# Update on Treatment of Depression

Written by Brian Hoyle

George I. Papakostas, MD, Massachusetts General Hospital, Boston, Massachusetts, USA, discussed the search for rapidly acting antidepressant treatments for major depressive disorder (MDD). Antidepressants are effective; analyses of 248 drug-placebo pairwise comparisons involving more than 36,000 patients revealed a significantly different response rate of 53.8% for all antidepressants used versus 37.3% for placebo ($p<0.05$) [Papakostas GI, Fava M. *Eur Neuropsychopharmacol* 2009]. Antipsychotics that have demonstrated benefits when used in augmented treatment of depression include aripiprazole, olanzapine, quetiapine, and risperidone [Papakostas GI. *J Clin Psychiatry* 2009].

However, the initial potential has not always borne out. Additional Phase 3 trials of dexmecamylamine failed to demonstrate efficacy in primary or secondary outcomes [Vieta E et al. *Eur Neuropsychopharmacol* 2014]. Similarly, 2 Phase 3 trials indicated the ineffectiveness of lisdexamphetamine in reducing Montgomery-Asberg Depression Rating Scale (MADRS) scores versus placebo during 8 weeks of adjunctive therapy ($p=0.883$ and $p=0.583$).

It is rare for a patient to experience treatment benefit during the first week. Placebo-controlled studies have shown benefit with scopolamine infusions given at regular intervals after the first infusion [Furey ML, Drevets WC. *Arch Gen Psychiatry* 2006]. A single dose of ketamine has also been demonstrated effective in lessening depression in patients with MDD.

The Rapidly-Acting Treatment for Resistant Depression (RAPID) program, funded by the National Institutes of Mental Health (NIMH) consists of 3 clinical trials, with a goal of developing therapies that act within 72 hours. Trial 1 is an ongoing randomized, double-blind study designed to explore the role of low-field magnetic stimulation in augmenting antidepressant activity in patients with MDD who are refractory to their current antidepressant. Trial 2, which is nearing initiation, will assess the activity of LY2456302, a selective kappa receptor antagonist, in a similar cohort of patients. Trial 3 will be a dose-effect relationship study of a single intravenous infusion of ketamine.

James W. Murrough, MD, Icahn School of Medicine, Mount Sinai, New York, New York, USA, discussed the role of ketamine for treatment-resistant depression (TRD). The rapid antidepressant effect of ketamine was demonstrated in TRD, with improved symptoms relative to placebo within 110 minutes after a single ketamine infusion and persistent benefit through Day 7 [Zarate CA Jr et al. *Arch Gen Psychiatry* 2006]. A greater and faster improvement in depression was found with ketamine compared with midazolam, with a lower MADRS score at 24 hours, and improvement in neurocognitive performance [Murrough JW et al. *Am J Psychiatry* 2013]. Repeated administration of ketamine may extend these benefits [Rasmussen KG et al. *J Psychopharmacol* 2013; Shiroma PR et al. *J Affect Disord* 2014].

Sub-anesthetic doses of ketamine are effective for TRD and well tolerated, stated Dr. Murrough. The effects of ketamine appear to be rapid and selective and may involve neurotrophic and neuroplastic mechanisms. However, caution is warranted given the possibility of drug abuse and the demonstrated cognitive decline in chronic users of higher doses of ketamine.

Sanjay J. Mathew, MD, Baylor College of Medicine, Houston, Texas, USA provided an overview of glutamatergic drug targets in TRD. Major reasons to target glutamate modulation in the treatment of severe mood disorders are listed in Table 1.

Prolonged stress alters release of glutamate, reduces receptors of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA), impairs astroglial cells, and reduces glutamate turnover. Ketamine can increase synapse formation [Duman RS et al. *Neuropharmacology* 2012], and may affect glutamatergic signaling at rest and regulation of bone-dependent neurotrophic factor (BDNF)–meditated signaling [Kavalali ET, Monteggia LM. *Am J Psychiatry* 2012]. Eleven compounds targeting glutamate receptors are under development.

