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.

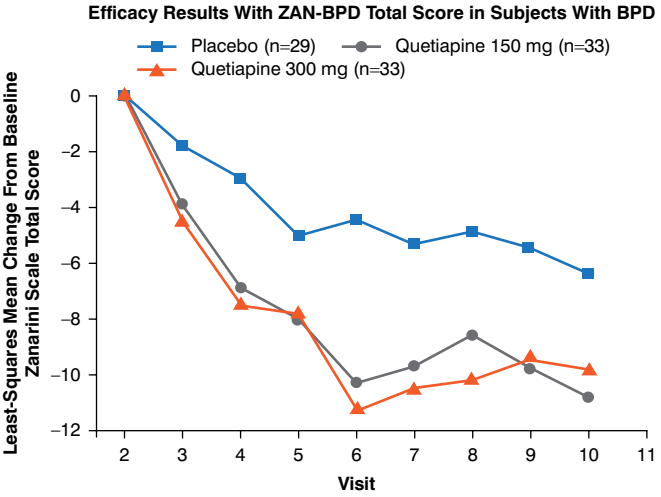
Exclusion criteria included patients with various psychiatric and nonpsychiatric conditions, such as comorbid current major depressive disorder or substance abuse, and pregnant women. Those with a history of nonresponse to an atypical antipsychotic agent were also excluded.

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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greatest from baseline (Visit 2) to Visit 6. The improvement was only significant (p=0.031) in the quetiapine 150-mg/day arm compared with placebo, however.

All secondary outcomes improved significantly in both quetiapine groups compared with the placebo group, except the improvement in the Young Mania Rating Scale score in the 300-mg/day group, which missed significance (p=0.06).

Eighty-eight percent of patients reported at least one adverse event (AE), with a higher risk of occurrence in the quetiapine 300-mg/day arm. The most common AEs in this group were sedation (HR, 2.16), appetite change (HR, 3.89), and dry mouth (HR, 16.8). The discontinuation rate in the study was high (33%). By 8 weeks, 42% of patients in the 300-mg/day group had discontinued, compared with 33% of the 150-mg/day group and with 20% of those receiving placebo. Sedation was a predictor of discontinuation (HR, 1.77).

Dr. Black concluded that, despite the high discontinuation rate, which is not uncommon in trials in BPD, the results of this study demonstrate efficacy of low-dose quetiapine in treating the symptoms of BPD. He recommended that future RCTs involving larger patient numbers and active comparators will further understanding of the effectiveness and safety of atypical antipsychotic drugs in patients with BPD.

TMS Shows Promise in Preventing Relapse in Patients With Resistant Depression

Written by Mary Beth Nierengarten

For patients with treatment-resistant depression, long-term maintenance therapy with 1 weekly session of repetitive transcranial magnetic stimulation (rTMS) shows promise in preventing relapse in patients who respond to acute rTMS treatment. René Benadhira, MD, Unité de Recherche Clinique, Paris, France, presented preliminary results on a 1-year, double-blind, randomized controlled trial evaluating the efficacy of rTMS as maintenance therapy for patients with treatment-resistant depression.

The study consisted of 2 phases. In Phase 1, all patients received acute treatment with active high-frequency stimulation with rTMS during 4 blocks of 5 consecutive working days in an open-label phase of the trial. In Phase 2, patients who responded to acute treatment were randomized to maintenance therapy with sham or rTMS for 11 months. During Phase 2, the rhythm of rTMS sessions was gradually reduced to 3 sessions per week for 2 weeks, 2 sessions per week for the following 2 weeks, 1 session per week for the third month (M3) and fourth (M4), and then 1 session every 2 weeks for the last 8 months (M5 to M12). The primary outcome was improvement in symptoms of depression based on the 17-item Hamilton Depression Rating Scale (HAM-D). Responders were defined as those who achieved >49% reduction in HAM-D score from baseline.

Prof. Benadhira reported on the intermediate analysis of 69 patients. Most patients were female (n=43) and had unipolar depression (79.7%). The mean age was ~51 years; the mean duration of education was ~11 years; and the mean duration of illness was ~8 years. At baseline, the mean HAM-D score was 22.59. Results of the Phase 1 part of the trial showed that 33 (48%) patients responded to acute treatment with rTMS, 15 (22%) achieved partial response, and 2 (2.9%) achieved remission (ie, defined as HAM-D <8). Of the 33 responders, 14 agreed to participate in Phase 2 of the trial and were randomized to active rTMS (n=9) or sham treatment (n=5). Results of Phase 2 showed significant difference in HAM-D score between active rTMS and sham at 4, 5, and 6 months (Table 1). Additional assessments of efficacy also showed significant differences between active rTMS and sham.

Table 1. Significant Difference in HAM-D Score Between Active rTMS and Sham Treatment, p Values

M1	M1–M2[a]	M1–M3[b]	M1–M4[b]	M1–M5[c]	M1–M6[c]	M1–M12[c]
Baseline						
Δ HAM-D	0.254	1.000	0.003	0.004	0.043	0.228
Δ CGI	0.799	1.000	0.19	0.328	0.846	0.202
Δ BDI	0.946	0.275	0.46	0.347	0.253	0.947
Δ HADS-dep	0.281	0.254	0.037	0.082	0.141	0.789
Δ HADS-anx	0.344	0.177	0.107	0.052	0.079	0.639
Δ VAS						
Sadness	0.714	0.187	0.019	0.028	0.163	0.306
Anxiety	0.419	0.77	0.143	0.04	0.661	0.884
Reassured	0.017	0.039	0.02	0.01	0.028	0.039
Relieved	0.884	0.77	0.107	0.141	0.77	0.509

anx=anxiety; BDI=Beck Depression Inventory; CGI-Clinical Global Impression Scale; dep=depression; HADS=Hospital Anxiety and Depression Scale; HAM-D=Hamilton Depression Rating Scale; M=month; rTMS=repetitive transcranial magnetic stimulation; VAS=visual analog scale.
[a]10 sessions per month.
[b]4 sessions per month.
[c]2 sessions per month.

Overall, the Phase 2 part of the study showed that all patients treated with rTMS maintained a response to treatment during the 4 weeks of further treatment. At 4, 5, and 6 months, patients on maintenance rTMS had significant improvement in depressive symptoms when compared with patients in the sham treatment group, as shown by the HAM-D scores. This significant difference in change in HAM-D score disappeared starting at Month 7, which, according to Prof. Benadhira, was due to the insufficient number of treatment sessions (ie, 1 session every 2 weeks).