INVEGA® (paliperidone ER)
Adverse Event of INVEGA - Neuroleptic Malignant Syndrome

SUMMARY

- A potentially fatal symptom complex referred to as NMS (neuroleptic malignant syndrome) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).[1]
- The management of NMS generally includes discontinuation of antipsychotics, hydration, and symptomatic supportive treatment (American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, 2020)[1,2]
- If a patient appears to require antipsychotic drug treatment after recovery from NMS, the reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.[1]
- Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics may be at increased risk of NMS.[1]

PUBLISHED LITERATURE

Double-Blind Trial

Kramer et al (2007)[3] conducted an international, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of flexibly dosed INVEGA (3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) in delaying symptom recurrence in patients with schizophrenia.

Study Design/Methods

- Patients diagnosed with schizophrenia for ≥1 year and who were experiencing an acute episode (defined as a Positive and Negative Syndrome Scale total score between 70-120) were eligible for enrollment in the study.
- Prior to randomization in the flexible dosing double-blind phase, there was a screening period, an 8-week open-label run-in phase (flexible dosing), and a 6-week open-label stabilization phase (fixed dosing).
- Five hundred and thirty patients enrolled in the open-label run-in phase. Two hundred and seven patients were randomized to the double-blind phase (variable duration); 105 received INVEGA and 102 received placebo.

Results

- There was one report of possible NMS.
  - The patient received INVEGA for 19 days and was also treated for extrapyramidal symptoms during the run-in phase. The incident occurred three days after the patient withdrew from the run-in phase.
  - Other than elevated creatinine kinase (2201 U/L), the patient had normal laboratory work and vital signs (including temperature) at the end of the study.

Case Reports

Case Reports – Paliperidone ER and NMS

Case Background	NMS Symptoms/Outcomes
Di Venanzio et al (2015)[4] reported a case of NMS for 30 year old female patient that was on quetiapine,	• The patient was admitted to the hospital with a flushed and sweaty face, hypersalivation.

haloperidol, paliperidone and fluphenazine decanoate, clonazepam, lorazepam. The patient had a mental disability and bipolar disorder type I. • The patient was admitted to the hospital with the following symptoms of hypersalivation, severe dysphagia, urinary incontinence, tremors, and rigidity.	• Antipsychotic therapy had been discontinued. Supportive therapy with parenteral nutrition and hydration was initiated. • Shortly after hospital admission, the patient developed a fever, elevated creatine kinase levels and displayed consciousness disorders. The consciousness disorder was presented with a GCS total score of 8, attention deficit, mutism, extreme negativism, unable to eat, rigidity, and no control of bowels. • The patient received supportive treatment (hydration, electrolyte restoration, oxygen and blood pressure aids, parenteral nutrition) concomitantly with antipyretics, antibiotics and anticoagulant medications. The patient also received dantrolene and diazepam for the first 20 days with no clinical benefit. Then rotigine patch therapy was then added on. • After 6 months, the patient reports utilizing a walker, eating independently, with periods of dysarthritic enunciation.
Araujo et al (2013)[5] reported a case of NMS in a 15-year-old female that was attributed to treatment with haloperidol, risperidone, and paliperidone. • The patient presented with first-onset, severe, psychotic symptoms and was medicated with these antipsychotics prior to hospital admission. The duration of prior antipsychotic treatment and dosages were not reported. • Upon hospital admission, the previous antipsychotic regimen was discontinued, and the patient began treatment with olanzapine for 7 days (dose not reported).	• Approximately 7 days after hospitalization, the patient became agitated, developed a fever, hypersalivation, muscle rigidity, and tremor. Creatinine kinase, lactic acid dehydrogenase, and white blood cell count were all elevated. • All antipsychotics were discontinued. The patient developed acute renal failure and hepatic cytolysis and was admitted to the ICU for 5 days where she was treated with benzodiazepines, biperiden, and bromocriptine. Despite treatment she remained in a catatonic state. • The patient improved after electroconvulsive therapy (2 series of 6 bilateral treatments), was discharged from the hospital, and was followed on an outpatient basis where she was treated with aripiprazole. No adverse events were reported with aripiprazole therapy.
Özdemir et al (2012)[6] reported a case of NMS in a 22-year-old man with a 5-year history of schizophrenia following a hospital admission for worsening psychiatric symptoms. • The patient was initiated on clozapine, titrated to 250 mg/day over 3 weeks. Amisulpride 200 mg/day was added due to severe hypersalivation. After 4 weeks, clozapine was tapered off due to persistent sedation, hypersalivation and lack of response. • By week 5, paliperidone ER 6 mg/day was added to amisulpride 200 mg/day while clozapine was tapered to 100 mg/day. By week 6, paliperidone ER was increased to 9 mg/day and clozapine was stopped.	• Ten days after the initiation of paliperidone extended release (ER), the patient was noted to be diaphoretic and in moderate distress. He had generalized rigidity, a fever (38.5°C oral), increased pulse (120 bpm) and a blood pressure of 140/90 mmHg by day 12. • Abnormal laboratory findings included, increased creatinine phosphokinase (3,946 IU/L, reference range: 0-200 IU/L) and increased AST (98 IU/L, reference range: 0-35 IU/L). Leukocytes, neutrophils, platelets, renal function and serum electrolytes were within normal range. Blood and urine cultures, chest X-ray and cranial CT were negative. • Amisulpride and paliperidone ER were discontinued and supportive care was initiated (parenteral hydration and as needed acetaminophen) following a preliminary diagnosis of NMS. The patient also received bromocriptine 7.5 mg/day

