

Employing mirtazapine to aid benzodiazepine withdrawal

Chandrasekaran P K

ABSTRACT

Insomnia and depression are frequently encountered in patients during withdrawal from substances. While there are no approved medications for treating them, off-label attempts to address these phenomena with mirtazapine have shown some promising results. This case describes the use of mirtazapine as an aid in benzodiazepine withdrawal and its potential benefits in alleviating insomnia and depression in a 32-year-old man. It was found to ameliorate sleep myoclonus that was thought to be associated with his withdrawal syndrome. It is hoped this report will generate interest and stimulate further research in this area of psychopharmacology.

Keywords: benzodiazepine withdrawal, depression, insomnia, mirtazapine, noradrenergic selective serotonin antidepressant, sleep myoclonus

Singapore Med J 2008;49(6):e166-e167

INTRODUCTION

Patients who abuse prescription drugs may exhibit certain patterns of addiction, such as escalating use, drug-seeking behaviour and doctor shopping. This is an increasing problem, even with the tightening of restrictions on over-the-counter medications. Shorter-acting benzodiazepine agents have a greater potential to cause dependence than the longer-acting ones. "Long-term" usage, according to Tyrer et al, is considered usage for three or more months, and the Committee on the Review of Medicines states that the tranquillising effects of benzodiazepine drugs do not persist beyond three or four months.^(1,2) However, dependence can occur in less than three months and withdrawal symptoms have been noted in patients who have received benzodiazepine agents for three weeks.⁽³⁾

The mechanism of dependence on benzodiazepine drugs is described subsequently. Any drug which relieves pain or anxiety centrally does so by occupying a specific receptor site, which exists for an endogenous substance resembling the drug. If that drug occupies the receptor site for more than a few days, the body will reduce or stop production of the endogenous substance which is being

consistently displaced. If the drug is then withdrawn, there will be nothing available to fill the receptor site until the body can return to its normal level of production, which may take several days for most drugs, but in the case of benzodiazepine agents, it may take much longer. In the meantime, uninhibited firing from the empty receptor sites will cause the withdrawal symptoms.⁽³⁾ Seizures do not occur when benzodiazepine drugs are withdrawn gradually, but muscular spasms may appear in the form of myoclonic jerks. Benzodiazepine withdrawal symptoms typically last at least four weeks, though according to Ashton's study, many symptoms, though improved by four weeks, may continue intermittently for months.⁽⁴⁾ Depression is frequently encountered in these patients, but there is uncertainty of the value of antidepressants in preventing emergent depression during withdrawal.⁽⁵⁾ On a collateral note, there are no approved medications with an indication for treating methamphetamine abusers or addicts at this time. Evidence-based approaches to medication development support the rationale that pharmacotherapies to decrease methamphetamine use, or reduce craving during abstinence, may be developed from altering the pharmacokinetics and pharmacodynamics of methamphetamine, or its effects on appetitive systems in the brain.⁽⁶⁾

Mirtazapine is a new generation noradrenergic, selective serotonin antidepressant (NaSSA) from the tetracyclic group. Its efficacy in treating depression has been proven and its hypnotic property has been especially beneficial in patients with disturbed sleep cycles. Its safety and efficacy in amphetamine detoxification have also been found to be significant.⁽⁷⁾ Likewise, it was found to improve patient compliance in alcohol detoxification programmes and facilitate the initial treatment phase of alcohol dependence. San and Arranz speculated that its 5-HT₃ antagonism benefited their depressed alcoholic patients, considering that antagonism of potentially up-regulated 5-HT₃ receptors may ameliorate serotonergic dysfunction, thus reducing reward and subsequently regulate alcohol intake.⁽⁸⁾ The impact of combined pharmacological and psychotherapeutic treatment on depressive and anxiety symptoms during the early withdrawal phase of alcohol was evident when mirtazapine provided significant further improvement and consequently, may prove to be a facilitator for long-term abstinence from alcohol.

NeuroBehavioural
Medicine,
Penang Adventist
Hospital,
465 Burmah Road,
Penang 10350,
Malaysia

Chandrasekaran PK,
MBBS, MPsychMed,
FNeuropsych
Consultant
Neuropsychiatrist

Correspondence to:
Dr Prem Kumar
Chandrasekaran
Tel: (60) 4 2227 772
Fax: (60) 4 2263 366
Email: premkumar@
pah.com.my

CASE REPORT

A 32-year-old man, with a chronic history of midazolam overuse over the past seven years, was found to have depressive features when he attempted to reduce the dose of the benzodiazepine which he had previously consumed up to an alarming 450 mg a day in divided doses. He had managed to decrease it to 150 mg a day, but could not further decrease the dose as he depended on it for its hypnotic effect, and also for the reduction of his anxiety about having "fits" at lower dosages. He was diagnosed to have a benzodiazepine-dependence syndrome with withdrawal-emergent depression, as well as non-epileptic sleep myoclonus. As he had not had significant benefit with the use of valproate in the past, he stopped it and relied purely on the high doses of midazolam for control of the involuntary jerks. He had also abused methamphetamines for about three years, but had stopped its misuse two years prior to contact.

