The data bolster support for the efficacy, safety, and tolerability of VLZ 40-mg/day and indicate the utility of the 20-mg/day dose.

Vortioxetine Improves Cognitive Function, Lessens Symptoms of Major Depression

Written by Brian Hoyle

A multinational, randomized, double-blind, placebo-controlled Efficacy Study of Vortioxetine on Cognitive Dysfunction in Adult Patients With Major Depressive Disorder (MDD) [FOCUS; NCT01422213] has demonstrated the drug's efficacy in improving cognitive function and lessening depression symptoms. The poster chronicling the study was presented by Roger S. McIntyre, MD, University Health Network, University of Toronto, Toronto, Ontario, Canada [APA 2014 (poster NR6-114)].

Vortioxetine is a novel multimodal antidepressant that functions as a human 5-HT_{3A} and 5-HT_{7} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} receptor agonist, and an inhibitor of the serotonin transporter. It is thought to act directly on the serotonin receptor and on the inhibition of serotonin reuptake. Vortioxetine was approved in 2013 for the treatment of MDD by the US Food and Drug Administration.

The FOCUS study comprised secondary analyses of the effect on specified end points of acute treatment with vortioxetine doses of 10 mg/day (n=195) and 20 mg/day (n=207) versus placebo (n=196) for 598 adults with recurrent moderate-to-severe MDD. The patients were aged ≥18 years and ≤65 years, diagnosed with recurrent MDD according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision; *DSM-IV-TR*) with a current depressive episode lasting 3 months or longer, and a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥26 at screening and baseline.

The primary outcome was the effect of cognitive assessments. Secondary outcomes were changes in depression symptom severity from baseline at Weeks 1, 4, and 8 in MADRS total score, MADRS response and remission, Clinical Global Impression-Severity of Illness (CGI-S), and the Clinical Global Impression-Improvement (CGI-I) scores.

The baseline characteristics of patients in the three study arms were similar. The mean baseline MADRS scores were indicative of moderate to severe depression in the patients (Table 1).

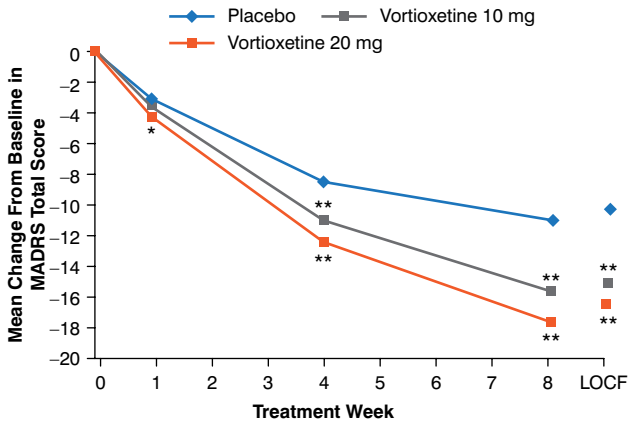
After 8 weeks, the mean MADRS decreased (improved) by 10.9, 15.6, and 17.6 points for the placebo, vortioxetine 10-mg, and vortioxetine 20-mg arms, respectively. The differences between the vortioxetine doses and placebo were significant (both p<0.001). The difference in the mean change from baseline to Week 8 in the MADRS total score was –4.7 and –6.7 for 10-mg/day and 20-mg/day vortioxetine, respectively (both p<0.001; Figure 1).

Table 1. Baseline Patient Characteristics

	Placebo (n=196)	Vortioxetine, 10 mg (n=195)	Vortioxetine, 20 mg (n=207)
Women, n (%)	129 (65.8)	134 (68.7)	133 (64.3)
Mean age, years (range)	45.6 (19 to 65)	45.4 (18 to 65)	46.1 (18 to 65)
Caucasian (%)	95.9	93.8	93.7
Median length of current major depressive episode, weeks	18	19	19
Previous major depressive episodes, mean number (range)	2.4 (1 to 11)	2.3 (1 to 11)	2.6 (1 to 13)
Assessment scores, mean	**n=194**	**n=193**	**n=204**
MADRS total score	31.3	31.6	31.7
CGI-S	4.55	4.60	4.62

CGI-S=Clinical Global Impression-Severity of Illness; MADRS=Montgomery-Asberg Depression Rating Scale.

