Recent Developments in the Psychopharmacology of Depression

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Slater Family Professor of Psychiatry, Harvard Medical School
<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
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<tr>
<td>Advisory Board/Consultant</td>
<td>Abbott Laboratories; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon, Inc.; Clinical Trials Solutions, LLC; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DiagnoSearch Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; GenOmind, LLC; GlaxoSmithKline; Grunenthal Gmbh; i3 Innovus/Ingenis; Janssen Pharmaceutical; Jazz Pharmaceuticals, Inc.; Johnson &amp; Johnson Pharmaceutical Research &amp; Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante, Inc.; Merck &amp; Co., Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Neuronetics, Inc.; NextWave Pharmaceuticals; Novartis AG; Nutrition 21; Orexigen Therapeutics, Inc.; Organon Pharmaceuticals; Otsuka Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; PharmaStar; Pharmavite® LLC.; PhrenoRx Therapeutics; Precision Human Biobehavioral; Prexa Pharmaceuticals, Inc.; Puretech Ventures; Psychogenics; Psylin Neurosciences, Inc.; Rexahn Pharmaceuticals, Inc.; Ridge Diagnostics, Inc.; Roche; RCT Logic, LLC; Sanofi-Aventis US LLC.; Sepracor Inc.; Servier Laboratories; Schering-Plough Corporation; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Synthelabo; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; Tetragenex Pharmaceuticals, Inc.; TransForm Pharmaceuticals, Inc.; Translating Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc.</td>
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<td>Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; Boehringer Ingelheim Gmbh; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; PharmaStar; United BioSource, Corp.; Wyeth-Ayerst Laboratories</td>
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<td>Research Support</td>
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<td>Stock/Other Financial Options</td>
<td>Compellis Pharmaceuticals, PsyBrain, Inc.</td>
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Royalty/patent, other income: Patent for SPCD and patent application for a combination of azapirones and bupropion in MDD, copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER. Patent for research and licensing of SPCD with RCT Logic; Lippincott, Williams & Wilkins; World Scientific Publishing Co. Pte Ltd.
Brain Energy Metabolism and MDD


**Fig. 1** Energy metabolism in the brain

**Fig. 3** The creatine kinase/phosphocreatine/creatine system as a buffering system of cellular ATP levels
Myochoondrial Dysfunction in MDD

Fig. 4 Mechanisms underlying mitochondrial dysfunction and psychiatric disorders

Brain Bioenergetics and Response to T3 Augmentation in MDD

Figure 1. The position of the phosphorus magnetic resonance spectroscopy ($^{31}$P MRS) acquisition slice (left) and a sample $^{31}$P MRS spectrum recorded from a healthy volunteer (right). The position of the slice for acquisition of $^{31}$P MRS data is indicated by lines overlaid on the mid-sagittal proton image. PME, phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; NTP, nucleoside triphosphate.

Brain Bioenergetics and Response to T3 Augmentation in MDD (cont.d)

Figure 3. Changes in total nucleoside triphosphate (NTP) levels (left) and phosphocreatine (PCr) levels (right) during treatment in two groups of major depressive disorder subjects (treatment responders and nonresponders).

Treatment Outcomes (% Remission) (STAR*D L-3 Augmentation)

Effects of Creatine on Brain Energy Metabolism

• Oral supplementation with creatine increased the cerebral reservoir of phosphocreatine (Lyoo et al, Psychiatry Res 2003; 123:87–100)

• An increased brain creatine reservoir may cause a shift in brain creatine kinase activity and ultimately be used to produce adenosine triphosphate (ATP) from phosphocreatine in response to energy demand (Lyoo et al, Psychiatry Res 2003; 123:87–100; Adhihetty et al, Neuromolecular Med 2008; 10:275–290; Andres et al, Brain Res Bull 2008; 76:329–343)

• Creatine exerts neuroprotective effects through mechanisms involving antiapptotic and antioxidant effects on mitochondrial functioning (Andres et al, Brain Res Bull 2008; 76:329–343)
Double-Blind, Placebo-Controlled Creatine (5 gr/day) Augmentation of SSRIs in Women with MDD (n=52)

