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

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Low Incidence of Neuroleptic Malignant Syndrome Associated With Paliperidone Palmitate Long-Acting Injectable
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.[1–4] This syndrome usually presents with rigidity, abrupt onset of fever, autonomic dysregulation, and altered mental status.[1] 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.[5]

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.[6–9] 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 diagnosis of NMS. The resulting raw incidence of NMS was 0.020% (95%

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

Hyperthermia malignant	Delirium
NMS	Depressed level of consciousness
Serotonin syndrome	Disorientation
Body temperature increased	Extrapyramidal disorder
Hyperpyrexia	Heart rate abnormal
Pyrexia	Heart rate increased
Catatonia	Hyperhidrosis
Dyskinesia	Hypertension
Dystonia	Hypotension
Freezing phenomenon	Labile blood pressure
Hyperkinesia	Labile hypertension
Hypertonia	Leukocytosis
Muscle necrosis	Loss of consciousness
Muscle rigidity	Muscle enzyme increased
Oculogyric crisis	Myoclonus
Oculogyration	Myoglobin blood increased
Opisthotonus	Myoglobin blood present
Rhabdomyolysis	Myoglobin urine present
Altered state of consciousness	Myoglobinemia
Autonomic nervous system imbalance	Myoglobinuria
Blood creatine phosphokinase abnormal	Parkinsonian crisis
Blood creatine phosphokinase increased	Parkinsonian rest tremor
Blood creatine phosphokinase MM increased	Parkinsonism
Blood pressure abnormal	Parkinson's disease
Blood pressure decreased	Stupor
Blood pressure fluctuation	Tachycardia
Blood pressure increased	Tremor
Cardiovascular insufficiency	Unresponsive to stimuli
Coma	White blood cell count abnormal
Confusional state	White blood cell count increased
Consciousness fluctuating	

Preferred terms used were from Medical Dictionary for Regulatory Activities (MedDRA, version 16.0).

confidence interval, 0.0028%–0.14%), and the incidence rate was 0.044% (95% confidence interval, 0.042%–0.13%) per year.

CASE REPORT

The patient identified with NMS was a 55-year-old, white man with a diagnosis of schizophrenia, paranoid type, since 17 years of age who was enrolled in a randomized, double-blind, parallel-group study of flexibly dosed PP1M versus Risperdal CONSTA (Risperidone LAI).[10] The patient had 4 prior hospitalizations for psychosis and a history of smoking, had no alcohol or drug abuse, and had no other significant medical history reported. The physical examination at screening was unremarkable, except for reduced hearing in the left ear, cerumen in both ear canals, gum disease, cavities, and a body mass index of 25.7 kg/m^2 (overweight). The patient was previously treated with flupenthixol decanoate 15 mg intramuscularly every 2 weeks for 6 years, which was discontinued 22 days prior to randomization. From day −6 to day −3 of the screening period, the patient was given paliperidone extended release 3 mg for oral tolerability testing. On days 1 and 8 of the double-blind period, the patient received an injection of 50 mg eq PP1M in the gluteal muscle. A predose pharmacokinetic plasma sample was collected on day 1, and paliperidone levels were below the limit of quantification.

On day 15, the patient was hospitalized for confused mental state and had experienced a fever (38.8°C) and little rigidity and had "trouble relaxing" his muscles. The diagnosis of mild NMS was made, and laboratory results showed elevated levels of CK (5824 U/L [reference range, 55–197 U/L]) and hepatic enzymes, including aspartate transaminase (128 U/L [reference range, 12–45 U/L]) and alanine transaminase (91 U/L [reference range, 7–40 U/L]). Blood pressure and pulse rate were normal.

On day 16, lorazepam 0.5 to 1 mg/d as a rescue medication was initiated and continued as needed for 2 days, and ciprofloxacin 500 mg twice daily for 6 days was given for suspected infection that was later ruled out. Treatment with PP1M was discontinued on day 19 (last dose was on day 8), and the patient was withdrawn from the study because of the serious treatment-emergent adverse event of NMS. On day 20, the CK level was 860 U/L, alanine transaminase was 52 U/L, and aspartate transaminase was 49 U/L. Benztropine 1 to 2 mg/d was given from days 19 to 26, then the dose was tapered and discontinued over 2 days. Flupenthixol decanoate 15 mg intramuscularly every 2 weeks was resumed on day 23. The pyrexia was treated with acetaminophen as needed. No additional treatment was given for dizziness, psychotic disorder, elevated liver enzymes, or elevated CK levels. On day 28, the patient went on a "leave of absence" from the hospital as he was reported to have done reasonably well but returned to the hospital on day 34 after feeling unwell, with disorientation. The patient had fever of 38.5°C on day 34, but his temperature soon returned to normal (patient's home was not air conditioned, and the city of residence was warm at that time). After all investigations were normal, the patient went on a second leave of absence from days 36 to 46. The patient was discharged from the hospital on day 46 following complete recovery.

DISCUSSION

From data of 5008 patients analyzed in the Janssen clinical trial database for NMS with PP1M and PP3M, a single case of NMS associated with PP1M LAI was identified. The most common manifestations of NMS, including altered mental state, muscle rigidity, fever, and elevated CK (>1000 U/L), were reported in this case. The severity of NMS appeared to be mild, and the patient recovered completely. This database review illustrates the low propensity for NMS events during PP1M or PP3M treatment and successful management of this complication in the single case identified with symptomatic treatment.

Given that NMS is a known and rare adverse event associated with use of antipsychotics, the investigator judged that the etiology of NMS was possibly related to PP1M. However, the patient was also receiving flupenthixol decanoate 15 mg intramuscularly every 2 weeks (variable half-life between 3 weeks and 3 months) for 6 years prior to randomization, which was discontinued 22 days before PP1M administration. Thus, it is possible that initiation of NMS on day 15 cannot be attributed 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.[11] In the present case, oral tolerability medication (paliperidone extended release), although below limit of quantification at baseline, may also be a contributory factor.

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.

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

To the Editors:

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 Theravalues Corporation (Tokyo, Japan). Study protocol was approved by institutional review board (Yale HIC number 1412015121) and registered on 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 Symptom Scale [PANSS], Calgary Depression Scale for Schizophrenia, and The Committee of Clinical Investigations (UKU) 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 χ^2 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 al[3] reported improvement in cognitive functioning and negative