	and a total of 5 mg lorazepam during the first week. • Seventy-two hours following the discontinuation of paliperidone ER and amisulpride, muscular rigidity and fever abated. By day 5, all other NMS symptoms resolved. CPK levels dropped to 309 U/L within 2 weeks. Lorazepam was replaced by diazepam 20 mg/day, after 10 days, and continued for 2 weeks. • As per his family's request, the patient was discharge from the hospital, although schizophrenic symptoms returned following discontinuation of antipsychotics.
Teng et al (2011)[7] reported on the appearance of NMS-like symptoms in a 32- year-old male patient following an abrupt switch from risperidone to paliperidone. • The patient has suffered from chronic schizoaffective disorder for 4 years, during which he exhibited symptoms of catatonia and depressed mood. • For the past 2 years, he was stabilized on risperidone 4 mg/day, venlafaxine 150 mg/day, and lithium 300 mg/day. • Risperidone was eventually switched to paliperidone 3 mg/day due to chronic hepatitis. All other medications remained unchanged.	• Three weeks after starting treatment with paliperidone, he displayed negativism, mutism, and slight muscle rigidity. He was brought into an outpatient clinic 4 weeks after starting treatment with paliperidone. • Due to the possibility of exacerbated catatonia, paliperidone was changed back to risperidone 4 mg/day. • He continued to complain of increased stiffness, difficulty swallowing, incontinence, agitation, and delirium. He was admitted to the emergency room 6 days later. • After discontinuation of therapy and supportive treatment with diazepam, bromocriptine, amantadine, and dantrolene, his symptoms showed improvement, and he was discharged 3 weeks later.
Nayak et al (2011)[8] reported on the occurrence of NMS in a 13-year-old male patient treated with paliperidone. • The patient suffered from behavioral deficits and mental retardation since childhood, and upon worsening of his symptoms, was initiated on oral paliperidone 3 mg twice daily. • After starting treatment, the boy experienced impairments in speech and motor function, as well as memory loss. • He was admitted to the psychiatric department three days following initiation of paliperidone with complaints of confusion, turning of head to one side, urinary incontinence, and fever.	• Upon examination, he had a fever (103°F), elevated blood pressure (140/80 mmHg), increased pulse rate (120 bpm), and symptoms of muscle rigidity, such as muscle tone in all four limbs, brisk reflexes, and tremors in the upper limbs. • Following medical evaluation, a preliminary diagnosis of NMS was made, and hematological testing was initiated. The hematology lab Results (total leukocyte count: 16,200/mm3; increased creatinine phosphokinase: 2,120 U/liter [reference range: 35-232]; platelet count: 1,052,000/mm3; serum iron: 8 µg/dl [reference range: 35-150]; SGOT: 123 U/liter [reference range: 15-37]; SGPT: 86 U/liter [reference range: 30-65]), along with renal function tests (within normal limits), CT scan Results (congenital hydrocephalus), and an assessment using the NMS scale (24/36), provided strong evidence to strengthen the diagnosis of NMS. • Oral paliperidone was discontinued, and the patient experienced a decrease in symptoms following treatment with IV fluids, antipyretics, and benzodiazepines. His confusion improved a day after initiating supportive treatment and within a week, was in a premorbid state.

