

# Agomelatine reduces craving in benzodiazepine addicts: a follow-up examination of three patients

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**ABSTRACT** The treatment of benzodiazepine withdrawal is difficult, and the search continues for substances that can reduce craving and the risk of relapse. Here, we report three cases of benzodiazepine addicts with histories of unsuccessful withdrawal attempts who experienced marked reductions in craving and improved relapse prognoses under add-on administration of agomelatine. These cases demonstrate a possible area of use for the antidepressant agomelatine in the treatment of benzodiazepine withdrawal and addiction. The extent to which this effect is due to the anti-craving effects of agomelatine, or its profile of receptor activation, should be further investigated in larger clinical and experimental studies.

*Keywords:* agomelatine, benzodiazepine withdrawal therapy, craving, MT<sub>1</sub>/MT<sub>2</sub> receptors  
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## INTRODUCTION

Agomelatine is a melatonergic receptor agonist and a 5-HT<sub>2C</sub> antagonist. It has antidepressant effects, and positive effects on sleep architecture in patients suffering from a major depressive disorder (MDD). The efficacy of agomelatine (25 mg/day) in treating MDD was recently shown in several placebo-controlled trials.<sup>(1)</sup> Other recent findings suggest that agomelatine regulates circadian rhythms via binding at endogenous melatonin receptors and antagonism of 5-HT<sub>2C</sub> receptors.<sup>(2-5)</sup> There is some evidence from animal trials that concurrent use of agomelatine might reduce the consumption of benzodiazepines.<sup>(6)</sup> There are also hints that agomelatine could be clinically effective in the discontinuation of benzodiazepine use in patients.<sup>(7)</sup> Furthermore, recently published studies have demonstrated the significantly superior anxiolytic effects of 25–50 mg of agomelatine when compared to placebo trials.<sup>(8,9)</sup> Several substances with vastly different modes of action, including pregabalin, mirtazapine and naltrexone, are currently being investigated regarding their efficacies in treating patients with addictions. Substances active at gamma-aminobutyric acid receptors and those with anxiolytic effects have received a special focus.<sup>(10,11)</sup> At present, nothing is known about the use of agomelatine for the treatment of benzodiazepine addiction. Types of benzodiazepine withdrawal must be classified separately – abrupt withdrawal or progressive withdrawal (over ten weeks). Available data indicate that the activation of the noradrenergic cells in the locus coeruleus plays an important role in the symptoms of withdrawal.<sup>(12,13)</sup> Accordingly, the main symptoms of benzodiazepine withdrawal are defined by noradrenergic overactivation, including anxiety, tachycardia, insomnia and nausea. The results of a Cochrane analysis in one study revealed carbamazepine to be the most efficacious among drugs given as add-on medications for withdrawal symptoms.<sup>(14)</sup>

## CASE REPORTS

We treated three patients who had been addicted to benzodiazepines for at least two years. Our patients suffered from benzodiazepine abuse for three, five and two years, as documented in their patient histories. They fulfilled the criteria for benzodiazepine dependency.

### Case 1

A 57-year-old man, with a daily intake of up to 3 mg lorazepam, was admitted to the hospital. He had a history of three-year benzodiazepine dependency and four unsuccessful detoxification treatments. He had aborted the detoxification treatments after a period of about one week because of massive cravings. He had no concomitant psychiatric illness, but had arterial hypertension that was treated with 5 mg nebivolol and 10 mg ramipril. His initial withdrawal symptoms consisted of perspiration, agitation, bilateral hand tremor, craving (Fig. 1) and anxiety.

### Case 2

A 44-year-old woman, with a daily intake of up to 4 mg lorazepam mainly in the evening over a five-year period, had aborted five attempted hospital treatments and relapsed because of symptoms of massive craving within, at the very most, a week after discharge from the hospital. There was no concomitant psychiatric illness or somatic comorbidities. Her initial withdrawal symptoms were raised blood pressure (up to 190 mmHg), tachycardia, craving (Fig. 1), nausea and agitation.

### Case 3

A 37-year-old woman, with a two-year history of benzodiazepine dependency that started after taking diazepam for sleep disturbance, had a daily intake of up to 20 mg diazepam. The

