

neurosyphilis. Bacterial meningitis was ruled out based on the CSF analysis (WBC  $144 \times 10^3$  and glucose) and the lack of bacterial growth on gram stain. Inasmuch, antibiotic therapy was not initiated. Empiric acyclovir 1000 mg IV every 8 hours was initiated as viral meningitis had not been eliminated, due to the lack of viral meningeal PCR testing. By HD-3, the CSF culture resulted without growth and the patient was alert and oriented. By HD-4 the patient was discharged, having received 6 doses of IV acyclovir, with 7 more days of oral therapy.

**Discussion.** In 2018, McDonald et al documented the first case of probable levetiracetam-related antiepileptic induced meningitis (AEIM). The mainstay of treatment is discontinuing the offending agent. Resolution of symptoms is typically 2 to 3 days after drug discontinuation as seen in this patient case report. Symptomatic resolution within days of stopping the suspected offending drug has been observed in all reported cases of AEIM where 1 to 2 weeks is generally seen with viral meningitis. Applying the Naranjo Scale yields a score of 4, which indicates possible levetiracetam-induced meningitis in this adult patient. Providers should be cognizant when prescribing antiepileptics to assess and monitor for aseptic meningitis that may appear with atypical symptoms.

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## Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Real-World Setting Among Patients with Treatment Refractory Depression

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### Abstract

**Background.** Ketamine, an *N*-methyl-D-aspartate receptor antagonist, has been “repurposed” as a rapid-acting antidepressant for treatment-resistant depression (TRD). The *s*-enantiomer of ketamine, “esketamine,” was FDA approved for TRD and depressive symptoms in adults with major depressive disorder with suicidal ideations/behaviors. Intravenous (IV) ketamine, although financially less expensive, is often not covered by insurance and intranasal (IN) esketamine, although covered by insurance can be expensive. There is a paucity of literature on efficacy data comparing subanesthetic IV ketamine and IN esketamine for TRD in a real-world scenario. Thus, we conducted this study comparing the efficacy and the number of treatments required to achieve remission/response with repeated use of subanesthetic IV ketamine/IN esketamine among TRD patients.

**Methods.** This was an observational study where we included adults ( $\geq 18$  years) with TRD who provided consent and had received up to 6 IV ketamine infusions (0.5 mg/kg, infused over

40 minutes) or up to 8 intranasal (IN) esketamine (56/84 mg) treatments for TRD at the Mayo Clinic Depression Center. Depression symptoms were measured utilizing the self-report 16-Item Quick Inventory of Depressive Symptomatology (QIDS-SR) scale before and 24 hours after ketamine/esketamine treatment. Remission and response were defined as QIDS-SR 16 score  $\leq 5$  and  $\geq 50\%$  change in QIDS-SR 16, respectively. Continuous variables are reported as means  $\pm$  SD and categorical variables as counts and percentages. The Wilcoxon rank-sum test was used to compare continuous variables. Chi-square and Fisher’s exact tests were used to compare categorical variables. The number of treatments to remission/response was calculated.

**Results.** Sixty-three adults with TRD, middle-aged ( $47.0 \pm 12.1$  years), predominantly female (65%), of which 76% ( $n = 48$ ) and 24% ( $n = 15$ ) received IV ketamine and IN esketamine, respectively. Mean (SE) change in QIDS-SR 16 score was  $-8.7 \pm 0.7$  ( $P < .001$ ), a significant reduction (improvement) from baseline (mean  $\pm$  SD =  $17.6 \pm 3.7$ ). Overall remission and response rates were 36.5% and 55.6%, respectively in the acute phase. Response (56.3% vs 53.3%) and remission rates (39.6% vs 26.7%) were similar among patients who received IV ketamine or IN esketamine, respectively ( $P > .05$ ). The mean number of treatments received to achieve response ( $2.5 \pm 1.6$  vs  $4.6 \pm 2.1$ ) and remission ( $2.4 \pm 1.3$  vs  $6.3 \pm 2.4$ ) were significantly lower among patients who received IV ketamine compared to IN esketamine ( $P < .005$ ). Most patients tolerated both treatments well.

**Conclusion.** Intravenous ketamine and intranasal esketamine showed similar response/remission in TRD patients but the number of treatments required to achieve response/remission was significantly lower with IV ketamine compared to IN esketamine. These findings need to be investigated in a randomized control trial comparing these two treatment interventions.