	• Follow-up visits were conducted at week three and four following discontinuation of paliperidone, at which time the patient showed no signs of neurological deficits.
Han et al (2011)[9] reported on the development of NMS in a 58-year-old woman during her switch from oral olanzapine to oral paliperidone. • She was prescribed olanzapine 10 mg/day for one and a half years for the treatment of schizophrenia. While receiving treatment, she gained approximately 14 kg and developed diabetes mellitus. • Her therapy was switched to paliperidone 3 mg/day while tapering down her dose of olanzapine. Seven days after the initiation of paliperidone, olanzapine was discontinued and the paliperidone dose was increased to 6 mg/day.	• On day 8 after initiating paliperidone, the patient experienced symptoms of body stiffness and was admitted to the emergency room due to muscle rigidity, dysarthria, confusion, and impairments in motor function. • She was diagnosed with NMS based on her physical examination, which included increase in body temperature (38.0° C), fluctuating blood pressure (70/50-125/85 mmHg), change in medication (olanzapine to paliperidone), and abnormal laboratory Results (creatine kinase (CPK): 26,791 U/L; lactate dehydrogenase (LDH): 1599 U/L; ALT: 259 U/L; AST: 143 U/L; Myoglobin: 276 ng/mL). • Paliperidone was discontinued, and the patient began treatment with benzotropine 2 mg/day and lorazepam 3 mg/day. • Seven days following discontinuation of paliperidone, her muscle rigidity improved moderately and her CPK levels were improved. On day 13 after discontinuation of paliperidone, the patient showed stable vital signs, a CPK level of 184 U/L, and a resolution of muscle rigidity symptoms. She was discharged with improvement in NMS on day 14.
Mantas et al (2010)[10] reported the appearance of NMS-like symptoms associated with the use of paliperidone ER in a 24-year-old male patient. • The patient was originally admitted to the hospital for conversion from clozapine to paliperidone ER due to poor outcomes and adverse effects. Over the next 13 days a slow tapering of clozapine 500 mg/day and valproate 1500 mg/day occurred. Paliperidone ER was initiated at 6 mg/day. • At discharge the patient's medication regimen was paliperidone ER (9 mg/day), clozapine (100 mg/day) and valproate (1000 mg/d). The patient was instructed to discontinue the clozapine after 3 days and the valproate after one week.	• The patient presented to the emergency department 18 days later mute and diaphoretic with severe generalized muscle rigidity. • Vital signs included labile blood pressure (90/50-125/80 mmHg) and a mild increase in temperature (37.5°C). An elevation in CPK (creatine phospkinase) at 466 IU resulted in preliminary consideration of NMS. • Paliperidone ER was discontinued and diazepam 40 mg/day was initiated. CPK level increased and peaked at 1169 IU. Bromocriptine 7.5 mg/day was added due to muscle rigidity and excessive dysphagia. Two weeks later the CPK level was within normal limits and muscle rigidity resolved. Quetiapine 300 mg/day was initiated. • The author commented that it is unclear whether the observed symptoms represented NMS or malignant catatonia. Abrupt discontinuation of clozapine is associated with NMS or catatonia. The increment of the dose from 6 to 9 mg, however implicated paliperidone ER in this adverse event. Co-administration of valproic acid may increase plasma drug levels of clozapine although the interaction is unlikely to be clinically significant.
Duggal (2007)[11] reported a possible case of NMS associated with the use of paliperidone ER.	• Six days after initiating paliperidone ER, the patient reported increased stiffness. Cogwheel rigidity and dysarthria were confirmed; benztropine 1 mg po BID was initiated.

• A 63-year-old female was admitted to the hospital for exacerbation of chronic paranoid schizophrenia. • Upon admission her current medications were maintained and included quetiapine 1300 mg/day, trifluoperazine 40 mg/day, and clonazepam 1 mg QHS. • With no improvement in symptoms after 8 days, paliperidone ER was initiated at 6 mg/day. Trifluoperazine was discontinued after two days. Quetiapine was tapered and discontinued five days after starting paliperidone ER while the dose of paliperidone ER was increased to 9 mg/day.	• Over the next two days increased rigidity, confusion, diaphoresis, tachycardia (116 bpm), labile blood pressure (116/73-153/93 mmHg) and a mild increase in temperature (99.6°F) resulted in a preliminary diagnosis of NMS. • A modest elevation in CPK (creatine phospkinase) at 313 U/L resulted in discontinuation of paliperidone ER. Bromocriptine 25 mg TID and dantrolene 25 mg daily were started. • The CPK level peaked at 607 U/L three days after discontinuation of paliperidone ER. Five days after discontinuation of the paliperidone ER, rigidity, confusion, and autonomic instability were resolved. CPK levels returned to normal after seven days. Eight days after discontinuing paliperidone ER, the patient was re-started, stabilized, and discharged on quetiapine (1200 mg/day), trifluoperazine (40 mg/day), and benztropine 0.5 mg BID. • The author commented that the temporal relationship between the appearance of NMS symptoms with the initiation of paliperidone ER therapy and the failure of re-emergence of NMS upon re-initiating quetiapine and trifluoperazine implicated paliperidone ER in this adverse effect. NMS has been associated with neuroleptic discontinuation therefore the role of quetiapine and trifluoperazine could not be excluded by the authors.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 22 November 2023.

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