

# Effects of Adjunctive Brexpiprazole on Sleep Imbalances in Patients with Major Depressive Disorder: An Open-Label, Flexible-Dose, Exploratory Study

## BACKGROUND:

- A large portion of patients suffering from major depressive disorder (MDD) endorse concomitant sleep disturbances.
- The presence of sleep disturbances has been detected as a risk factor for the development and aggregation of depression.
- The use of antidepressants often can be associated with short-term improvement in sleep outcomes that may not persist, as well as unwanted side effects in some patients.
- Data on the effects of sleep architecture when augmenting antidepressant therapy with second generation antipsychotics (SGA's) is limited.

## OBJECTIVE

- To explore the effects of brexpiprazole (Rexulti) as an adjunctive treatment to antidepressant monotherapy on sleep-wake patterns in depressed patients with sleep disturbances.

## METHODS

- **Design:** Open-label, flexible-dose, noncontrolled experimental study; Duration: 14 weeks
- **Inclusion criteria:** 18-65 years of age, diagnosis of MDD according to DSM-IV, current major depressive episode of greater than 10 weeks, inadequate response to at least 1 antidepressant treatment during the episode, currently taking an SSRI or SNRI at a stable dosage, currently experiencing sleep disturbances, have a mean latency to persistent sleep of  $\geq 20$  minutes during 2 consecutive nights of polysomnography (PSG) monitoring, have a latency to persistent sleep of no less than 15 minutes on either night, as well as an average sleep efficiency of  $< 85\%$  on both nights. More extensive criteria in supplemental index.
- **Exclusion criteria:** Patients with a current psychiatric disorder or Axis I disorder other than MDD, Axis II disorder, history of hallucinations, delusions, or psychotic symptoms, patients at a significant risk of suicide, pregnancy, patients taking interacting medications (per the investigators), patients diagnosed with insomnia prior to the current major depressive episode (MDE), cognitive dysfunction, substance use disorder within previous 6 months, failed urine drug screen, history of neuroleptic malignant syndrome (NMS), patients meeting diagnostic criteria for any sleep disorder other than insomnia, abnormal EKG. More extensive criteria in supplemental material.
- **Primary outcomes measured:** change in sleep quality, sleep architecture, insomnia, and daytime alertness and functioning
- **Secondary outcome measures:** incidence of treatment-emergent adverse effects, change in laboratory values or vital signs, change in EKG parameters, and risk of suicide
- 44 patients were enrolled to receive brexpiprazole titrated to a dose of 3 mg per day (2 mg if tolerability became an issue)
- No power due to being an exploratory noncontrolled study
- Intent-to-treat data handling method

## RESULTS

- 41 patients completed the study with 3 lost to follow-up
- **Primary outcome measure:** Sleep efficiency improved by 10.4% per PSG and by 15.4% per CSD-M. Total sleep time improved by 49 minutes per PSG and 84.5 minutes per CSD-M. Sleep onset latency improved by 19.7 minutes per PSG and by 42.6 minutes per CSD-M. Wake-time after sleep onset improved by 26.4 minutes per PSG and 48 per CSD-M. Number

of awakenings did not improve significantly per PSG or CSD-M. Per PSG, an increase of 3.5% in the fraction of stage N2 sleep was observed with a duration increase of 43.1 minutes and a reduction of 2.2% in the fraction of stage N3 sleep with a decreased duration of 3.1 minutes. Severity of insomnia, as measured by the patient-rated Insomnia Severity Index (ISI), improved 9.2 points (47%). The degree of sedation, as measured by the patient-rated Epworth Sleepiness Scale (ESS), improved 2.1 points. Morning, but not daytime or evening, Bond-Ladar Visual Analog Scale (BL-VAS) scores improved. Reaction time, as measured by the Psychomotor Vigilance Test (PVT), improved 0.2 seconds. Cognitive and Physical Functioning Questionnaire (CPFQ) scored improved 8.4 points. Montgomery Asberg Depression Rating Scale (MADRS) scores improved 16 points. CGI-S scores improved 1.8 points. All p-values were significant at  $< 0.05$ .

- **Secondary outcome measures:** A total of 31 patients experienced 1 or more adverse events, although no serious AE's were reported. The highest incidence was nausea and sedation, followed by headache, somnolence, upper respiratory infection, weight gain, and fatigue. Three patients experienced extrapyramidal side effects. Two patients experienced suicidal ideation during the study.
- **Author's conclusion:** Brexpiprazole as an adjunct in MDD patients who had inadequate response to antidepressant treatment can lead to clinical improvement of sleep disturbances and depressive symptoms, as well as improvement of daily alertness and functioning. Brexpiprazole is safe and well-tolerated.

#### STRENGTHS

- Appropriate subjective and objective measurement of outcomes
- Extensive detailed report of when specific outcomes were measured (when PSG was done, when scales were evaluated, etc.)
- Appropriate inclusion criteria
- Appropriate objective and study rationale

#### LIMITATIONS

- Failure to account for placebo-effect
- Strong potential for bias given conflicts of interest
- Failure to address long-term effects that would influence clinical application
- Multiple testing centers with variability in protocol
- Failure to account for environmental factors and confounding variables such as diet and exercise
- Inappropriate reporting of variability (SE)

#### CONCLUSION

- The limitations of the study and lack of strong evidence of clinically significant improvements reduce the clinical usefulness of brexpiprazole in the studied population.
- Given the current research and evidence supporting augmenting antidepressants with other SGA's, it's unlikely that brexpiprazole would be a preferred agent at this time.
- Future research would be beneficial with a larger sample size, longer duration, and placebo-controlled trial to determine the clinical usefulness of brexpiprazole.

**Reference:** Krystal AD, Mittoux A, Meisels P, Baker RA. Effects of adjunctive brexpiprazole on sleep disturbances in patients with major depressive disorder: An open-label, flexible-dose, exploratory study. *Prim Care Companion CNS Disord.* 2016;18(5).