With this in mind, Dr. Saveanu and colleagues conducted the multiphase, multisite, randomized controlled iSPOT-D trial. This ongoing real-world effectiveness trial, with no placebo arm, was designed to identify genetic, physical, and psychological markers that predict specific response to a range of ADMs in a large group of outpatients diagnosed with MDD. Focusing on outcomes that may affect how personalized medicine is implemented in depression, the study was designed to identify predictors and moderators of outcomes in order to change how ADMs are selected.

To be included in the study, participants were required to be 18 to 65 years old, meet the DSM criteria for MDD, and score ≥16 on the Hamilton Rating Scale for Depression, 17-Item (HAM-D-17).

Exclusion criteria included suicidal ideation or planning, contraindication to study ADMs, recurrent or current substance dependence, and other mental disorders.

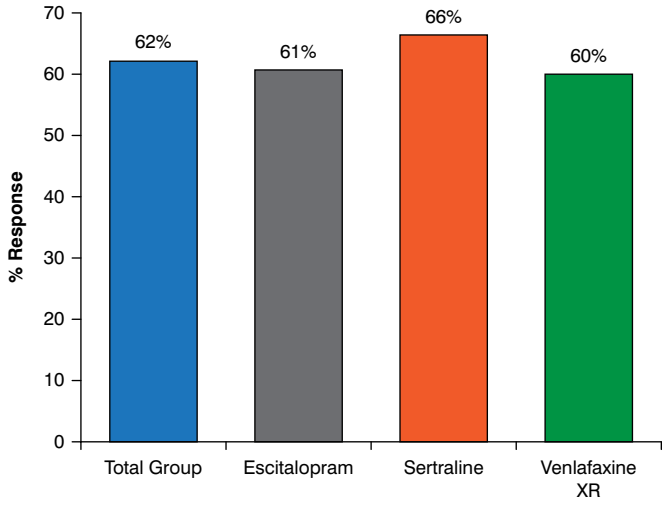
Outcome measures were obtained 8 weeks after ADM treatment. The study's primary outcome was rate of treatment response (defined by ≥50% improvement) and remission (defined by score ≤7) using the clinician-rated HAM-D-17 score. Secondary outcomes included rate of treatment response (defined by ≥50% improvement) and remission (defined by score ≤5) using the self-reported Quick Inventory of Depressive Symptomatology, 16-Item (QIDS-SR16) score; functional capacity; and side effect burden to the three ADMs.

In Phase 1 of the trial, participants (n=1008; mean age 37.8 years; 57% female) were randomly assigned to receive escitalopram (10 mg/day; maximum 20 mg/day), sertraline (50 mg/day; maximum 200 mg/day), or venlafaxine XR (75 mg/day; maximum 225 mg/day), the three first-line ADMs prescribed worldwide.

HAM-D-17 response rates were similar and consistent across the escitalopram, sertraline, and venlafaxine arms (61% vs 66% vs 60%, respectively; Figure 1), as were HAM-D-17 remission rates (48% vs 46% vs 42%, respectively). QIDS-SR16 response rates (55.7% vs 55.6% vs 48.4%) and remission rates (41.0% vs 38% vs 33.8%, respectively) were also similar across the three arms. Side effects were also mostly mild, and they occurred in a similar number of participants among the three groups (85% vs 80% vs 79%, respectively).

The results of the first half of this study indicate that escitalopram, venlafaxine, and sertraline produce similar and consistent response rates in patients with MDD, with similar and mild side effects. These findings even the clinical research playing field for identifying predictors and moderators of response that can be translated into patient care, Dr. Saveanu concluded.

Figure 1. HAM-D-17 Response Rates Across the Three ADM Arms (defined by ≥ 50% improvement)



HAM-D-17=Hamilton Rating Scale for Depression, 17-Item; XR=extended release.
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Single-Dose Ketamine Associated With Rapid Improvement of Depressive Symptoms

Written by Mary Beth Nierengarten

Data from a randomized clinical trial show that patients with moderate to severe depressive symptoms treated with a single dose of ketamine show rapid improvement of depressive symptoms compared to patients treated with a psychoactive placebo control.

Sanjay J. Mathew, MD, Baylor College of Medicine, Houston, Texas, USA, and Michael E. Debakey, VA Medical Center, Houston, Texas, USA, reported on outcomes of the Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial [Murrough JA et al. *Am J Psychiatry* 2013], a two-site, parallel-arm, double-blind, randomized controlled trial that evaluated the rapid antidepressant efficacy of ketamine compared with an active placebo control (ie, midazolam) in patients with treatment-resistant major depression.

The study included patients with a primary diagnosis of major depressive disorder randomized in a 2:1 ratio to a single intravenous infusion of ketamine (0.5 mg/kg; n=47) or midazolam (0.045 mg/kg; n=25) between November 2010 and August 2012. Patient characteristics and demographics were similar between the two groups, with all patients showing chronic, treatment-resistant depression with moderate to severe symptom severity.