**FIGURE 2.** Percentage Change in Hamilton Depression Rating Scale (HAM-D) Score for Women With Major Depressive Disorder Assigned to Creatine Monohydrate or Placebo Augmentation of SSRI

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Creatine</th>
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<tr>
<td>27</td>
<td>25</td>
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<tr>
<td>25</td>
<td>23</td>
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<td>24</td>
<td>19</td>
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<tr>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>22</td>
<td>17</td>
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</tbody>
</table>

Mean changes in total score with 95% confidence intervals are shown. Changes in depression score were analyzed by using mixed-effects model repeated-measures analysis. Main effects for treatment group, visit, and their interaction were included in the model. Age and baseline HAM-D score were also included as covariates in the model.

Significant difference between groups in intent-to-treat analysis (p<0.001).

Lyoo et al
Am J Psych
epub
Cytokine Abnormalities in MDD

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>MDD mean ± SD</th>
<th>Control mean ± SD</th>
<th>Rank sum Z</th>
<th>Rank sum p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP-1α</td>
<td>463.8 ± 706.88</td>
<td>60.33 ± 95.91</td>
<td>-3.420</td>
<td>0.0004*</td>
</tr>
<tr>
<td>MCP-1</td>
<td>191.00 ± 381.69</td>
<td>56.66 ± 106.19</td>
<td>-8.585</td>
<td>0.0001*</td>
</tr>
<tr>
<td>IL-1α</td>
<td>223.75 ± 258.50</td>
<td>2.06 ± 8.45</td>
<td>4.316</td>
<td>0.0004*</td>
</tr>
<tr>
<td>IL-1β</td>
<td>42.53 ± 105.19</td>
<td>1.29 ± 4.07</td>
<td>-6.060</td>
<td>0.0001*</td>
</tr>
<tr>
<td>IL-2</td>
<td>65.19 ± 316.57</td>
<td>10.58 ± 43.43</td>
<td>-4.316</td>
<td>0.0004*</td>
</tr>
<tr>
<td>IL-3</td>
<td>40.53 ± 261.34</td>
<td>1.14 ± 4.53</td>
<td>-0.903</td>
<td>0.3667</td>
</tr>
<tr>
<td>IL-4</td>
<td>13.72 ± 50.31</td>
<td>2.90 ± 11.45</td>
<td>-3.269</td>
<td>0.0011*</td>
</tr>
<tr>
<td>IL-5</td>
<td>24.03 ± 100.63</td>
<td>3.78 ± 12.69</td>
<td>-1.046</td>
<td>0.2954</td>
</tr>
<tr>
<td>IL-6</td>
<td>5.98 ± 14.22</td>
<td>1.23 ± 6.16</td>
<td>-3.291</td>
<td>0.0010*</td>
</tr>
<tr>
<td>IL-7</td>
<td>1.70 ± 3.10</td>
<td>0.17 ± 1.16</td>
<td>-3.280</td>
<td>0.0010*</td>
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<tr>
<td>IL-8</td>
<td>231.19 ± 754.78</td>
<td>1.09 ± 3.50</td>
<td>-7.556</td>
<td>0.0000*</td>
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<tr>
<td>IL-10</td>
<td>8.68 ± 36.76</td>
<td>0.70 ± 3.39</td>
<td>-4.192</td>
<td>0.0000*</td>
</tr>
<tr>
<td>IL-12p70</td>
<td>17.40 ± 84.09</td>
<td>0.39 ± 1.91</td>
<td>-3.425</td>
<td>0.0006*</td>
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<tr>
<td>IL-13</td>
<td>21.45 ± 98.85</td>
<td>4.13 ± 14.51</td>
<td>-2.825</td>
<td>0.0047</td>
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<tr>
<td>IL-15</td>
<td>0.96 ± 5.06</td>
<td>0.24 ± 1.62</td>
<td>-4.005</td>
<td>0.0001*</td>
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<tr>
<td>Eotaxin</td>
<td>167.08 ± 365.27</td>
<td>23.57 ± 62.61</td>
<td>-4.861</td>
<td>0.0000*</td>
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<tr>
<td>GM-CSF</td>
<td>141.30 ± 606.87</td>
<td>8.52 ± 24.81</td>
<td>-4.330</td>
<td>0.0000*</td>
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<tr>
<td>IFN-γ</td>
<td>24.46 ± 25.43</td>
<td>6.67 ± 11.90</td>
<td>-5.057</td>
<td>0.0000*</td>
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<tr>
<td>IP-10</td>
<td>163.01 ± 171.24</td>
<td>130.71 ± 120.09</td>
<td>-1.456</td>
<td>0.1453</td>
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<tr>
<td>TNF-α</td>
<td>7.84 ± 45.34</td>
<td>3.13 ± 11.73</td>
<td>0.415</td>
<td>0.6784</td>
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</table>