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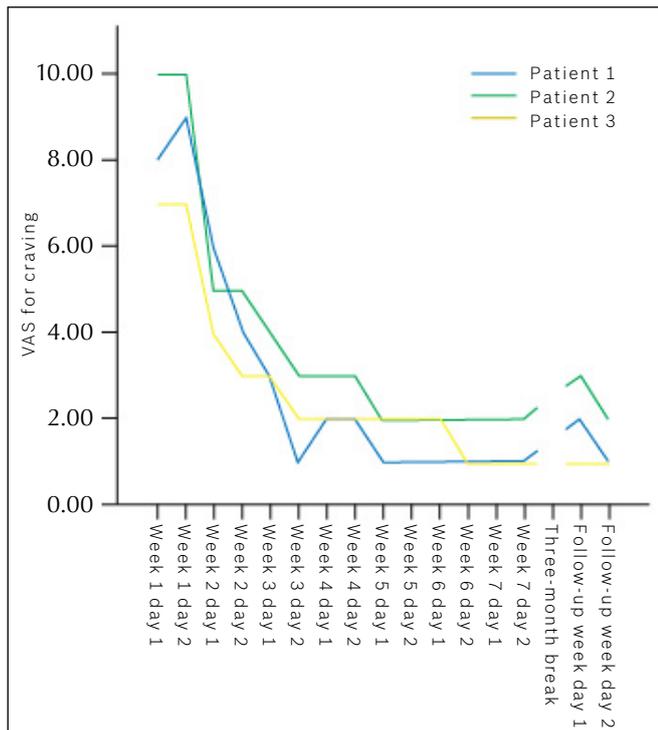


Fig. 1 Graph shows the reduction of craving under agomelatine therapy.

patient had successfully completed three former hospital treatments (three, five and six weeks, respectively), but relapsed after no more than six weeks. Although the patient had migraine, there was no concomitant psychiatric illness or other somatic comorbidities. The patient's initial withdrawal symptoms were craving (Fig. 1), raised blood pressure (up to 210 mm/Hg), tachycardia, bilateral hand tremor, anxiety and sleep disturbances.

In all three patients, agomelatine was administered at a dose of 25 mg. This was an off-label use, an approach we decided to take because all patients had shown symptoms of sleep disturbance and anxiety during previous detoxification treatments. All the patients were monitored over a period of seven weeks and examined once more at a three-month follow-up. During this time, standardised visual analogue scales (VAS) for craving were recorded twice weekly. Drug screens for benzodiazepines and other substances were also performed weekly over the entire observation period. Benzodiazepine withdrawal was minimised in all patients with the administration of lorazepam, which was tapered off by the end of the third week (dosage 1-1-1, 0.5-0.5-0.5, 0.25-0-0-0-0.25 in all patients). Apart from agomelatine, no additional concurrent psychiatric medication was administered. All three patients went through benzodiazepine withdrawal without relapse, and cravings were clearly reduced in all cases with agomelatine administration (scores up to 1/10 on the VAS; Fig. 1). The withdrawal symptoms were described as considerably less intense under therapy with agomelatine. Symptoms such as perspiration, agitation, anxiety and sleep disturbances appeared to be less common. In addition to markedly reduced cravings, all three patients reported their initial withdrawal symptoms to be considerably milder compared to previous unsuccessful attempts

at cessation. At the follow-up examination after three months, none of the patients reported a relapse, and all drug screens were negative. After three months, the patients had not relapsed, and their scores on the craving scale remained low (Fig. 1).

## DISCUSSION

The use of agomelatine as a concurrent medication for the treatment of benzodiazepine addiction should be clinically and experimentally examined in larger studies. In our case study, which is limited by the small number of patients and the short time period of follow-up, we found an anticraving effect of the medication. Whether this effect is mediated through the endogenous  $MT_1$  and  $MT_2$  melatonin receptors or a blockade of  $5-HT_{2C}$  receptors (as is the case for substances like mirtazapine) remains to be investigated.<sup>(11)</sup> Controlled experimental studies, especially prospective studies with more patients, are warranted. In our study, agomelatine seems to be an effective prophylactic against relapse in patients with a history of unsuccessful attempts at cessation of benzodiazepine use, as agomelatine markedly reduced craving in our patient group. Based on this observation, it is necessary to clarify if the anxiolytic effect of agomelatine plays the same proposed role for other substance classes.

Our study was limited in several ways. Besides the short-term follow-up and the small number of patients, we did not compare the effects of agomelatine with other potential treatments for benzodiazepine withdrawal. We also did not examine the discontinuation of agomelatine after treatment and the potential symptoms of agomelatine discontinuation.<sup>(9)</sup> Our results were focused on craving scales and not objective classical withdrawal symptoms (for example, those measured by specific withdrawal scales like the Discontinuation Emergent Signs and Symptoms Scale or the Physician Withdrawal Checklist). However, there is an interesting message within this case series. A limited number of patients had the benefit of therapy with agomelatine. First, as the anxiolytic and sedative effects of agomelatine may play a role in reducing craving and preventing relapse during benzodiazepine withdrawal, clinical studies with larger groups of patients should be undertaken. It should be clarified whether agomelatine is effective as an add-on medication in the treatment of benzodiazepine withdrawal, and if the anticraving effects demonstrated here are maintained over a longer period of time. Finally, it is necessary to clarify the mechanisms of action of agomelatine in the treatment of benzodiazepine withdrawal.

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