Midazolam was slowly tapered down over eight weeks to a divided dose of 60 mg a day and mirtazapine was added as a substitution therapy, in a sense, for his insomnia and depression, and the dose was then increased from 15 mg to 45 mg *nocte*. His nocturnal myoclonic jerks emerged for short periods after every dose reduction of the benzodiazepine but would stabilise after a few days, suggesting that it was probably contributed by his chronic benzodiazepine abuse and his physical dependence on it. Over the next 16 weeks, midazolam was periodically decreased by 7.5 mg in a step-wise manner to a dose of 30 mg a day, and mirtazapine further increased to 60 mg *nocte* after a short period of breakthrough depression precipitated by financial problems. His mood clinically improved over a duration of 11 weeks. He tolerated the prescribed dose of the NaSSA agent with no adverse effects and there were no accounts of any myoclonic jerks.

The long-term management plan was to taper off midazolam completely over 12 weeks and to maintain mirtazapine at the current dose, and to begin decreasing it only after he has completed 24 weeks of being in remission from his depression. In the six months since starting on the plan, his confidence in the dual effects of the antidepressant, coupled with concurrent motivational interviewing, helped him overcome his psychological dependence on the benzodiazepine, and he was open to suggestions of finally stopping its use in the near future. He even initiated discussions on reducing the dosage further.

DISCUSSION

The management of benzodiazepine dependence in non-abusing patients with a licit prescription includes the switch to a long-acting compound, graded reduction and additional pharmacological and/or psychological treatments.⁽⁵⁾ Alternatives to benzodiazepines are preferable and may include antidepressants, anticonvulsants, buspirone,

antihypertensive agents and the newer neuroleptic medications. Antidepressant pharmacotherapies include the sedating trazodone, tertiary tricyclics like amitriptyline and doxepin, and newer agents such as nefazodone and mirtazapine.⁽⁹⁾ Lennane suggested a reduction by one-sixth of the total benzodiazepine dose every three days to a week, depending on a patient's decision to experience more severe symptoms for a shorter time or less severe symptoms for a longer time.⁽³⁾

Insomnia is a common sequela associated with substance-use disorders, early abstinence or protracted withdrawal.⁽⁹⁾ Thus, the above approach was successful in facilitating the tapering down of the benzodiazepine by virtue of mirtazapine's hypnotic property. Although antidepressants generally have a longer onset of action, they are nevertheless the best agents for long-term treatment if compared to benzodiazepines.⁽⁹⁾ Taking into consideration that this patient would have to be on mirtazapine for a prolonged period, this approach would again prove to be of benefit, and as expected, improvement was observed in his mood state. Mirtazapine has also rarely been known to cause seizures.⁽¹⁰⁾ Interestingly, it helped control the nocturnal myoclonus in this patient to some extent, suggesting that it may have an additional role in the management of patients who have seizure disorders associated with benzodiazepine dependence. This case report brings to light the off-label use of mirtazapine in easing benzodiazepine withdrawal with emergent depression, and its possible usefulness in sleep myoclonus associated with said withdrawal syndrome.

REFERENCES

1. Tyrer P, Owen R, Dawling S. Gradual withdrawal of diazepam after long-term therapy. *Lancet* 1983; 1:1402-6.
2. Systematic review of the benzodiazepines. Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam, and flurazepam. Committee on the Review of Medicines. *Br Med J* 1980; 280:910-2.
3. Lennane KJ. Treatment of benzodiazepine dependence. *Med J Aust* 1986; 144:594-7.
4. Ashton H. Benzodiazepine withdrawal: an unfinished story. *Br Med J (Clin Red Ed)* 1984; 288:1135-40.
5. Lingford-Hughes AR, Welch S, Nutt DJ; British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2004; 18:293-335.
6. Vocci FJ, Appel NM. Approaches to the development of medications for the treatment of methamphetamine dependence. *Addiction* 2007; 102:96-106.
7. Kongsakon R, Papadopoulos KI, Sagnansiritham R. Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. *Int Clin Psychopharmacol* 2005; 20:253-6.
8. San L, Arranz B. Mirtazapine: only for depression? *Acta Neuropsychiatr* 2006; 18:130-43.
9. Longo LP, Johnson B. Addiction: Part I. Benzodiazepines--side effects, abuse risk and alternatives. *Am Fam Physician* 2000; 61:2121-8.
10. The Medications: Mirtazapine. In: What Meds [online]. Available at: www.whatmeds.com/meds/mirtazapine.html. Accessed March 13, 2007.