Figure 1. Estimated MADRS Total Scores From Baseline to Week 8 and LOCF



*p<0.01, **p<0.001 vs placebo.
LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale.
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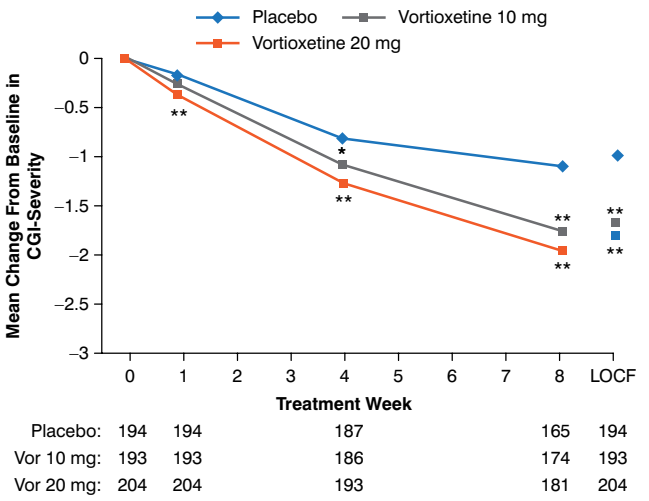
Figure 2. CGI-S Scores and LOCF



*p<0.01, **p<0.001 vs placebo.

CGI-S=Clinical Global Impression-Severity of Illness; LOCF=last observation carried forward.

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Vortioxetine 10 mg was distinguished from placebo on six of the 10 MADRS items at Week 4 and all 10 items at Week 8. Vortioxetine 20 mg was distinguished from placebo on 3 MADRS items at Week 1, 9 items at Week 4, and all 10 items at Week 8. The improvement in the rating of depression was manifest clinically, as indicated by improvement in CGI-S of –0.08 and –0.18 at Week 1 (p=0.077 and p<0.001, respectively); –0.27 and –0.43 at Week 4 (p=0.004 and p<0.001, respectively); and –0.65 and –0.85 at Week 8 (both p<0.001) for vortioxetine 10 and 20 mg versus placebo, respectively (Figure 2).

Vortioxetine was well tolerated. Most frequent adverse effects for the placebo, vortioxetine 10-mg, and vortioxetine 20-mg arms were nausea (4.1%, 16.4%, and 20.8%, respectively) and headache (7.1%, 8.2%, and 12.6%, respectively).

The secondary analyses establish the efficacy of the two vortioxetine doses on lessening depression in patients with MDD.

TMS Improves Anxiety Symptoms in Depression

Written by Nicola Parry

Gretchen J. Diefenbach, PhD, Institute of Living at Hartford Hospital, Hartford, Connecticut, USA, presented data from a meta-analysis of randomized controlled trials (RCTs) in transcranial magnetic stimulation (TMS) among depressed patients. The results showed that TMS appears effective in treating anxiety symptoms in patients with depression.

Although studies have increasingly shown evidence for the efficacy of TMS among patients with depression [Slotema CW et al. *J Clin Psychiatry* 2010; Schutter DJ. *Psychol Med* 2009], its anxiolytic effect is poorly documented. However, based on the comorbidity of anxiety and depression, this is an important area to investigate. Additionally, among patients with depression who also have anxiety, its symptoms tend to be more severe and also may be more treatment resistant.

To further investigate this, Dr. Diefenbach and colleagues conducted a meta-analysis of data from RCTs to establish the pooled anxiolytic treatment effect of TMS among depressed patients. They used the Hamilton Depression Rating Scale as an outcome measure to assess anxiety symptom change, specifically using the anxiety/somatization subscale, which comprises 6 items: anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight.

They performed a literature search of the Scopus, Medline, and PsycINFO databases, using search terms including *transcranial magnetic stimulation* or *TMS* or *rTMS*; *controlled trial* or *sham* or *RCT*; and *depression* or *depressive disorder* or *MDD*, which identified 634 articles through June 2013. To be included in the meta-analysis, studies were required to be an RCT comparing TMS versus sham that treated depressive symptoms as the primary target, with TMS targeting the dorsolateral prefrontal cortex. They also had to comprise an adult sample with major depressive disorder, register the Hamilton Depression Rating Scale, and be published in English. Of these 634 articles, 64 met the inclusion criteria, but none of the publications contained all the relevant data, so authors were contacted directly. Complete data were subsequently acquired for 12 studies. Of the combined study participants (n=709), 395 received TMS and 314 received sham treatment.

There was no significant difference in mean pretreatment scores between the 2 groups. The statistics associated with the null result are as follows: rTMS group mean score, 7.56; sham group mean score, 7.48; $t(25)=0.15$; p=0.88. However, analysis of the in-group pooled treatment effect showed a moderate treatment effect for sham and a large treatment effect for TMS, with the difference between them trending toward statistical significance (p=0.065; Figure 1). There was also a moderate but significant difference (p<0.001) in posttreatment between-group effect sizes. Patients who received TMS reported lower anxiety somatization subscale scores than those who received sham. The large fail-safe number (n=102) suggests that these meta-analytic findings are robust.

The researchers did not pursue analyses of treatment moderators, since there was no significant difference (p=0.56) in between-study heterogeneity, which implied that the results were generally uniform across the different studies.