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## Opioid Prescription Dispensing Patterns in Patients with Bipolar Disorder: Real-World Evidence from the IBM Market Scan Research Databases

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### Abstract

**Objective.** Prescription opioid dispensing patterns over time were assessed for individuals with bipolar disorder (BD) vs matched controls.

**Methods.** Health insurance claims data from the IBM Market-Scan Commercial Database and Multi-State Medicaid Database were analyzed. Individuals aged 18 to 64 with  $\geq 1$  inpatient or  $\geq 2$  outpatient claims for BD during the year preceding the analysis year (2015-2019) were included, with age- and sex-matched controls. Baseline demographic and clinical characteristics were evaluated. Opioid dispensing during each analysis year was defined as either chronic (coverage for  $\geq 70$  days in any 90-day period, or  $\geq 6$  prescriptions dispensed during analysis year) or nonchronic ( $\geq 1$  prescription dispensed, not meeting chronic definition).

**Results.** BD patients had a higher prevalence of medical and psychiatric comorbidities, including pain diagnoses, vs controls. Among patients with BD in the Commercial database, chronic opioid dispensing decreased from 11% (controls: 3%) in 2015 to 6% (controls: 2%) in 2019, and in the Medicaid database, from 27% (controls: 12%) to 12% (controls: 5%). Among patients with BD in the Commercial database, nonchronic dispensing decreased from 26% (controls: 17%) in 2015 to 20% (controls: 12%) in 2019, and from 32% (controls: 26%) to 25% (controls: 14%) in the Medicaid database.

**Conclusion.** Between 2015 and 2019, there was a significant decrease in chronic and nonchronic prescription opioid dispensing among BD patients and controls across both the Commercial and Medicaid databases. Despite this finding, it is important to note that both chronic and nonchronic opioid dispensing was consistently higher for BD patients vs controls over time, across both databases.

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## A Structured Benefit-Risk Assessment to Evaluate a Combination of Olanzapine and Samidorphan for the Treatment of Schizophrenia and Bipolar I Disorder

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### Abstract

**Background.** A combination of olanzapine and samidorphan (OLZ/SAM) that provides the efficacy of olanzapine while mitigating weight gain was recently approved by the FDA for the treatment of schizophrenia and bipolar I disorder. To improve communication of the OLZ/SAM benefit-risk profile, a structured framework was utilized.

**Methods.** The Benefit-Risk Action Team framework was used to evaluate OLZ/SAM, with analyses completed for each pivotal study. ENLIGHTEN-1 evaluated antipsychotic efficacy and safety. ENLIGHTEN-2 evaluated the weight profile of OLZ/SAM vs olanzapine. Benefit-risk outcomes were selected based on study outcome parameters, known risks of olanzapine and samidorphan, and public health importance. A subset of opioid antagonist risks was not assessed due to clinical trial exclusions; however, they were factored into the overall evaluation. Risk differences and confidence intervals were analyzed.

**Results.** In ENLIGHTEN-1, OLZ/SAM had a lower risk of psychiatric discontinuation and nonresponse to treatment compared with placebo; higher risks of hyperprolactinemia, weight gain ( $\geq 7\%$ ), sedation, and worsening of fasting triglycerides and glucose, and no difference for fasting total and LDL cholesterol, neutropenia, orthostatic hypotension, and movement disorders. In ENLIGHTEN-2, OLZ/SAM had reduced risks of weight gain and waist circumference increase compared to olanzapine along with similar risks of relapse and psychiatric discontinuation and no difference in metabolic worsening, neutropenia, hyperprolactinemia, orthostatic hypotension, sedation, and movement disorders.

**Discussion.** Based on this assessment, OLZ/SAM has comparable efficacy and a safety profile consistent with olanzapine, with reduced weight gain. A structured approach to assessing the benefit-risk profile of a product facilitates transparent evaluation and communication.

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## Development of the MIND-TD Questionnaire as a Screening Tool for Tardive Dyskinesia

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### Abstract

**Introduction.** MIND-TD is a collaboration of healthcare professionals (HCPs) who are committed to raising awareness of tardive dyskinesia (TD), a persistent and potentially disabling movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents. The MIND-TD questionnaire was developed to help HCPs screen for TD and facilitate discussion with patients.

**Methods.** In August 2020, an expert panel of 13 HCPs (4 psychiatrists, 6 neurologists/movement disorder specialists [MDSs], and 3 advanced practice providers [APPs]) met virtually to discuss potential screening questions for TD. This work was continued by