Low Incidence of Neuroleptic Malignant Syndrome Associated With Paliperidone Palmitate Long-Acting Injectable A Database Report and Case Study

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Recommended Citation
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A Database Report and Case Study

To the Editors:

Neuroleptic malignant syndrome (NMS) is a rare, potentially fatal, and idiosyncratic adverse reaction that occurs in approximately 0% to 3% of individuals taking conventional antipsychotic medication. This syndrome usually presents with rigidity, abrupt onset of fever, autonomic dysregulation, and altered mental status. Other symptoms associated with NMS include tremor, extrapyramidal symptoms, altered electrocardiogram, and laboratory abnormalities, such as elevated serum creatine kinase (CK), impaired liver function tests, leukocytosis, electrolyte abnormalities, renal impairment, and altered coagulation (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for NMS). The primary cause of NMS is thought to be dopamine receptor blockade, particularly with the use of antipsychotic medications.

Available evidence of NMS associated with oral antipsychotics suggests that second-generation oral antipsychotics have a lower incidence of NMS, with less severity and infrequent fatal outcomes, compared with first-generation oral antipsychotics. In contrast, little is known about the frequency and management of NMS associated with long-acting injectables (LAIs) prescribed for treatment of schizophrenia, including LAIs of paliperidone (9-OH metabolite of risperidone) such as paliperidone palmitate 1-monthly (PP1M) and 3-monthly (PP3M). The concern about NMS development due to LAI antipsychotics and the associated hospitalization, morbidity, and mortality limits LAI usage in clinical practice in the United States. Also, LAIs may be underutilized because of the perception that an LAI antipsychotic is not quickly cleared from the patient’s system and may hinder NMS management. This letter discusses the incidence and nature of NMS associated with paliperidone palmitate LAI formulations identified from Janssen clinical trial databases of PP1M and PP3M and the treatment implications for NMS associated with second-generation antipsychotic LAI formulations.

All cases of NMS in the Janssen PP1M and PP3M phases 1 to 3 clinical trial databases were searched cumulatively through April 30, 2018. Specific Medical Dictionary for Regulatory Activities (MedDRA, version 16.0) preferred terms used in the search for NMS are listed in Table 1. Individual case review was performed for each patient who experienced at least one of the terms listed. In each identified case, reports of treatment-emergent adverse events, vital signs, physical examination, laboratory findings, and clinical management of the event were reviewed. The incidence rate of NMS was calculated based on the number of identified cases divided by the total person-time at risk.

The Janssen clinical trial database search identified 1 credible case of NMS from 5008 patients who received 1 or more injection of PP1M or PP3M and were followed for 2271.6 patient-years. A second case of NMS was identified but was not included in this study because the patient (from a single-dose pharmacokinetics study in Japan; NCT01606254) was diagnosed with NMS more than 3 months (approximately 3 half-lives) after the last injection of PP1M. Furthermore, the patient was receiving other antipsychotics at the time of injection of PP1M. The resulting raw incidence of NMS was 0.020% (95% confidence rate 0.008% to 0.043%).

Table 1. List of Preferred Terms Used in the Search for NMS in the Janssen Clinical Trial Database

<table>
<thead>
<tr>
<th>Preferred terms used were from Medical Dictionary for Regulatory Activities (MedDRA, version 16.0).</th>
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Hyperthermia malignant NMS
Serotonin syndrome
Body temperature increased
Hyperpyrexia
Pyrexia
Catatonia
Dyskinesia
Dystonia
Freezing phenomenon
Hyperkinesia
Hypertonia
Muscle necrosis
Muscle rigidity
Oculogyric crisis
Oculogyration
Opisthotonus
Rhabdomyolysis
Altered state of consciousness
Autonomic nervous system imbalance
Blood creatine phosphokinase abnormal
Blood creatine phosphokinase increased
Blood creatine phosphokinase MM increased
Blood pressure abnormal
Blood pressure decreased
Blood pressure fluctuation
Blood pressure increased
Cardiovascular insufficiency
Coma
Confusional state
Consciousness fluctuating

Delirium
Depressed level of consciousness
Disorientation
Extrapyramidal disorder
Heart rate abnormal
Heart rate increased
Hyperhidrosis
Hypertension
Hypotension
Labile blood pressure
Labile hypertension
Leukocytosis
Loss of consciousness
Muscle enzyme increased
Myoglobin
Myoglobin blood increased
Myoglobin blood present
Myoglobin urine present
Myoglobinemia
Myoglobinuria
Parkinsonian crisis
Parkinsonian rest tremor
Parkinsonism
Parkinson’s disease
Stupor
Tachycardia
Tremor
Unresponsive to stimuli
White blood cell count abnormal
White blood cell count increased
intramuscularly every 2 weeks was resumed then the dose was tapered and discontinued to 2 mg/d was given from days 19 to 26, transaminase was 49 U/L. Benztropine 1 transaminase was 52 U/L, and aspartate emergent adverse event of NMS. On the study because of the serious treatment-day 8), and the patient was withdrawn from discontinued on day 19 (last dose was on ruled out. Treatment with PP1M was for suspected infection that was later continued as needed for 2 days, and ciproflox- a rescue medication was initiated and con- tinued solely to PP1M, but rather could be initiation of NMS on day 15 cannot be attrib- uted solely to PP1M, but rather could be related to a combined effect of both LAI antipsychotic agents (flupenthixol decanoate and PP1M). Also, worsening of symptoms on day 34 could likely be related to the flupenthixol depot given on day 23, further supporting the additive effect of the 2 drugs. Findings from a retrospective study also showed that the use of depot flupenthixol was significantly associated with increased risk of NMS. Potential limitations of this study include possible underreporting of adverse drug reaction, inadequate sensitivity of the search method, and relatively short follow-up time of patients (on average, ~5.4 months).

