamate; GSK-3, glycogen synthase Kinase 3; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor. Adapted with permission from (Lener et al., 2017; Zanos et al., 2018).
Double-Blind, Placebo-Controlled, Crossover Study of i.v. Ketamine, a Selective NMDA Receptor Antagonist, in TRD (n=18)

Figure 2. Change in the 21-item Hamilton Depression Rating Scale\(^8\) (HDRS), Brief Psychiatric Rating Scale\(^4\) (BPRS) positive symptoms subscale, and Young Mania Rating Scale\(^8\) (YMRS) scores over 1 week (n=18). Values are expressed as generalized least squares means and standard errors for the completer analysis. * indicates P<.05; † P<.01; ‡ P<.001.

Figure 3. A. Proportion of responders (50% improvement on 21-item Hamilton Depression Rating Scale\(^9\) [HDRS]) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18). B. Proportion of remitters (HDRS score ≤7) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18).

Zarate et al, Arch Gen Psychiatry. 2006;63:856-864
Intravenous Ketamine in Adult Patients with Treatment-Resistant Depression: A Dose-Frequency Study*


*TRD assessed with ATRQ by SAFER rater
A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in TRD*

Figure 2: MADRS Total Score LS Mean Change from Baseline to End Point – ANCOVA LOCF Analysis (Intent-to-Treat Analysis Set-DB)

- Period 1
  - Placebo (N=33)
  - Esk28 (N=11)
  - Esk56 (N=11)
  - Esk84 (N=12)

- Period 2
  - Placebo (N=6)
  - Esk28 (N=8)
  - Esk56 (N=9)
  - Esk84 (N=5)

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<td>-4.2 (2.09)</td>
<td>-6.3 (2.07)</td>
<td>-9.0 (2.13)</td>
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<td>Period 2</td>
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</tr>
</tbody>
</table>
| CI: confidence interval; DB: double-blind; Esk: esketamine; MADRS: Montgomery-Asberg Depression Rating Scale; SE: standard error

• Assuming equal variance across treatments and periods, the effect size combining both periods ranged from 0.52 for 28 mg, 0.92 for 56 mg, and 1.20 for 84 mg esketamine

*TRD assessed with the ATRQ
Meta-Analysis of Esketamine Augmentation in TRD Studies

Figure 1: Forest Plot of SMD in change in primary outcome scores between adjunctive esketamine and placebo

Papakostas et al, submitted for publication
Double-Blind Study of Rapastinel (GLYX-13), Modulator of the NMDA Receptor, in TRD*

GLYX-13 Significantly Reduced HDRS-17 Scores

Baseline HDRS-17 was 26 (n=33), 26 (n=25), 25 (n=20), 25 (n=17), 25 (n=21) for Placebo and GLYX-13, 1, 5, 10, and 30 mg/kg, respectively.

*TRD assessed with ATRQ by site rater
Double-Blind, Placebo-Controlled Study of Adjunctive Basimglurant, Negative Allosteric Modulator of the mGlu5 Receptor, in TRD*

*MADRS Clinician Rated | MADRS Patient Rated | QIDS Depression Scale

Days of Treatment

Least Square Means (MMRM)

Primary Endpoint | Post-Hoc Analysis | Secondary Endpoint

- Placebo  
- 0.5 mg/d  
- 1.5 mg/d

* R01.5mg vs. Placebo; p<0.05; One tail, Unadjusted for multiple comparisons. Quiroz et al, ACNP 2014

*Treatment History Assessed with the ATRQ converted to an electronic form and administered on a computer
HAM-D Scores in Double-Blind Study of the Kainate (Glutamate) Receptor Antagonist Topiramate (100-200 mg/day) Augmentation in TRD (n=53)

![Graph showing HAM-D scores over time with Topiramate and Placebo treatments.](image)

- p < .000

Adjunctive Pregabalin (75-300 mg/day) (pregabalin increases the activity of the neuronal glutamate transporter type 3 (EAAT3)) in Partial Responders With Major Depressive Disorder and Residual Anxiety

