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Amineptine and Midazolam Dependence

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ABSTRACT

A case report of a patient with amineptine and midazolam dependence is presented. A literature search was done for other cases of amineptine abuse and their presentations and medical investigations are compared. This is the first locally reported case of amineptine abuse and highlights the fact that amineptine is a potential drug of abuse.

Keywords: case report, amineptine, midazolam, dependence

INTRODUCTION

Amineptine is a substance containing an imipramine-like tricyclic ring. It has psychostimulant and antidepressant properties. It acts by releasing dopamine at synapses and inhibits dopamine uptake. At high doses, serotonin uptake is affected. The drug has a reversible toxicity on the liver. It has been reported to have a rapid onset of action without the characteristic time lag of tricyclic antidepressants[1-3].

The first reports of amineptine dependence appeared in the late 1970s. The patients highlighted had bipolar disorder[4], dysthymia[5], borderline personality disorder[5], and schizophrenia[6]. In this paper, we highlight a patient with amineptine dependence. In addition, this patient was also dependent on midazolam. He used midazolam to balance the high from amineptine, almost like *ying* and *yang* balance. He is also the first locally reported case. This paper highlights amineptine as a potential drug of abuse.

CASE REPORT

Mr LM, a 45-year-old Chinese production operator, was admitted in February and August 1995 for amineptine and midazolam dependence. In 1990, a general practitioner prescribed him with amineptine when he experienced low mood as a result of work, domestic and financial problems. At that time, he had difficulty repaying a housing loan and was also having problems communicating with his colleagues and his wife. His marital problems led him to have an extramarital affair. Amineptine gave him a sense of "decisiveness" and increased speed of thinking. From experimentation, he discovered the pleasurable effect of amineptine. His daily intake increased from 200 mg to 2,000 mg within a few weeks. He would experience pleasurable effects within 20 minutes of taking the drug. As his daily intake increased, he would get too stimulated and would then add midazolam to reduce the intensity of stimulation. He was introduced to the effects of midazolam by his colleagues. He found that his speed of thinking would lessen after 4 hours. Once the thinking stabilised, he would then take more amineptine to reach the next "high". His total intake of midazolam was 45 mg a day. Through trial and error, he found that a combination of 7.5 mg of midazolam and 300 mg of amineptine provided just the right amount of stimulation for him. He was subjectively aware of the difference in withdrawal symptoms from the two drugs. Amineptine withdrawal produced a slowness of thought while midazolam withdrawal produced tremulousness in him.

LM is the youngest in a family of three boys. His parents, in their fifties, live alone. There is a strong family history of alcohol dependence in his father and paternal uncles. They were never treated for this. His childhood was unremarkable. After completing his secondary education, he worked in several jobs at the supervisory level. With the onset of his drug dependence, his occupational functioning declined steadily and he now works as a production operator in a factory.

He has been married to a 49-year-old teacher for 25 years. The couple has 2 children aged 21 and 17 years. He was having difficulties communicating with his wife and the chronic marital discord resulted in him having an extramarital affair. He has no forensic record. He does not drink but is a heavy smoker. He has no past psychiatric or medical history. He describes his pre-morbid personality as someone who craves excitement and novelty although he could not elaborate on this.

In the mental state, he was kempt, euthymic, relevant and did not display any psychotic features. However, he experienced craving for amineptine during withdrawal. Amineptine withdrawal also produced a slowness of thought. The physical examination was unremarkable. Blood investigations revealed a mild leucocytosis of 11 x 10^9 and elevation of gamma glutamyl transferase. His renal function was normal.

Detoxification was carried out as an inpatient. Amineptine doses were tapered by 50 mg every other day. Diazepam was started at a dose of 10 mg a day and tapered gradually. Relapse prevention, which

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Table I – Characteristics of amineptine dependent patients

	Case 2	Case 3	Case 4	Case 5	Case 6 (present case)
Demography					
Case 1 50-year-old male Causacian, journalist	48-year-old male Caucasian, separated	30-year-old female Caucasian, single unemployed	50-year-old male Pakistani, businessman	41-year-old male Pakistani, pharmacist	45-year-old male Chinese, production operator
Symptoms					
Anxiety, depressed mood, loss of appetite, loss of weight 10 kg over 5/12. History of alcohol abuse	Insomnia, loss of appetite, loss of weight 3 kg, acute confusional state, headache, nausea. No history of alcohol abuse/dependence.	Acute psychosis, persecutory delusions, auditory hallucinations, pressured speech, labile mood. No history of alcohol abuse/dependence.	Acute psychosis. No history of alcohol abuse or dependence	Irritable mood, insomnia acute psychosis (aggression, bizarre visual and auditory hallucinations). No history of alcohol abuse/dependence	Depressed mood
Diagnosis					
Dysthymia Avoidant P.D.	Borderline P.D.	Paranoid schizophrenia	Bipolar disorder	Major depression	Dysthymia
Investigation					
↑ blood glucose 3.48% ↑ in SGOT, SGPT, GGT	–	–	Leucocytosis Liver function test normal	Leucocytosis ↑ GGT	Leucocytosis (transient) ↑ GGT
Treatment and outcome					
Detoxification Maintenance amineptine 200 mg/day(-1) Relapsed and defaulted	Detoxification AOR discharge	Detoxification Long-stay psychiatric ward	Relapsed Defaulted follow-up	Detoxification Craving present	Detoxification Marital counselling Relapse prevention Regular follow-up
Highest amineptine dose					
2 g/day	2 g/day	3 g/day	3.5 g/day	3 g/day 60 mg of bromazepam/day	2 g/day and 45 mg/day of midazolam