In summary, based on the search conducted in the Janssen clinical trial database, the occurrence of NMS events associated with PP1M or PP3M was very low (4/10,000 patient-years); clinicians must, however, be cautious to identify potential NMS symptoms after administration of LAI antipsychotics, especially when patients have been recently taking long-acting first-generation antipsychotics. The presented case indicates that NMS can be managed symptomatically even when the patient is on an LAI antipsychotic, and it underscores the importance of early detection and pharmacological intervention in preventing the progression of this potentially life-threatening complication of antipsychotic use.

ACKNOWLEDGMENTS
Ramji Narayanan, ISMPP CMPP (SIBRO Clinpharm Pvt. Ltd., India) provided writing assistance, funded by Janssen Global Services, LLC, and Ellen Baum, PhD (Janssen Global Services, LLC) provided additional editorial support for the development of this manuscript.

AUTHOR DISCLOSURE INFORMATION
S.G., A.S., M.M. are employees of Janssen Research & Development, LLC, and hold company stock. J.M.K. has been a consultant and/or advisor to and/or has received honoraria from Alkermes, Allergan, Bristol-Myers Squibb, IntraCellular Therapis, Janssen, Lundbeck, Minerva, Neurocrine, Otsuka, Pierre Fabre, Reviva, Sunovion, Takeda, and Teva and is a shareholder of LB Pharma, MedAvante, and The Vanguard Research Group. C.U.C. has been a consultant and/or advisor to or has received honoraria from Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante, Medscapes, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, ROVI, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. N.D. has participated as an investigator in clinical studies and has no other potential conflict of interest to declare.

Registration: ClinicalTrial.gov NCT00 210717.

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Effects of Curcumin on Cognitive Functioning and Inflammatory State in Schizophrenia: A Double-Blind, Placebo-Controlled Pilot Trial

Curcumin, derived from turmeric root, is a polyphenol with antioxidant and anti-inflammatory properties.1,2 To our knowledge, only 2 studies have tested the effectiveness of add-on curcumin in patients with schizophrenia.2,3 In an open-label study, 1 g/d of curcumin (n = 7) and 4 g/d of curcumin (n = 8) improved overall neurocognitive index over 12 weeks. More recently, a randomized, double-blind, placebo-controlled study showed that 360 mg/d of curcumin (n = 17) increased brain-derived neurotrophic factor levels compared with placebo (n = 19) after an 8-week trial. Although this study did not show any significant changes in clinical symptoms and cognitive functioning, improvement on brain-derived neurotrophic factor levels suggested possible long-term benefits of curcumin in cognition and clinical symptoms.2

We tested the effects of add-on curcumin for the treatment of cognitive impairment in schizophrenia in an 8-week randomized, double-blind, placebo-controlled, parallel, fixed-dose pilot clinical trial. A total of 12 outpatients with schizophrenia were randomized to curcumin (180 mg/d) or placebo in a 1:1 ratio. Written informed consent was obtained from all participants. A commercially available surface-controlled water-soluble form of 300 mg of curcumin (30% formulation: 90 mg pure curcumin) or matching placebo capsules were provided by Theravales Corporation (Tokyo, Japan). Study protocol was approved by institutional review board (Yale HIC number 1412015121) and registered at ClinicalTrials.gov (NCT02476708). We monitored medication adherence by means of pill count method and patient reports.

The primary outcome measure was between-group changes in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery.4 Secondary outcomes included changes in inflammatory markers (interleukin 6 [IL-6], tumor necrosis factor α, and high-sensitive C-reactive protein [hs-CRP]) and clinical outcomes (Positive and Negative Syndrome Scale [PANSS], Calgary Depression Scale for Schizophrenia, and The Committee of Clinical Investigations [UKI] side effect scale).

All statistical analyses were performed in SPSS Statistics version 24.0 (IBM, NY). Baseline differences and treatment effect in clinical symptoms, cognitive functioning, and inflammatory markers were assessed with nonparametric tests. Pearson χ² analysis and Fisher exact tests were used for all categorical variables.

The study sample (9 male, 3 female) mostly consisted of chronic schizophrenia patients with mean ± SD duration of illness 21.66 ± 14.84 years (range, 5–51 years). Mean ± SD age of the total sample was 41.33 ± 12.73 years, and education level was 12.33 ± 2.42 years. At baseline, no significant difference was found in sample characteristics, inflammatory markers, and clinical outcomes between treatment arms. Table 1 summarizes changes in inflammatory markers, clinical outcomes, and cognitive functioning. Compared with placebo, add-on curcumin treatment significantly improved working memory (Z = 2.200, P = 0.028) and reduced IL-6 levels (Z = 2.402, P = 0.016). No significant effect of curcumin on PANSS and Calgary Depression scores was found. No significant adverse events were reported during the study. The majority of the patients reported that they took the medications as prescribed. Only 2 patients returned 10 capsules in total during the whole study period (4 curcumin and 6 placebo capsules).

In this pilot study, we found that add-on curcumin improved working memory in patients with schizophrenia. Add-on curcumin also reduced IL-6 levels after 8 weeks of treatment. Although improvements in other cognitive domains, negative symptoms, and total PANSS score were observed with add-on curcumin, these changes did not reach statistical significance.

To a degree, our findings are in line with previous studies. In an open-label study, Woodbury-Farina et al11 reported improvement in cognitive functioning and negative