**TABLE 2. Clinical Outcomes at Week 9 and After Pregabalin Augmentation at Week 17**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 9</th>
<th>Week 17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDRS-17 scores</td>
<td>13.5 ± 3.1</td>
<td>9.1 ± 2.9</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>HDRS-AS scores</td>
<td>6.3 ± 2</td>
<td>3.6 ± 1.7</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>HDRS total – AS scores</td>
<td>7.2 ± 2.3</td>
<td>5.5 ± 1.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>0</td>
<td>13 (65)</td>
<td></td>
</tr>
<tr>
<td>Remitters, n (%)</td>
<td>0</td>
<td>7 (35)</td>
<td></td>
</tr>
</tbody>
</table>

Citocline or CDP-Choline (100 mg BID), Increases EAAT2 Expression, a Glutamate Transporter, Combination Therapy for Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

Fig. 2. Repeated measures for comparison of the effects of two treatments on Hamilton Depression Rating Scale (HDRS). Values represent mean ± standard deviation. P-values show the result of the independent t-test comparing HDRS scores between the two groups at each time point. NS indicates non-significant; *, $P < 0.05$. 

Double-Blind Study of the Dopaminergic NMDA Receptor Antagonist Amantadine (150 mg/day) Augmentation of Imipramine in TRD Patients (n=50)

Double-Blind Study of D-Cycloserine (1 gr/day) (a Partial Agonist at the Glycine Recognition Site of the Glutamatergic NMDA Receptor) Augmentation in Treatment Resistant Depression (n=26)


Fig. 2. Proportion of responders [\geq 50\% improvement on 21-item Hamilton Depression Rating Scale (HAMD)] during 6 wk adjuvant treatment with d-cycloserine (N = 13) and placebo (N = 13). * p = 0.039.
A Double-Blind Study of the NR2B Subunit Selective N-Methyl-D-Aspartate Antagonist, CP-101,606, in Patients With Treatment-Refractory Major Depressive Disorder


<table>
<thead>
<tr>
<th>TABLE 2. Summary of Statistical Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Change from baseline in MADRS total score by time point, CP-101,606 vs placebo</td>
</tr>
<tr>
<td>Period 2, wk 0 (day 2)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 0 (day 5)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 1 (day 8)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 1 (day 12)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 2 (day 15)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Change from baseline in 17-item HDRS total score by time point, CP-101,606 vs placebo</td>
</tr>
<tr>
<td>Period 2, wk 0 (day 2)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 0 (day 5)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 1 (day 8)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
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<tr>
<td>Period 2, wk 1 (day 12)</td>
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<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
<tr>
<td>Period 2, wk 2 (day 15)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
</tr>
<tr>
<td>LS means</td>
</tr>
</tbody>
</table>

^Least-squares mean.

^This represents the P value for the primary analysis. Note that all other P values are presented only for descriptive purposes.
L-4-chlorokynurenine is Currently Evaluated As an Adjunct in Resistant MDD

The prodrug L-4-chlorokynurenine (4-Cl-KYN; AV-101) is rapidly absorbed, actively transported across the blood-brain barrier, and converted in astrocytes to 7-chlorokynurenic acid (7-Cl-KYNA), a potent and specific antagonist of the glycine B coagonist site of the N-methyl-D-aspartate (NMDA) receptor.
Org 26576, an AMPA Receptor Positive Allosteric Modulator, in Patients Diagnosed with Major Depressive Disorder

