

Autopsy-proven Mirtazapine Withdrawal-induced Mania/Hypomania Associated with Sudden Death

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Abstract

Manic episodes induced by antidepressant withdrawal are rarely reported. Mirtazapine is a tetracyclic, piperazinoazepine compound and is a noradrenergic, adrenergic, serotonergic, histaminergic, and muscarinic-antagonist antidepressant that is used for the treatment of major depression and other psychiatric illnesses. There are several reported cases of manic/hypomanic episodes induced by mirtazapine withdrawal based on suspected clinical symptoms that were not confirmed by autopsy and toxicology. We present the first reported case of mirtazapine withdrawal-induced mania/hypomania associated with sudden death and confirmed by autopsy and toxicology. Our patient was a 26-year-old male who had been diagnosed with schizophreniform disorder, borderline intellectual functioning, polysubstance abuse, mild mental retardation, and attention deficit hyperactive disorder. He took only mirtazapine in the final and terminal weeks of his life and stopped taking mirtazapine 4 days before his death. He exhibited a sudden manic/hypomanic episode and died during a physical altercation during this episode. A full autopsy with comprehensive toxicologic analysis of his body fluids and tissues was performed. Autopsy revealed that he died from blunt force trauma of the head, neck, and trunk with extremely low and markedly subtherapeutic levels of mirtazapine and desmethylmirtazapine in the blood (mirtazapine: 0.005 mg/L; desmethylmirtazapine 0.011 mg/L). Advanced selective radioligand and neurochemical assays for density and affinity-binding parameters of dopamine transporter and heat shock protein 70 did not reveal any evidence of excited delirium or autonomic hyperactivity state. We recommend that toxicologic analysis of blood for antidepressants should become routine parts of autopsy protocols for the investigation of sudden death following terminal manic/hypomanic episodes for further elucidation of mania/hypomania induced by antidepressant withdrawal.

Keywords: Autopsy, mania/hypomania, mirtazapine, sudden death, toxicology

INTRODUCTION

Mirtazapine is a tetracyclic piperazinoazepine compound, structurally related to mianserin, and is a noradrenergic, adrenergic, serotonergic, histaminergic, and muscarinic antagonist antidepressant that is used for the treatment of major depression and other psychiatric illnesses including anxiety disorders, panic disorder and social anxiety disorder, obsessive-compulsive disorder, undifferentiated somatoform disorder, and schizophrenia.^[1,2] Manic and hypomanic episodes induced by mirtazapine withdrawal are not commonly reported. There have been several reported cases which have been based on suspected clinical symptoms that were not confirmed by autopsy and toxicology.^[3-6]

Our case will be the first reported autopsy-confirmed terminal mania, associated with sudden and unexpected traumatic death, with autopsy confirmation by comprehensive postmortem

toxicologic analyses of body fluids, which showed extremely low and markedly subtherapeutic levels of mirtazapine in the blood, vitreous humor, urine, and bile. The deceased stopped taking his prescribed mirtazapine about 4 days before his terminal manic episode and death.

CASE DESCRIPTION

Our patient was a 26-year-old Hispanic male who had been diagnosed with schizophreniform disorder, borderline intellectual functioning, cannabis abuse, polysubstance abuse, mild mental retardation, and attention deficit hyperactive

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disorder. He had been receiving treatment occasionally for 6 years before his death.

His medical records revealed that he was prescribed with and took mirtazapine, aripiprazole, and quetiapine in the final year of his life. The records indicate that he took only mirtazapine in the final and terminal weeks of his life and stopped taking mirtazapine 4 days before his death.

In the evening of the day of his death, the patient, who lived with his family, began spontaneously climbing the houses of neighbors, jumped on the roofs, and attempted entering their houses forcefully. He went to one house, began banging the windows and doors, eventually made a forced entry through a door, and began attacking and fighting with the inmates of the house. He then grabbed a young child, began to attack her and attempted to kill her. He was struck multiple times by a resident in the home with an object in an attempt to stop him from harming the child. The police was called, and upon arrival of the police, the patient began fighting with the police, a taser device was deployed, and as the police was attempting to take him into custody, he became unresponsive and died at the scene.