focussed on cognitive behavioural strategies, problem solving and psychological traps, was carried out during the first inpatient stay. Regular follow-up was advised upon discharge but he defaulted.

Three months after the first admission, he had a reinstatement of his dependence. He took 1,000 mg of amineptine with about 30 mg of midazolam in the ratio mentioned earlier. He relapsed because of difficulties adjusting to his new job and felt a need for excitement. His mental state was the same as during his first admission.

Detoxification was carried out in the same way during the second admission and he was discharged with low dose amineptine of 5 mg a day. This time round, tapering was done gradually as he experienced poor concentration and fatigue without amineptine. The patient titrated his doses of amineptine from 100 mg per day to 50 mg per day to 25 mg per day in 6 months. After 6 months, he stopped taking amineptine and has been able to cope with bouts of fatigue and poor concentration by drinking water. He still works as a production operator but plans to quit and work in a bank. A repeat full blood count and liver function test done at 3-month follow-up showed no abnormalities. He is still on regular follow-up and is clinically well.

DISCUSSION

This case is interesting in a few aspects. Firstly, this patient was taking both amineptine and midazolam in a set ratio to achieve just the right balance of "highs" and "lows". Secondly, although he has a strong family history of alcohol dependence, he does not drink. The patient's symptoms meet the Edward's criteria for dependence. He has tolerance to the drug, withdrawal symptoms, relief of withdrawal symptoms on taking the drug, craving for the drug, a decline in occupational functioning and reinstatement after a period of abstinence. The psychiatric diagnosis in LM is substance use disorder.

A search in the literature revealed 5 other case reports. All except one patient are males. Half of the cases were unemployed and the details of each of these cases are shown in Table I. An analysis of their clinical symptoms is tabulated in Table II.

The diagnoses given to the 6 cases (inclusive of this present case) varied, ranging from a personality disorder to schizophrenia. Of the cases in the literature, 5 have since defaulted follow-up and 1 is in a chronic ward setting. The highest doses of amineptine per day ranged from 2 – 3.5g/day. There was 1 case in the literature with amineptine dependence and benzodiazepine (bromazepam)

Table II – Psychological symptoms of patient dependence on amineptine

Symptoms*	No. (n=6)
Anxiety	1
Depression	2
Insomnia	2
Appetite and weight loss	2
Acute psychosis	3
Irritability, labile mood	1
Acute confusional state	1

* Symptoms not mutually exclusive. All cases have more than 1 symptom

dependence[4]. This patient was also taking the drugs in divided doses although the article did not elaborate on the exact drug ratios taken. Since the case reported is not the only case taking amineptine and benzodiazepine, it would be good to find out in what ratios the two drugs were taken. The dosages of amineptine used are similar to the doses used by our patient. Although our patient has no major psychiatric illness, his poor coping skills has no doubt contributed to his current difficulties.

A mild leucocytosis was reported in 3 of the 6 cases[4]. The literature did not state if the leucocytosis was transient. Although there was 1 report of a raised blood glucose level[5, case 1 of Table I], an examination of this case history revealed that the patient had undergone a radical pancreatectomy and gastric resection 15 years earlier which could explain the high blood glucose. Derangement in liver enzymes was noted in 3 of the 6 cases, especially involving the gamma glutamyl transferase[4,5]. None of the cases had symptoms of jaundice, pruritus, abdominal pain, fever and chills. It has been ascertained that amineptine inhibits the mitochondrial oxidation of fatty acids and produces microvescicular steatosis of the liver in mice[8]. A French survey of amineptine done from 1977 – 1983 revealed that amineptine accounted for 63 of the 91 collected cases of liver injury caused by antidepressants (70%)[7].

CONCLUSION

In conclusion, it is clear that amineptine has the potential for abuse and dependence. Therefore, the prescribing of this drug by general practitioners and other medical practitioners should be done judiciously. The patients likely to be at risk of developing amineptine dependence are those with a history of drug or alcohol abuse or dependence. Doctors must be wary of any rapid increase in dose of amineptine ingested as this would suggest abuse of this medication.

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