<table>
<thead>
<tr>
<th>Part I</th>
<th></th>
<th>Part II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Org 26576(^a) (n=16)</td>
<td>Placebo (n=8)</td>
</tr>
<tr>
<td><strong>MADRS, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31.06 (5.67)</td>
<td>29.63 (4.72)</td>
</tr>
<tr>
<td>Day 2, CFB</td>
<td>−5.25 (7.74)</td>
<td>−6.38 (7.63)</td>
</tr>
<tr>
<td>Day 4, CFB</td>
<td>−9.69 (7.12)</td>
<td>−8.50 (7.91)</td>
</tr>
<tr>
<td>Day 7, CFB</td>
<td>−10.63 (7.60)</td>
<td>−9.00 (8.76)</td>
</tr>
<tr>
<td>Day 10, CFB</td>
<td>−13.08 (12.25)</td>
<td>−10.33 (9.83)</td>
</tr>
<tr>
<td>Endpoint, CFB(^b)</td>
<td>−13.19 (10.18)</td>
<td>−10.75 (9.88)</td>
</tr>
<tr>
<td><strong>MADRS response at endpoint, N (%)(^b,c)</strong></td>
<td>7 (43.8)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td><strong>MADRS remission at endpoint, N (%)(^b,c)</strong></td>
<td>4 (25.0)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td><strong>CGI - Severity, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.63 (0.89)</td>
<td>4.50 (0.76)</td>
</tr>
<tr>
<td>Day 7, CFB</td>
<td>−0.75 (1.18)</td>
<td>−0.75 (0.89)</td>
</tr>
<tr>
<td>Endpoint, CFB(^b)</td>
<td>−1.19 (1.42)</td>
<td>−0.75 (1.04)</td>
</tr>
<tr>
<td><strong>CGI-Improvement at endpoint, N (%)(^b,d)</strong></td>
<td>6 (37.5)</td>
<td>2 (25.0)</td>
</tr>
</tbody>
</table>

CFB: change from baseline; CGI: clinical global impression; MADRS: Montgomery-Asberg Depression Rating Scale; SD: standard deviation.

\(^a\)Part I dose variable depending on treatment day and study block. Range was 100 mg BID to 600 mg BID. Time points relevant to all Part I study blocks are presented.

\(^b\)Observed case data are presented for all visits except Endpoint, where last observation carried forward is presented.

\(^c\)Response defined as ≥50% decrease from baseline to endpoint on MADRS total score. Remission defined as ≤10 at endpoint on MADRS total score.

\(^d\)CGI improvement defined as a score of 1 (very much improved) or 2 (much improved).

Dextromethorphan/Quinidine (45/10 mg/day) (Dextromethorphan is an NMDA receptor Antagonist) Pharmacotherapy in Patients with TRD: A Proof of Concept, Open Clinical Trial

Double-blind Study in Moderate to Severe MDD of AXS-05 (45 mg Dextromethorphan/105 mg Bupropion) vs. Bupropion (105 mg), Twice Daily for 6 Weeks (n=80)

Remission Rates

- Bupropion plus Dextromethorphan
- Bupropion plus Placebo

Antidepressant Efficacy of the Antimuscarinic Drug Scopolamine (4 mcg/Kg), Which Increases mTORC1 Signaling: A Randomized, Placebo-Controlled Clinical Trial

Furey and Drevets, Arch Gen Psychiatry. 2006;63:1121-1129
Double-Blind Study of Oral Scopolamine (1 mg/day) Augmentation on Citalopram in MDD

Figure 2. Results of 2-Factor Repeated-Measures Analysis of Variance

*P < .05, **P < .01.

Targeting the Opioid System: The Role of Opioid System Modulators for the Treatment of MDD
Double-Blind, SPCD Study of ALKS 5461 (buprenorphine plus the mu antagonist Alks 33) vs. Placebo

Figure 4: MADRS Change from Baseline at Week 4

MADRS LS Means

- Placebo
- ALKS 5461 2/2
- ALKS 5461 8/8

Stage 1
Stage 1 baseline MADRS (all subjects): 30.6
-9.6
-13.3

Stage 2
Stage 2 baseline MADRS (all subjects): 23.8
-11.4
-1.8

-8.7
p=0.004

-5.0

Pooled Analysis of the FORWARD-4 and FORWARD-5 SPCD Studies of ALKS 5461

doi: 10.1038/s41380-018-0284-1. [Epub ahead of print]
Other Molecular Targets in the Development of Treatments for TRD
Double-Blind, Crossover Trial (n=29) of a Single-Dose Psilocybin (0.3 mg/kg) or Niacin, Both in Conjunction with Psychotherapy, in Patients with Cancer-Related Anxiety and Depression

Rapid Antidepressant Effects of the Psychedelic Ayahuasca in TRD: a Randomized Placebo-Controlled Trial (n=29)

Fig. 2. HAM-D scores at baseline and seven days after dosing. Statistical analysis shows a significant difference between ayahuasca (squares) and placebo (circles) seven days after dosing (p = 0.019). Between-group effect size is high (Cohen’s d = 0.98). Values are (mean ± s.e.m.). HAM-D scores: mild depression (8–16), moderate (17–23), severe (≥24).

