Title
Catatonia Associated with Initiating Paliperidone Treatment

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Authors
McKeown, Nathanael J
Bryan, James H
Horowitz, B Zane

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We present a case of catatonia, which occurred shortly after starting a new antipsychotic, paliperidone, an active metabolite of risperidone. Catatonia may be caused by a variety of conditions, including metabolic, neurologic, psychiatric and toxic processes. Interestingly, risperidone, which has been thought to cause several cases of catatonia, has also been recommended as a potential treatment. We discuss potential mechanisms for causes of drug-induced catatonia as well as potential treatment options. [West J Emerg Med. 2010; 11(2):186-188.]

INTRODUCTION
Catatonia can be caused by a variety of metabolic, neurologic, psychiatric, and toxic conditions. Risperidone, an atypical antipsychotic, has been reported to induce catatonia in several patients, although paradoxically, antipsychotics, including risperidone, have been used successfully to treat catatonia. Paliperidone, a major active metabolite of risperidone, was approved by the United States Food and Drug Administration (FDA) in December, 2006, for the treatment of schizophrenia. We report what we believe is the first case of catatonia temporally related to paliperidone, after a single dose.

CASE REPORT
An 84-year-old female with history of major depression and anxiety was evaluated by her psychiatrist for worsening anxiety and given a single dose of 3 mg of paliperidone. Eight hours later she became increasingly agitated and, according to her daughter, “looked like she was going to crawl out of her skin.” She then told her daughter “make it go away, make it go away,” and subsequently stopped speaking and responding to any physical or verbal stimuli, although she appeared awake and alert. She had no prior documented episodes of catatonia. Her daughter brought her into the local emergency department (ED).

In the ED, she had a temperature of 37.3°C, pulse 80 beats per minute, blood pressure 161/72 mm Hg, respiratory rate 20 breaths per minute and oxygen saturation of 98% on room air. Her medications were citalopram, trazodone, levothyroxine, and paliperidone. She lived with her daughter, who related no recent trauma. The patient previously took risperidone, but it had been discontinued after several months because of mild akathisia, with both restlessness and tremor.

Physical exam showed an alert, well appearing elderly female in no acute distress. Her pupils were equal round and reactive to light; she would not comply with extraocular muscle testing. She did open her mouth on request and stuck out her tongue midline; there was no erythema, and mucous membranes were moist. Cardiopulmonary exam was unremarkable; abdominal palpation did not cause any change in her facial expression and was soft without masses. While she complied with several requests for the cranial nerve exam she would not move her fingers or toes when asked, but was noted to turn her head in all directions and roll from side to side, moving all extremities equally. Her brachioradialis and achilles reflexes were equal and Babinski reflexes were downgoing. She exhibited stupor and mutism with fixed postures.

Finger-stick glucose was 114 mg/dL. Intravenous diphenhydramine, 25 mg and benztropine, 0.5 mg were given for dystonia without any change. Noncontrast head computed tomography (CT) was performed due to concern for stroke and was unremarkable. Laboratory tests showed white blood cell count of 7.4 K/mm³ with 60% neutrophils, her hematocrit was 37.6%, and platelets were 203 K/mm³. Electrolytes and renal function showed sodium 135 mmol/L, potassium 3.5 mmol/L, chloride 101 mmol/L, bicarbonate 20 mmol/L, calcium 9.8 mg/dL, blood urea nitrogen 12 mg/dL, and creatinine 1.0 mg/dL.

Due to the lack of inpatient psychiatric beds, she was observed in the ED for 12 hours. Psychiatric consultation had no specific recommendations. Sixteen hours after the dose
of paliperidone, without other therapy, she began to talk and interact. More detailed neurological exam showed no focal deficits. Her mood and affect were appropriate. She did not recall the events of the previous evening but remembered her daughter talking, although she was unable to respond.

DISCUSSION

Catatonia is a neuropsychiatric syndrome characterized by a combination of mental, motor, vegetative, and behavioral signs and symptoms. It has been described as a syndrome with prominent motor signs, with positivistic or excitatory symptoms, including mitgehen, in which there are excited movements with light stimulation, even with instructions to the contrary. Other signs include stupor, immobility, mutism, and negativism, including gegenhalten (increasing resistance to passive movement of the limbs), waxy flexibility, posturing, stereotypic movements, echolalia, and echopraxia. Mutism and stupor are generally regarded as principal signs of catatonia, although neither are certainly pathognomonic.

The Diagnostic and Statistical Manual of Mental Disorders, DSM – IV, defines catatonia as the presence of at least two of the following: motoric immobility, excessive motor activity, extreme negativism/mutism, posturing/stereotyped movements/prominent mannerisms or grimacing, and echolalia or echopraxia.

