CASE REPORT

Something old, something new: a successful case of meprobamate withdrawal

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SUMMARY

Meprobamate, a benzodiazepine-like drug, was commonly prescribed for anxiety in the 1960s and 1970s, but fell out of favour, at least in part, due to the risk of dependence, for which there is little published evidence to guide clinical management. We discuss a 70-year-old man with a 45-year history of meprobamate dependency and multiple failed previous withdrawal attempts who was successfully withdrawn from meprobamate using diazepam during a 2-week inpatient stay on a specialist Addictions ward. An appropriate diazepam dose was established using the Clinical Institute Withdrawal Assessment scale for benzodiazepines (CIWA-B). This dose was then slowly reduced over 12 days. Multidisciplinary input, especially psychological therapy tackling his underlying anxiety disorder during his admission, was thought to be particularly helpful.

BACKGROUND

Meprobamate was first synthesised in 1950, and was commonly prescribed for anxiety disorders in the 1950s and 1960s (tradenames Miltown, Equanil and Meprospan).[1] Within a year of production, it became a bestseller, with as many as 1/20 Americans having used it.[2 3] Meprobamate has a similar mechanism of action to barbiturates in its modulatory actions on gamma-aminobutyric acid A ($GABA_A$) receptors.[4] Its use tailed off rapidly when its risk/benefit profile was found to be significantly poorer than benzodiazepines, especially its severe withdrawal syndrome. However, a small, but significant, number of patients continue to take meprobamate despite its diminishing availability and escalating costs. The European Medicines Agency recommended suspension of marketing authorisations for medicines containing meprobamate in the European Union in January 2012.[5] It is currently still available in the UK. However, if European Medicines Agency recommendations are followed, it is likely that it will be withdrawn in the future. If so, patients still taking meprobamate will need to be withdrawn from the drug safely and effectively.

The management of meprobamate withdrawal is also relevant to current clinical practice, as it is a metabolite of carisoprodol—a drug commonly used for the treatment of musculoskeletal conditions, in particular lower back pain (tradenames Soma, Vanadom); see figure 1 for comparison of the molecular formulae and structure of meprobamate and carisoprodol.[6] It is, therefore, not surprising that evidence has been accumulating that carisoprodol, if taken for a significant period (3–52 weeks in case reports), can cause a similar withdrawal syndrome.[7 8]

There is a very limited evidence base to guide the management of patients with meprobamate dependence although there are case reports using benzodiazepines, barbiturates and chlorpromazine.

CASE PRESENTATION

A retired 70-year-old man presented with a 45-year history of meprobamate dependence and, after becoming concerned via online patient communities of the planned discontinuation of its manufacture, was seeking help in managing his withdrawal from this drug.

Prior to admission, he was stable on 6 g meprobamate/day (15×400 mg tablets). He took 13 tablets in the morning and two further tablets at varying times during the day. In the 2 weeks preceding admission to hospital, he had attempted to start a self-managed cross-titration of meprobamate with diazepam that he had obtained from a relative. This was abandoned when he started to experience symptoms of fatigue and lethargy.

He had made two previous attempts at medically assisted withdrawal treatment, 38 and 8 years ago. During the most recent attempt, he had experienced symptoms of anxiety, severe nausea and vomiting. He had also reported mucosal ulcerations

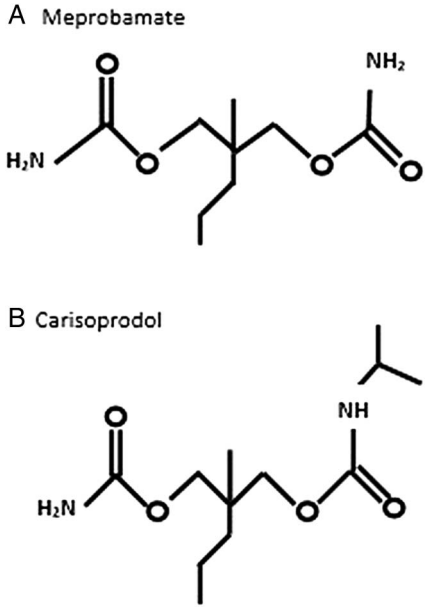

Figure 1 The chemical structures of (A) meprobamate and (B) carisoprodol.