Lanicemine (AZD6765) is being tested as a blocker of NMDA. A Phase 2b adjunctive trial of lanicemine in TRD found significant changes in MADRS scores from baseline versus placebo

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Table 1. Glutamate Modulation as a Target in Severe Mood Disorders

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| • Glutamate is the most abundant amino acid neurotransmitter in the central nervous system, with multiple pharmacologic targets |
| • Glutamate is crucial to brain bioenergetics and metabolism |
| • Gluamate and NMDA receptor are key to fundamental mental processes including learning and memory |
| • Cycloserine, a partial NMDA receptor agonist, quickly improves insomnia, anorexia, and stress |

NMDA=N-methyl-D-aspartate.

after 3 weeks at doses of 100 mg (n=51; p<0.01) and 150 mg (n=51; p<0.05). The effect persisted at 4 and 5 weeks with the lower dose. However, at 8 weeks, no differences versus placebo were evident. The same study found a significant improvement in clinical global impression (CGI) scores at 2 weeks that persisted to 8 weeks.

Riluzole is a drug that inactivates voltage-dependent sodium channels and P/Q-type calcium channels, potentiates the AMPA receptor, and is a gamma-aminobutyric acid (GABA)-A receptor agonist. It has demonstrated neuroprotection in models of ischemia and Parkinson's disease and increases glutamate clearance from synaptic spaces [Frizzo ME et al. *Cell Mol Neurobiol* 2004]. Seven small open-label studies or case series of riluzole in MDD and other mood and anxiety disorders have shown it is well tolerated and effective in lessening depressive symptoms.

Dr. Mathew concluded that the glutamate system provides many pharmacologic targets, not all NMDA receptor antagonists have ketamine-like action, and it is unclear whether nonketamine glutamatergic drugs act rapidly.

Dan V. Iosifescu, MD, Ichan School of Medicine, Mount Sinai, New York, New York, USA, presented an overview of novel devices to treat depression. Transcranial magnetic stimulation (TMS) to modulate cortical activity using an alternating magnetic field was studied with the NeuroStar TMS System. TMS had a significant effect on the primary endpoint of proportion of remitters (14.1% vs 5.1% with sham at 6 weeks) in patients who are refractory to multiple antidepressants [George MS et al. *Arch Gen Psychiatry* 2010]. The US Food and Drug Administration (FDA) approved TMS for treatment of MDD based on 1 failed trial [O'Reardon JP et al. *Biol Psychiatry* 2007], stated Dr. Iosifescu, yet it may have merit combined with antidepressant medications or cognitive behavioral therapy.

Repetitive TMS has been shown to correct abnormal long-term potentiation and synaptic plasticity [Oberman L et al. *Front Synaptic Neurosci* 2010] and to induce activation of the brain-derived neurotrophic factor (BDNF)–tyrosine kinase B (TrkB) signaling pathway in rat hippocampal neurons and drive increased production of BDNF [Schaller G et al. *J Neural Transm* 2014].

The Deep TMS system, approved by the FDA in 2013 for refractory MDD, requires fewer treatments that take less time compared with standard TMS. A multicenter, multinational, Phase 3 study of deep TMS in 233 patients showed it was associated with a greater improvement in the Hamilton Depression Rating Scale (HDRS)–21 score at 5 weeks compared with sham treatment [Levkovitz et al. manuscript under review]. Continuing deep TMS therapy beyond 4 weeks up to 22 weeks increased both remission and patient response [Harel EV et al. *World J Biol Psych* 2014].

Contraindications for TMS include a history of seizures or epilepsy in patients or immediate relatives, prior head injury, cardiac disease, deafness or hearing loss, metabolic or systemic diseases, and comorbid neurologic disorders [Bersani FS et al. *Eur Psychiatry* 2013].

Synchronized TMS uses lower energy than repetitive TMS, which reduces the risk of seizure, and is synchronized with the alpha frequency of the patient. In a multicenter study, synchronized TMS versus sham treatment, significantly reduced the primary endpoint of Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) score at 6 weeks relative to baseline (p<0.033) in the 120 patients in the per-protocol analysis [Leuchter et al. manuscript submitted]. It also reduced $HAM\text{-}D_{24}$ (p<0.006), $HAM\text{-}D_{28}$ (p<0.013), Inventory of Depressive Symptomatology–Self-rated (p<0.056), and MADRS scores (p<0.014).

Noninvasive neurostimulation therapies have proven efficacy in depression, concluded Dr. Iosifescu, and is an area of vibrant research for treatments with more focused stimulation, deeper penetration, and improved efficacy and safety.