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

measurement of exhaled carbon monoxide (CO_{EXH}) at 1, 2, and 3 months. At each monthly visit, each subject also received a medical examination and behavior group therapy counseling and provided self-assessed ratings of his or her withdrawal symptoms and adverse effects.

Subjects in the two groups did not differ in marital status, age, years of education, gender makeup, and smoking behavior variables that included onset of tobacco use, years of smoking, and Fagerström Test for Nicotine Dependence (Table 1). Other similarities included lifetime consumption of cigarettes, prevalence and types of depressive disorders, and alcohol consumption.

Table 1. Characteristics of Groups

Characteristics	Placebo Group (n=17; 7 males, 10 females)	NAC Group (n=14; 2 males, 12 females)	p Value
Current age, years	51.93±7.022	50.76±11.819	0.748
Years of education	10.86±5.318	9.18±5.040	0.375
Smoking onset age	16.86±2.507	16.18±3.340	0.534
Years of smoking	35.00±7.766	33.29±11.889	0.648
Pack-year	32.64±18.519	31.43±18.369	0.846
FTND	4.50±1.743	4.82±2.186	0.657

Data are mean±standard deviation.
FTND=Fagerström Test for Nicotine Dependence.

Significant decreases in the primary outcomes of daily smoking and CO_{EXH} were evident in those receiving NAC (Table 2). Withdrawal symptoms and adverse effects were similar in both groups (data not shown in poster).

Table 2. Effects of NAC and Placebo Treatment on Primary Outcomes

		Cigarettes (No./Day)	p Value	CO_{EXH} (ppm)	p Value
NAC	Baseline	20±3	<0.001	21±3	0.003
	12 weeks	9±3		10±3	
Placebo	Baseline	19±3	NS	16±2	NS
	12 weeks	16±2		15±2	

Data are mean±standard deviation.
NAC=N-acetylcysteine; NS=not significant.

Analysis of other variables revealed a significant difference in the Hamilton Depression Rating Scale score, with higher scores at baseline and 12 weeks for those receiving placebo (Table 3).

Table 3. Effect of Treatments on Other Outcome Variables

Variable		T0 (Baseline)	Week 12 (Endpoint)	p Value
HAM-D	Placebo	13.6±4.4	12.1±4.6	0.018
	NAC	12.7±7.1	7.2±6.3	
BMI	Placebo	26.2±6.6	26.4±6.9	0.046
	NAC	27.1±5.0	26.5±5.3	
SBP	Placebo	121.4±23.4	118.9±15.3	0.893
	NAC	128.2±16.7	121.8±13.3	
DBP	Placebo	75.7±12.7	77.1±11.1	0.554
	NAC	75.5±8.2	79.1±5.4	
Sheehan (social)	Placebo	3.7±3.1	2.6±3.6	0.594
	NAC	1.6±2.5	1.0±2.0	
Sheehan (work)	Placebo	2.6±3.2	2.7±3.9	0.092
	NAC	1.7±2.5	0.9±2.1	
Sheehan (family)	Placebo	4.0±3.7	2.9±3.0	0.103
	NAC	1.7±2.5	6.6±1.5	

Data are mean±standard deviation.
BMI=body mass index; DBP=diastolic blood pressure; HAM-D=Hamilton Depression Rating Scale score; SBP=systolic blood pressure; Sheehan=Sheehan Disability Scale.

The results support the potential of NAC as a smoking cessation agent and should serve as a springboard for more clinical trials to substantiate this role of NAC.

rTMS Improves Generalized Anxiety Disorder Compared With Sham Treatment

Written by Mary Beth Nierengarten

Preliminary data indicate that repetitive transcranial magnetic stimulation (rTMS) is superior to a sham treatment for patients with generalized anxiety disorder (GAD). Gretchen J. Diefenbach, PhD, Institute of Living at Hartford Hospital, Hartford, Connecticut, USA, presented the results of an ongoing randomized controlled trial to assess the efficacy of rTMS versus sham treatment for patients with moderate to severe GAD.

In total, 32 patients were enrolled in the study. All patients were at least 18 years of age, with a principal or a coprincipal diagnosis of moderate to severe GAD. Patients were excluded if they had a brain trauma or a disorder, a