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).

These results suggest that maintenance therapy with 1 session of rTMS per week may be able to prevent relapses in these patients, said Prof. Benadhira, who also emphasized the need for a larger study to confirm the result.

Higher Doses of Levomilnacipran May Benefit Patients With Severe Depression

Written by Nicola Parry

Gregory M. Asnis, MD, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA, presented a poster with results of a Phase 3 trial to evaluate the efficacy and tolerability of levomilnacipran extended-release (ER) dose in adult patients with major depressive disorder (MDD) [APA 2014 (poster NR6-087); NCT00969709]. The results of the study indicated that higher doses of levomilnacipran ER may benefit some patients, including those with moderate to severe depression.

Levomilnacipran ER, a potent, selective serotonin and norepinephrine reuptake inhibitor (SNRI), is approved for use in the treatment of MDD in adults, with dose-proportional pharmacokinetic effects demonstrated in some studies [Chen L et al. APA 2013 (poster NR9-37)].

To be included in the 8-week, double-blind, multicenter, parallel-group, placebo-controlled study, patients were required to be 18 to 65 years and meet *DSM-IV-TR* criteria for MDD, with a current major depressive episode ≥8 weeks, and a score of ≥30 on the Montgomery-Asberg Depression Rating Scale (MADRS). Patients were randomized to placebo (n=179) or once-daily levomilnacipran ER 40 mg (n=181), 80 mg (n=181), or 120 mg (n=183); doses were initiated at 20 mg and titrated to the target dose over 7 days.

Exclusion criteria included patients with various psychiatric conditions, as well as nonpsychiatric conditions that may interfere with the study. Those with a history of nonresponse to ≥2 antidepressants were also excluded.

In the intention-to-treat (ITT) patient population, the primary outcome was the change in MADRS total score from baseline to the end of Week 8. Secondary outcome was Sheehan Disability Scale (SDS) total score.

Least squares mean difference (LSMD) was used to assess the relationship between levomilnacipran dose and efficacy. Compared with placebo, the LSMD for depressive symptoms (MADRS total score change) was significantly different (p=0.0186; p=0.0038; p=0.0005) for all levomilnacipran ER dose groups (40 mg, –3.23; 80 mg, –3.99; 120 mg, –4.86). The data also suggested a linear relationship between dose and efficacy.

In patients with more severe MDD (baseline MADRS ≥35), LSMD values demonstrated that improvements in depressive symptoms were significantly greater in the 80 mg (–5.14; p=0.0098) and 120 mg (–6.21; p=0.0016) groups, but not in the 40 mg group (–3.81; p=0.0558).

On the SDS, the LSMD was also significantly different for the levomilnacipran ER 80 mg (–2.51; p=0.0151) and 120 mg (–2.57; p=0.0141) groups but not for the 40 mg group (–1.41; p=0.1687).

Levomilnacipran ER was generally well-tolerated across the dosage groups. Serious adverse events (AEs) occurred in ≤2% of patients in all treatment groups, with no deaths reported. The incidence of treatment-emergent adverse events (TEAEs) was 63.6% in the placebo group, and was similar across all three levomilnacipran ER dosage groups (40 mg, 75.8%; 80 mg, 82.7%; 120 mg, 76.7%). However, a dose-related effect was observed for urinary hesitation and erectile dysfunction, which occurred in 6.1% and 9.5% of patients in the 120-mg group, respectively.

In summary, higher doses of levomilnacipran ER are associated with greater improvements in MADRS and SDS, with no overall increase in the incidence of TEAEs with higher doses. Higher doses of levomilnacipran ER may therefore benefit some patients with MDD, including those with more severe symptoms, concluded Dr. Asnis.

Potential Value of N-acetylcysteine in Reducing Cigarette Smoking

Written by Brian Hoyle

A randomized, double-blind, placebo-controlled study from researchers in Brazil and Australia has demonstrated the prowess of N-acetylcysteine (NAC) in reducing cigarette smoking for individuals previously refractory to smoking cessation efforts. Although the small number of patients precludes a definite conclusion, the potential of NAC in smoking cessation therapy is indicated. The study presenter was Eduardo Prado, MD, Londrina State University, Londrina, Brazil [APA 2014 (poster NR-8218)].

NAC is a cysteine prodrug that functions to restore glutamate homeostasis and promotes glutathione synthesis by virtue of its antioxidant activity. It has also been implicated in reducing the nicotine craving in cigarette smokers. However, the latter has not been rigorously assessed. Forty subjects were enrolled in the present 12-week study. Thirty-four subjects who had failed previous attempts to stop smoking were randomly assigned to receive 3000 mg/day of NAC (n=17) or placebo (n=17) for 12 weeks. Eleven subjects in the NAC group and 7 in the placebo group completed the study.

The primary outcome was smoking cessation as gauged by examination of the daily log of cigarette smoking maintained by each subject and objectively by