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A2-7621

Prepared for
CNS Response

Comparing Levels of Evidence for Treatment
of Treatment-Resistant Depression with
Referenced-EEG® to Current Practice

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October 17, 2008

EXECUTIVE SUMMARY

Background: Major Depressive Disorder (MDD) is a major cause of morbidity and mortality in the United States, resulting in high direct and indirect costs to society. While treatment for MDD is widely available, more complex scenarios involving treatment-resistant depression (TRD) are more difficult to manage. Re-imbursement and quality control for treatment of depression by many payers in the United States is guided by the American Psychiatric Association (APA) treatment guidelines, the Texas Medication Algorithm Project (TMAP) treatment algorithm and the results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study. In addition, there is extensive off-label use of drugs for augmentation of treatment of TRD. Referenced-EEG[®] (rEEG[®]) is a new electroencephalographic technology that assists physicians in selecting specific medications appropriate to the specific physiologic abnormalities found in neuro-behaviorally disordered patients.

Project Objectives: The objective of this project is to compare the levels of evidence supporting the use of rEEG for treatment of TRD to a) current treatment guidelines (APA, TMAP), b) study reports (STAR*D) for treatment of TRD and to c) off-label use of drugs for treatment of TRD.

Rationale: The rationale for comparing the levels of evidence is to attempt to showcase the acceptability of using rEEG as compared to currently accepted guidelines and practices. The APA guidelines and TMAP algorithms are widely accepted references for guiding treatment of depression and TRD. While both the APA guidelines and the TMAP algorithm provide a systematic approach to the treatment of MDD and TRD, little evidence is provided to support the treatment choices outlined for TRD. The significant use of off-label drugs, i.e., drugs not appropriately approved by the FDA for treatment of TRD confirms challenges of treating TRD. Assessing and comparing the levels of evidence offered by rEEG studies to those evidence supporting current guidelines and practices can make a compelling argument.

Study Methods: We assessed studies conducted to evaluate the effect of rEEG for TRD and published in the peer-reviewed literature or in conference meetings and graded the levels of evidence. We also graded the level of evidence provided in support of the APA treatment guidelines for TRD, the TMAP algorithm, and the STAR*D study reports. We used the Centre for Evidence Based Medicine (CEBM) scale for levels of evidence to compare the studies and

supportive evidence. We also performed a systematic search in PubMed for studies or literature documenting off-label use of drugs for treatment of TRD and assessed the results of those studies and the level of evidence each provided.

Results: We found that all studies supported the effectiveness of rEEG[®] and the CEBM levels of evidence ranged from 2b–4. The APA guidelines, TMAP algorithm, and STAR*D all explicitly address treatment of TRD. The APA guidelines provide little specific evidence for the TRD treatment recommendations and did not reference any studies specifically evaluating TRD. TMAP was primarily designed using expert panel consensus. The remission rates in STAR*D trials ranged between 6.9%–24.7%, implying that the results can be considered negative. The search for off-label use studies yielded 14 articles that reported evidence with respect to the effectiveness of off-label drugs in the treatment of TRD. The studies evaluated the effects of quetiapine, risperidone, and aripiprazole augmentation. Overall, the findings provided evidence that supported their use as augmentation agents for treatment of TRD.

Conclusions: Referenced-EEG[®] was associated with relatively high remission rates in the treatment of TRD with reasonable levels of evidence. The evidence provided for off-label use of drugs for augmentation of anti-depressant treatment was overall supportive of the practice with these specific treatment modalities. Little evidence was offered for the APA guidelines and TMAP specifically for TRD, and the STAR*D evidence was not supportive of the regimens evaluated. The evidence supporting the use of rEEG is at least comparable to evidence supporting other modes of treatment for TRD and, on some occasions, superior. Evidence supporting rEEG[®] appears superior to that supporting APA or TMAP treatment guidelines for TRD and certainly the results of the STAR*D Level 3 and Level 4 studies that are commonly used by payers. While evidence supporting the use of rEEG is comparable to evidence supporting the effectiveness of off-label drugs where documented, many other modalities of off-label drugs used for TRD remain to be tested and lack a body of evidence to support their use. Thus, evidence supporting the use of rEEG is at least comparable, if not superior to evidence supporting other currently recommended or practiced modes of treatment for TRD. The findings of this project provide a compelling basis for the consideration of rEEG as a beneficial modality of medication selection for the treatment of TRD. These findings may warrant the consideration of rEEG for inclusion in treatment guidelines and perhaps a basis for re-imburement.