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to his tongue and throat, which he associated with meprobamate withdrawal. On neither occasion had he been able to complete withdrawal.

His medical history included controlled hypertension, benign prostatic hypertrophy and a hiatus hernia. There was a family history of mental illness: his mother suffered from a generalised anxiety disorder, his son had been diagnosed with bipolar affective disorder and his daughter had major depression.

His childhood and development were largely unremarkable apart from mild social anxiety developing in his teens. He did well academically at school and completed tertiary education. He went on to perform well in his chosen career. At the age of 25 years, he developed increasing anxiety especially during presentations at work, but also socially, and sought help from his general practitioner. He had never been dependent on alcohol or illicit substances.

At the point of admission, the only notable feature of the mental state examination was of mild disinhibition. He was not overtly anxious and was euthymic.

A management plan was agreed with the patient that he would immediately stop the drug and it would be substituted with diazepam, the amount given titrated against emerging withdrawal symptoms assessed using the Clinical Institute Withdrawal Assessment scale for benzodiazepines (CIWA-B).[1] His initial CIWA-B score was 17/80.

For the first 72 h, his diazepam requirements were 40 mg/day in four divided doses. CIWA-B assessments were performed three times daily during this time, during which his scores varied from 13 to 17. A linear dose reduction was prescribed over the next 12 days. CIWA withdrawal scales were performed twice daily throughout and he scored 0 for the final 7 days of his diazepam reduction regime (figure 2).

In addition to pharmacological treatment, he had several sessions with a consultant psychologist using cognitive–behavioural therapy and relapse prevention models. He had the opportunity to discuss his historical anxiety in public places, particularly speaking in public (an important aspect of his professional life). It was agreed that he would have graded exposure to social encounters that may have previously triggered his symptoms. This started with visits to a cafe and making an order with the waitress, progressing to teaching of medical students shortly prior to discharge. He accomplished these tasks without suffering any symptoms of anxiety.

He was discharged following a 14-day admission. At the point of discharge, there was no anxiety and no craving, and he was highly motivated to remain abstinent.

DISCUSSION

Meprobamate dependence is well recognised. A double-blind study observed that 44/47 patients who were prescribed meprobamate experienced a withdrawal syndrome including insomnia, tremors, vomiting, anxiety, muscle twitching, anorexia and ataxia.[9] Three patients developed grand-mal seizures in the same study. In another study, death has also been attributed to abrupt withdrawal of meprobamate.[10]

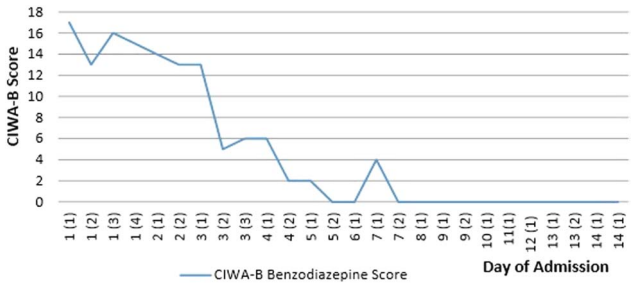

Figure 2 Clinical Institute Withdrawal Assessment scale for benzodiazepines (CIWA-B) withdrawal scores during admission.

While meprobamate is rarely prescribed today, carisoprodol is still widely prescribed and has an associated withdrawal syndrome (principally headache, back pain, anxiety and insomnia) ascribed to its metabolism to meprobamate.[7] Marketing authorisation for carisoprodol was suspended in the European Union in 2008, after a review concluded that it was associated with an increased risk of abuse, addiction, intoxication and psychomotor impairment.[11] It is possible that addiction specialists may see an increase in patients presenting with meprobamate withdrawal secondary to carisoprodol use, which remains widely prescribed in the USA and is available online.