Palhano-Fontes et al, Psychological Medicine 1–9. https://doi.org/10.1017/S0033291718001356
Two Identical Double-Blind Studies of NK-1 Antagonist Orvepitant in MDD (Study 733 utilized the independent SAFER rating method for subject selection vs. Study 833, which utilized the Medavante methodology, with independent ratings for all visits)

Ratti et al, J Psychopharmacol 2013 May;27(5):424-34

Figure 1. Mixed models repeated measures (MMRM) adjusted mean change from baseline (± standard error of the mean (SEM)) in HAM-D score at each visit by treatment. (A) Study 733, (B) study 833. *p<0.05 vs placebo. BL: baseline.
Dextromethadone

- Dextromethadone is an orally available N-methyl-D-aspartate (NMDA) receptor antagonist with potential rapid onset efficacy in individuals with depression and treatment resistant depression.
- A single-site, randomized, double-blind, placebo-controlled Phase 1 clinical trial of dextromethadone administered orally for 10 days to healthy volunteers admitted for 14 days to a Clinical Research Unit (CRU) (NCT03638869) showed that the administration of REL-1017 significantly increased BDNF plasma levels in healthy subjects compared to placebo, ranging from twice to 17 times the pre-treatment BDNF levels. The increase began as early as day two and persisted through day 10.
- These findings further support and are consistent with the results of preclinical studies demonstrating that REL-1017 exerts an antidepressant-like activity in animal models of depressed behavior comparable to that of ketamine.
- The U.S. Food and Drug Administration (FDA) has granted REL-1017 Fast Track designation for the adjunctive treatment of major depressive disorder (MDD). Relmada is currently evaluating REL-1017 in a Phase 2 clinical trial assessing tolerability, safety and antidepressant efficacy in patients with MDD.

In addition to CRF, arginine vasopressin (AVP), a cyclic nonapeptide, is a primary factor in the regulation of HPA axis activity, with its expression level in the paraventricular nucleus increasing with both acute and repeated stress.

V1B receptor mRNA is expressed in the majority of anterior pituitary corticotrophs that secret ACTH; within the brain, significant populations can be found within the hypothalamus and limbic brain regions, which regulate stress and affect.

Two identical studies were designed to evaluate the efficacy and tolerability of the first nonpeptide vasopressin V(1b) receptor antagonist, SSR149415, in the treatment of major depressive disorder (MDD).

In one MDD trial where paroxetine separated from placebo, SSR149415-treated patients did not show significant improvement from baseline on any outcome measure compared with placebo-treated patients.

In the other MDD study, SSR149415 250 mg (P = .04), but not escitalopram (P = .15), demonstrated significant improvement compared to placebo on the HDRS total score at week 8. SSR149415 had no deleterious effects on the HPA axis.

Orexin Receptor Antagonists in MDD

• The orexin signaling system, which originates in the lateral hypothalamus, plays an important role in sleep-wake control and appears to regulate stress, reward, and mood.

• The orexin receptor antagonist almorexant had antidepressant-like effects in animal models of depression (Nollet et al, Neuropharmacology. 2011 Jul-Aug;61(1-2):336-46. )

• A study of filorexant (MK-6096), an orally bioavailable potent and selective antagonist of orexin 1 and orexin 2 receptors, failed to separate from placebo in MDD (Connor et al, Int J Neuropsychopharmacol. 2017 Aug 1;20(8):613-618).

• Seltorexant is a potent and selective antagonist of the orexin-2 receptor that is being developed for the treatment of insomnia and major depressive disorder (De Boer et al, J Psychopharmacol. 2018 Jun;32(6):668-677.).
Conclusions

• Dopaminergic modulators have shown efficacy
• Gabaergic and glutamatergic drug treatments have robust evidence of efficacy in TRD
• Neuroinflammation in MDD has become an important target for the development of new therapies for TRD
• Mitochondrial and bioenergetic abnormalities in MDD suggest the usefulness of strategies increased brain energy metabolism
• Neurogenesis-promoting and opioid modulating compounds are promising therapies for TRD