A full autopsy was performed which revealed fatal blunt force trauma injuries of the head, face, neck, trunk, and extremities, with contusions and lacerations of the liver and hemoperitoneum. Comprehensive quantitative toxicologic analyses of femoral vein blood, intraperitoneal blood, vitreous humor, bile, and urine revealed the presence of only ibuprofen, cannabinoids, mirtazapine and its metabolite, desmethylmirtazapine. Alcohol, synthetic cannabinoids, bath salts, and other common acidic, neutral, or basic drugs were not detected in the blood, vitreous humor, bile, or urine. The levels of the detected drugs are shown in Table 1. Qualitative toxicologic analysis of the brain tissue revealed nondetectable levels of mirtazapine in the brain; however, desmethylmirtazapine was detected in the brain tissue. The plasma therapeutic level for mirtazapine is 0.03–0.08 mg/L.^[7] The ratio of the levels of mirtazapine in postmortem blood to levels in plasma is 2.5,^[8] therefore the expected therapeutic postmortem blood levels of mirtazapine would be 0.08–0.2 mg/L. The mirtazapine blood levels in our reported case are very much below the expected postmortem therapeutic blood levels for mirtazapine.

Advanced selective radioligand and validated neurochemical assays for density and affinity-binding parameters of striatal dopamine transporter and heat shock protein 70 did not reveal any evidence of excited delirium or autonomic hyperactivity state. The cause of death was determined to be blunt force trauma of the head, neck, and trunk associated with a terminal, premortem mirtazapine withdrawal/discontinuation-induced hypomania/mania.

DISCUSSION

Autopsy and toxicologic analysis of body fluids in our case exculpated excited delirium or autonomic hyperactivity state, acute drug intoxication by stimulants such as cocaine, phencyclidine, and amphetamine, and the presence of any other confounding drugs except cannabinoids. He was a habitual user of marijuana and was not known to exhibit any adverse reaction to cannabinoids.

The levels of mirtazapine in the blood of our patient were 16–40 times lower than the expected postmortem blood therapeutic levels of mirtazapine. The known half-life of mirtazapine is 20–40 h,^[1] and the markedly low postmortem blood levels we have observed confirm the premortem forensic scenario that our patient stopped taking his prescribed mirtazapine several days prior to his terminal manic episode and death.

Desmethylmirtazapine is the only metabolite of mirtazapine that contributes to its pharmacodynamic profile but is not believed to contribute significantly to the overall effects of the drug due to very low blood concentrations, like we have in our case.^[2,9]

Our case fulfills the diagnostic criteria for antidepressant discontinuation or withdrawal “manic state” as have been proposed by Narayan and Haddad.^[10] Most reported cases of antidepressant withdrawal mania are due to sudden discontinuation and may be associated with a broad variety of symptoms that may include anxiety, restlessness, depression, insomnia, diarrhea, vomiting, and rarely hypomania or mania. Withdrawal-induced cholinergic overdrive and the actions of the cholinergic-noradrenergic system remain one of the most investigated hypotheses for explaining antidepressant withdrawal-induced mania. It has been postulated that upon

Table 1: Levels of mirtazapine, desmethylmirtazapine, ibuprofen, and cannabinoids detected by toxicologic analyses of postmortem samples of blood, vitreous humor, bile, and urine

Drug	Femoral blood	Peritoneal blood	Vitreous humor	Bile	Urine
Mirtazapine (mg/L)	0.005	0.006	0.003	0.003	0.006
Desmethylmirtazapine (mg/L)	0.011	Negative	0.012	QNS	0.059
Ibuprofen (mg/L)	8.2	10			
Delta-9-THC (ng/mL)	16	6.3			
Delta-9-THC-COOH (ng/mL)	37	33			
Delta-9-THC-OH (ng/mL)	4.4	5.1			

QNS=Sample quantity not sufficient for analysis, THC=Tetrahydrocannabinol, THC-COOH=Carboxy-tetrahydrocannabinol, THC-OH=Hydroxy-tetrahydrocannabinol

cholinergic overdrive, the monoaminergic synthetic pathways are activated in an effort to maintain homeostasis. When the cholinergic overdrive abates, the monoaminergic system should downregulate in tandem. However, in some patients, for unknown reasons, the system fails to downregulate, which leads to relative monoaminergic (serotonergic and adrenergic) excess and resultant mania and hypomania.^[4]

We do not know exactly what role cannabinoids may have played in our case. In the cases of mirtazapine withdrawal-induced mania reported by Verma and Mohapatra^[4] and by Soutullo *et al.*,^[6] there was a presence of other nonconfounding drugs that included lithium carbonate and sertraline, respectively. We do not have any explanation about the role, if any, that these drugs may have played in the induction of mania/hypomania by mirtazapine withdrawal in our case or in their cases.

We recommend that specific and targeted toxicologic analysis for mirtazapine and other antidepressants should become routine components of autopsy protocols of sudden traumatic and nontraumatic deaths that exhibit terminal psychotic, manic, and hypomanic episodes. We believe that such routine toxicologic analyses will identify more fatal cases of antidepressant withdrawal-induced mania/hypomania that may be associated with sudden and unexpected deaths.

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Conflicts of interest

There are no conflicts of interest.

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