In our patient, consistent with other published reports, withdrawal symptoms of anorexia, palpitations, poor sleep, anxiety and fear were reported, which had largely resolved within 72 h of admission. There was no evidence of seizure activity or fever.

There is a paucity of literature informing treatment for meprobamate withdrawal. In 2005, Shehab *et al*[12] described the successful management of a woman presenting with seizure activity of unknown aetiology, who was subsequently discovered to have chronic meprobamate dependence. She was treated with phenytoin, carbamazepine and clonazepam. This approach differs from the historical literature, where meprobamate withdrawal was managed through slow reduction (sometimes with additional chlorpromazine).[13] In a recent case report by Demir *et al*,[14] a patient was withdrawn from phenprobamate (which is metabolised to meprobamate) with diazepam, plus, for an unspecified time, both paroxetine and quetiapine. We have demonstrated in this case report that diazepam can be used safely and effectively as a monotherapy. Unless there is severe comorbid mood disorder or psychosis, we would suggest diazepam alone should be sufficient and, besides, paroxetine and quetiapine both have potentially serious side effect profiles, and paroxetine has its own significant withdrawal syndrome.

This is the first contemporary report of the clinical management of meprobamate dependence. The successful use of diazepam is more congruent with current clinical practice, and is timely in the context of the likely discontinuation of meprobamate manufacture and continued prescribing of carisoprodol.

Learning points

- Patients with chronic and severe meprobamate dependence can be successfully withdrawn using diazepam.
- Meprobamate manufacture may soon be discontinued in Europe and clinicians may see an increase in patients requiring assistance in withdrawing from the drug.
- Carisoprodol, a muscle relaxant drug, is metabolised to meprobamate and exhibits a chronic dependence syndrome similar to that in meprobamate.
- We propose that the complexities of such withdrawals, especially after decades of dependence, would be safest and most effectively carried out in a specialist inpatient setting.

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REFERENCES

1 Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. *J Clin Psychopharmacol* 1989;9:412–16.
2 Ramchandani D, López-Muñoz F, Alamo C. Meprobamate-tranquilizer or anxiolytic? A historical perspective. *Psychiatr Q* 2006;77:43–53.
3 Horwitz AV. Book review: happy pills in America: from Miltown to Prozac; the age of anxiety: a history of America's turbulent affair with tranquilizers; before Prozac: the troubled history of mood disorders in psychiatry. *N Engl J Med* 2009;360:841–4.
4 Rho JM, Donevan SD, Rogawski MA. Barbiturate-like actions of the propanediol dicarbamates felbamate and meprobamate. *J Pharmacol Exp Ther* 1997;280:1383–91.
5 European Medicines Agency. *Assessment Report for meprobamate-containing medicinal products for oral use*. Procedure number EMEA/H/A-107/1316. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/meprobamate_107/WC500128266.pdf
6 http://www.drugs.com/carisoprodol.html
7 Reeves RR, Parker JD. Somatic dysfunction during carisoprodol cessation: evidence for a carisoprodol withdrawal syndrome. *J Am Osteopath Assoc* 2003;103:75.
8 Reeves RR, Burke RS. Carisoprodol: abuse potential and withdrawal syndrome. *Curr Drug Abuse Rev* 2010;3(1):33–8.
9 Haizlup TM, Ewing JA. Meprobamate habituation. *N Engl J Med* 1958;258:1181–6.
10 Swanson L, Okada T. Death after withdrawal of meprobamate. *JAMA* 1963;184:780–1.
11 MHRA. Carisoprodol and meprobamate: risks outweigh benefits. *Drug Saf Update* 2008;1:5.
12 Shehab A, Khanbhai A, Gupta AK, *et al*. Meprobamate withdrawal after forty years of drug treatment. *J Appl Res* 2005;5:193–5.
13 Little JC. A case of primary addiction to meprobamate. *BMJ* 1963;2:794.
14 Demir B, Demir Y, Aksoy I, *et al*. Phenprobamate dependence: a case report. *Addict Behav* 2015;45:232–3.