Our patient exhibited several of these features, including immobility, with posturing at times, and extreme negativism, including mutism. While her presenting differential was broad, lack of fever, headache, and a normal white count were inconsistent with infection. A lumbar puncture was not obtained, but complete reversal of symptoms without other therapy would also argue against meningitis or encephalitis. Non-convulsive status epilepticus or partial complex seizures should also be considered, although there was no history of a previous seizure disorder. An electroencephalogram (EEG) should be obtained if clinical suspicion warrants.

Catatonia has been associated with schizophrenia, major depressive disorder, as well as other medical conditions, including alcoholism, bi-frontal tumors, encephalitis, transient ischemic attack, chronic obstructive pulmonary disease, rheumatic heart disease, Alzheimer’s and vascular dementia, central diabetes insipidus, closed head injury, end stage renal disease, and renal tubular acidosis. Neuroleptic malignant syndrome, as well as severe extrapyramidal reactions, may also present initially with catatonic features, and has been considered by some to be a subset of catatonia.

While no studies have specifically evaluated the prevalence of drug-induced catatonia, studies regarding general causes of catatonia suggest that 17-19% of all cases diagnosed as medical catatonia are actually drug-induced catatonia. Another study found that antipsychotic-induced catatonia accounted for 24% of all catatonic patients referred to the ED of a general hospital.

Drug-induced catatonia has mostly been reported with psychotropic drugs, including fluphenazine, haloperidol, risperidone, and clozapine, non-psychotropic drugs such as steroids, disulfiram, ciprofloxacin, several benzodiazepines, as well as drugs of abuse, including phencyclidine, cannabis, mescaline, LSD, cocaine and ecstasy. While psychiatric disorders may simply cause catatonia, it does appear that medications themselves can either cause or unmask an underlying predisposition to catatonia.

The mechanism by which medications cause catatonia is not known. Mechanisms have been proposed based on animal models: 1) dopamine hypoactivity at the D2 receptor, 2) GABA hypoactivity at the GABA_A receptor and hyperactivity at the GABA_B receptor, 3) serotonin hyperactivity at 5-HT1A receptor and hypoactivity at 5-HT2A receptor, and 4) glutamate hypoactivity at the NMDA receptor.

Paliperidone is the active major metabolite of risperidone. It was approved by the FDA in December 2006 and released to consumers in the United States in January 2007. Its therapeutic activity is believed to be a result of both central dopamine type 2 and serotonin type 2 receptor antagonism. It is also an antagonist at α1 and α2 adrenergic receptors and H1 histaminergic receptors. Plasma concentrations are estimated to peak approximately 24 hours after dosing with a terminal half-life of approximately 23 hours. Bioavailability is 28% with apparent volume of distribution of 487 L. Plasma protein binding of paliperidone is 74%. Unlike risperidone, paliperidone is not extensively metabolized by the cytochrome P450 enzymes and is not expected to cause clinically relevant pharmacokinetic drug interactions.

ED evaluation of patients who present with catatonic symptoms requires a comprehensive evaluation and a wide differential and should not be initially attributed to the underlying psychiatric disorder. Treatable common causes of catatonia should be ruled out. Further diagnostic and laboratory studies may include complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, urinalysis, cerebral spinal fluid evaluation, CT, magnetic resonance imaging, EEG, and other studies as clinical history and physical findings dictate.

In most cases of drug-induced catatonia, stopping the implicated drug and supportive care is usually sufficient. Benzodiazepines and electroconvulsive therapy have also been recommended as potential treatments. Typical antipsychotics such as haloperidol should be avoided, although a trial of atypical antipsychotics (e.g. risperidone, olanzapine) has been suggested for patients who do not respond to other measures. Caution should be taken in considering using paliperidone in patients who have already had previous adverse reaction to risperidone. Anticonvulsants, valproate, and carbamazepine have also been reported to be effective but may take longer to work than benzodiazepines.

The Naranjo scale of adverse drug reactions is a validated score that assesses the probability of a causal relationship between a drug and a clinical event and is
reported based on several criteria as definite, probable, possible, and doubtful. Although this medication-catatonia relationship was scored as “possible” on the Naranjo scale, there had been no other change in medications or initiation of other medications, which may have been responsible for her condition. Also of note is no previous history of catatonic-like symptoms presented prior to initiation or after discontinuation of the paliperidone.

**SUMMARY**

A number of medications have been associated with catatonia, including antipsychotics. Providers should consider multiple etiologies when evaluating a patient who presents with catatonia-like symptoms. Paliperidone, similar to risperidone, may be a cause of drug-induced catatonia.

**REFERENCES**