An anesthesiologist administered the 40-minute infusion and monitored continuous vital signs throughout the infusion. After 24 hours, all patients were discharged and sent home. They then were followed at 2, 3, and

7 days. At Day 7, patients who did not respond to treatment resumed prior treatment. Patients who did respond were invited to participate in a follow-up exploratory phase of the trial for an additional 4 weeks.

The primary outcome of the study was change in depression severity 24 hours after drug administration based on the clinically administered Montgomery-Asberg Depression Rating Scale (MADRS). Nonresponders were defined as patients with <50% improvement from baseline in the score on the MADRS.

At 24 hours, the researchers found that patients treated with ketamine had a significant reduction in depressive symptoms compared with those treated with midazolam based on the MADRS score that was 7.95 points lower in the ketamine group (mean 14.77 vs 22.72; $p \leq 0.0014$). Patients in the ketamine group were also more likely to have a response at 24 hours compared with the midazolam group (64% vs 28%; $p \leq 0.006$).

Dr. Mathew highlighted that among the significant improvements in depressive symptoms in the ketamine group, improvements in the inability to feel and lassitude were particularly robust.

The study also found that the patients who responded to ketamine generally maintained improvement in depressive symptoms for several days beyond the initial 24 hours.

At Day 7, 21 patients who had responded to ketamine and 4 who had responded to midazolam participated in an exploratory phase of the trial that looked at time to relapse in these patients given a single infusion of ketamine or midazolam. These results also showed a more durable benefit in the ketamine group.

According to Dr. Mathew, secondary analyses of these data are under way. Results of one study on the impact of ketamine on suicidal ideation showed a reduction in suicidal thoughts with ketamine versus midazolam [Price RB et al. *Depress Anxiety* 2014].

Low-Dose Quetiapine Improves Symptoms of Borderline Personality Disorder

Written by Nicola Parry

Donald W. Black, MD, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA, presented results of a placebo-controlled trial demonstrating that low doses of long-acting quetiapine significantly improve symptoms in patients with borderline personality disorder (BPD).

Although no drugs are currently approved for treatment of BPD, studies have shown the benefit of antipsychotic agents for this indication, particularly when symptoms of mood instability, anger and irritability, and self-harm are prominent. Open-label studies have demonstrated that the atypical antipsychotic drug quetiapine is efficacious and well tolerated in treating these patients.

Dr. Black and colleagues conducted a randomized controlled trial (RCT) to investigate the efficacy and tolerability of extended-release quetiapine in the treatment of BPD [Black DW et al. *Am J Psychiatry* 2014. In press; NCT00880919]. To be included in the study, patients were required to be from 18 to 45 years old, meet DSM-IV criteria for BPD, and show a score of ≥9 on the Zanarini Rating Scale for BPD (ZAN-BPD) at screening.

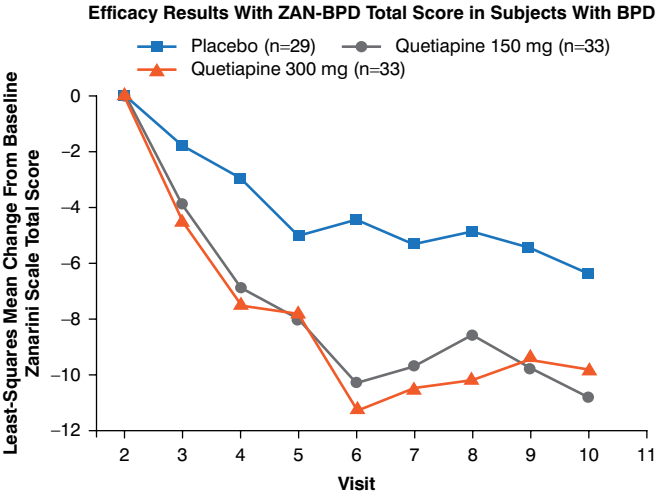
Exclusion criteria included patients with various psychiatric and nonpsychiatric conditions, such as comorbid current major depressive disorder or substance abuse, and pregnant women. Those with a history of nonresponse to an atypical antipsychotic agent were also excluded.

A total of 95 patients were randomly assigned to groups receiving quetiapine 150 mg/day (n=33), quetiapine 300 mg/day (n=33), or placebo (n=29). All patients received a 50-mg starting dose on Day 1, which increased to 150 mg/day after 1 week; patients in the 300-mg/day arm were changed to that level after 4 weeks. The study comprised three treatment phases: screening (Visits 1 and 2), treatment (Visits 2 to 10), and discontinuation (Visits 10 and 11).

Primary outcome was ZAN-BPD total score. Secondary outcomes included the Borderline Evaluation of Severity over Time (BEST) index of BPD symptoms and ZAN-BPD subscales.

Patients in all arms of the study experienced symptom improvement, as demonstrated by reduced ZAN-BPD total score (Figure 1). In both quetiapine arms, improvement was

Figure 1. Changes in ZAN-BPD Total Score



BPD=borderline personality disorder; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder.

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