*p values (with asterisks) significant after Bonferroni correction for 20 tests (p < 0.0025).

MDD = Major Depressive Disorder, SD = standard deviation.
Clinical Trial of Adjunctive Cyclooxygenase-2 inhibitor Celecoxib Treatment in MDD Patients: a Double-Blind and Placebo-Controlled trial


Figure 1. Mean±SD of the two protocols on the Hamilton Depression Rating Scale scores. ns, nonsignificant; ** ≤ 0.01 and *** ≤ 0.001.
SAMe, Methylfolate and Omega-3 Fatty Acids and Inflammation

• The anti-inflammatory effects of SAMe have been attributed to its ability to reduce the expression of the pro-inflammatory cytokine TNF-α and to increase the expression of the anti-inflammatory cytokine IL-10 (McClain et al, Alcohol 2002;27(3):185-92).

• Folic acid protects motor neurons against inflammation and apoptosis in SOD1 G93A transgenic mice (Zhang et al, Neuropharmacology. 2008 Jun;54(7):1112-9).

Double-Blind Study of SAMe (1600 mg/d) Augmentation in SSRI-Resistant Depressed Patients

Papakostas G et al; Am J Psychiatry 2010; 167:942–948

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).
Double-Blind Study of L-Methylfolate (L-MTHF) Augmentation of SSRIs - Sequential Parallel Comparison Design (SPCD)

Figure 1. Pooled Response Rates in Two Trials of L-Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression

<table>
<thead>
<tr>
<th>Trial 1 (7.5 mg/day for 30 days) (N=148)</th>
<th>Trial 2 (15 mg/day for 30 days) (N=75)</th>
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<td>SSRI plus MTHF</td>
<td>18.3%</td>
</tr>
<tr>
<td>SSRI monotherapy</td>
<td>18.8%</td>
</tr>
<tr>
<td>SSRI plus MTHF</td>
<td>32.3%</td>
</tr>
<tr>
<td>SSRI monotherapy</td>
<td>14.6%</td>
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</table>

a Response was defined as a reduction of ≥50% in Hamilton Depression Rating Scale score during treatment or a final score of ≤7. Significant difference between groups in trial 2 (p=0.04). The pooled analysis was conducted as described in Fava et al. (25).

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
Amantadine and Inflammation

• Treatment with amantadine (AMA), an N-methyl-D-aspartate (NMDA) receptor antagonist reduces the production of the pro-inflammatory cytokines, specifically interferon-gamma (IFN-gamma) and tumor necrosis factor-alpha (TNF-alpha).

• In addition, amantadine treatment increased the production of the negative immunoregulator, interleukin-10 (IL-10).

• Furthermore, the combined treatment of amantadine with the SSRI fluoxetine, but not imipramine, had a stronger immunomodulatory effect on cytokine production than amantadine alone.

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

Women

Men

P<.05

A large majority of studies have provided evidence of reduced glutamate metabolite levels in the frontal cortex and cingulate regions of patients with major depressive disorder in the midst of a current depressive episode (Sanacora et al, Neuropharmacology 62 (2012): 63-77).

Depressed subjects show across studies consistent structural abnormalities in brain regions closely associated with stress-responsiveness and emotional/cognitive processing in depressed subjects (Koolschijn, et al, Hum. Brain Mapp. 30, 3719-3735.)
Double-Blind, Placebo-Controlled, Crossover Study of i.v. Ketamine in TRD (n=18)

Figure 2. Change in the 21-item Hamilton Depression Rating Scale (HDRS), Brief Psychiatric Rating Scale (BPRS) positive symptoms subscale, and Young Mania Rating Scale (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 [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
HAM-D Scores in Double-Blind Study of the Kainate (Glutamate) Receptor Antagonist Topiramate (100-200 mg/day) Augmentation in TRD (n=53)


*p<.000
Pooled Analyses of Studies of Pregabalin in GAD Patients with Depression: HAM-D-17 Changes [pregabalin increases the activity of the neuronal glutamate transporter type 3 (EAAT3)].

Stein DJ et al, European Neuropsychopharmacology (2008) 18, 422–430
Double-Blind Study of the Glutamate Release Inhibitor Lamotrigine (up to 400 mg/day) Augmentation of Paroxetine in TRD Patients (n=96)

Barbee et al, J Clin Psychiatry 2011; 72(10):1405-1412
Riluzole Increases Glial Glutamate Transporter (GLT1) Expression


Open-Label Study of Riluzole (50 mg bid) Augmentation in TRD

Double-Bind Study in MDD Patients of Monotherapy with Memantine (5-20 mg/day), a Non-Competitive Glutamate NMDA Receptor Antagonist with Greater Potency for NMDA Receptors Containing the NR2C Subunit than for NR2A Subunit-Containing Receptors

Minocycline Effects on Inflammation and Neuronal Plasticity

• The second-generation tetracycline antibiotic drug minocycline has powerfully anti-inflammatory and neuroprotective effects (Maes et al., Metab Brain Dis 2009;24:27–53.; Ponzini, Neurosci lett 2012;506:136–40).

• Minocycline inhibits mitochondrial permeability-transition mediated cytochrome c release from the mitochondria (Kim and Suh. Behav Brain Res 2009;196:168–79)

• Minocycline attenuated lipopolysaccharide (LPS)-induced expression of pro-inflammatory cytokines, and that this drug prevented LPS-induced development of depressive-like behaviors in mice (O'Gonnor et al., Mol Psychiatry 2009;14:511–22)
Open-Label Study of Minocycline (150 mg/day) as Adjunctive Therapy for Patients with Unipolar Psychotic Depression (n=25)

Fig. 1. HAM-D total score at each assessment from baseline to week 6 (ITT, LOCF).

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

Furey and Drevets, Arch Gen Psychiatry. 2006;63:1121-1129
Low-Dose Combination of Buspirone and Melatonin in NSF and Neurogenesis Assays

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

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.
Kappa Antagonists in MDD

• Few case reports have described the efficacy of the mu agonist/kappa antagonist buprenorphine in treatment-resistant MDD. [Bodkin et al, J Clin Psychopharmacol 1995;15:49–57]

• Buprenorphine is often described as a mixed mu/kappa antagonist, although compelling evidence suggests it is actually a partial kappa agonist.
HAM-D-17 Scores: ALKS 5461 (buprenorphine plus the mu antagonist Alks 33) vs. Placebo

Change in HAM-D-17 Total Score from Baseline

<table>
<thead>
<tr>
<th>Cohort Type</th>
<th>N</th>
<th>Score</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1:1 Cohort</td>
<td>14</td>
<td>6.7</td>
<td>0.032</td>
</tr>
<tr>
<td>8:1 Cohort</td>
<td>14</td>
<td>5.0</td>
<td>0.337</td>
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</tbody>
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*Results obtained using the Exact Wilcoxon Test

Ehrich et al, NCDEU Annual Meeting, 2012
Conclusions

• Compounds that increase brain energy metabolism may be useful augmentation strategies in TRD

• Medications and nutraceuticals with antiinflammatory properties have shown promise in the treatment of MDD

• Drugs that modulate glutamatergic neurotransmission have shown antidepressant effects, in some cases quite rapid

• Agents that increase neurogenesis and neuronal plasticity appear to have antidepressant effects

• Kappa antagonists may have antidepressant properties