*Psychiatria Danubina, 2013; Vol. 25, No. 4, pp 416-418* *Case report*


# TREATMENT OF SEVERE SLEEP DISORDER RELATED TO ALCOHOL-DEPENDENCE WITH HIGH-DOSE AGOMELATINE – A CASE REPORT

**Martin Grosshans[1], Jochen Mutschler[2] & Falk Kiefer[1]**

[1] *Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Mannheim, University of Heidelberg/Medical Faculty Mannheim, Germany*

[2] *Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Zürich, Switzerland*

received: 7.7.2013; revised: 25.9.2013; accepted: 18.10.2013

* * * * *

## INTRODUCTION

Among abstinent alcohol-dependent (AD) patients, sleep disorders are a wide-spread and persistent problem entailing the risk of relapsing into drinking (Brower 2003). The polysomnographic characteristics of AD patients include prolonged sleep-latency and decreased sleep-efficiency (Brower et al. 2001). Furthermore, abstinent alcohol-dependent patients show abnormal evening melatonin-profiles (Kuhlwein et al. 2003).

However, although a variety of pharmacological substances (hypnotics, sedative antidepressants, anticonvulsants, antipsychotics) are available, the treatment of alcohol-related sleep disorders is often complicated by various adverse side-effects, i.e. dependence, daytime-sedation, weight gain, and sexual dysfunction. The latter is a particularly unpopular and frequent side effect of many antidepressants, markedly reducing life quality and leading to poor compliance (Papakostas 2008).

Agomelatine, a structural analog of melatonin, is an agonist for the MT1 and MT2 receptors and a 5-$HT_{2C}$ antagonist, representing a new class of antidepressants. It has been approved for the treatment of adults with major depression (de Bodinat et al. 2010). The recommended dose-range of agomelatine for this indication is 25-50 mg/day. However, early phase-I trials indicated the drug to be well tolerated (in daily doses from 5 to 1200 mg), with 800 mg being defined as the maximal well-tolerated dose based on one subject who experienced postural dizziness with 1200 mg. Even in high doses, agomelatine was not associated with pronounced adverse effects: the most common ones were mild sedation and headache (Kasper & Hamon 2009, Olie & Kasper 2007). This was encouraging, in view of the tolerability problems associated with other antidepressants (Papakostas 2008). As to sexual function, agomelatine, other than for instance paroxetine, effected no impairment in sexually active healthy volunteers (Montejo et al. 2010).

However, the documentation of post-marketing experience with agomelatine includes reports on increases in liver-enzyme activity as an adverse effect under therapy with the drug. This led the European Medicines Agency to recommend routine liver-function tests as a precautionary measure prior to the onset and after 6 weeks, 12 weeks, and 12 months of treatment with agomelatine (EMA 2012). It should be noted that agomelatine is contraindicated in patients with impaired hepatic function, for example due to cirrhosis or active liver disease.

## CASE REPORT

"Mr. G.",a 67-year old male patient, has received ambulatory treatment in our outpatient clinic since 2007. Critical alcohol consumption set in at the age of 21. From the age of about 45 he has been addicted to alcohol. Over the years in our outpatient care, Mr. G. had to undergo one fully and one partially inpatient detoxification, each in the wake of a relapse. For more than half a year now, the patient has been consistently abstinent, regularly attending our outpatient clinic (every two weeks). In addition, he is participating in a supervised self-help group for alcoholics meeting in our department once a week. The patient is married and sexually active, watching his physical fitness and body weight.

Over the last eight years, Mr. G. has developed severe chronic sleep disorders in association with his alcohol dependence, with difficulties in both falling and remaining asleep (suffering from prolonged periods of wakefulness and frequent early-morning awakening). For many years, his insomnia was treated by the family doctor. Among the drugs from various classes of psychotropic agents (tricyclic antidepressants, sedative antipsychotic agents) administered in the course of time, only two compounds turned out to be effective in inducing sleep to the patient's satisfaction: mirtazapine and zolpidem. During 6 months of treatment, mirtazapine normalized the sleeping pattern, but the patient refused to continue taking it due to inacceptable hyperphagia-associated weight gain (over 5 kg in 8 weeks) and sexual dysfunction with impaired erectility and delayed orgasms. The patient responded well to

zolpidem, but after 8 months of intermittent prescriptions the family doctor refrained from further prescribing the drug on account of its habit-forming potential, requesting our department to take over the management of the patient's insomnia.

After taking over, we talked with the patient on the possibility of an off-label therapy of his sleep disorders with agomelatine (symptoms of depression were not present, Ham-D21: 9 points, BDI: 8 points). We informed him of the potential liver toxicity of agomelatine, and hence of the necessity to regularly control his liver function under treatment. It was pointed out to the patient that the drug would be prescribed only in small units, and that in case of a relapse into alcohol consumption the treatment would be stopped at once. Following detailed clarification, the patient consented to undergo a therapy trial with agomelatine under the conditions just elaborated on.

Prior to the onset of therapy the patient's sleeping problems were specified and quantified by means of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989). The PSQI is a questionnaire for self-rating sleep quality and sleep disturbances. Nineteen individual items generate 7 "component" scores: subjective sleep-quality, sleep latency, sleep duration, habitual sleep-efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The sum of the 7 scores yields the global score.

Liver-enzyme activity was controlled by laboratory tests for determining plasma transaminases. The test results were normal before the treatment. The agomelatine therapy started with 25 mg/day. The sleeping pattern showed no improvement. After 3 weeks the dosage was doubled. With 50 mg/day, the patient had no problems to fall asleep, but could not sleep through, waking up after 2-3 hours. Four weeks later we increased the dose to 75 mg/day, thereby exceeding the recommended maximal daily dosage. With this amount of agomelatine, the patient could not only fall asleep quickly, but also maintain sleep, to his satisfaction, for about five and a half hours each night. He reported his daytime tiredness had abated considerably; he was now capable of reading with concentration and of better pursuing other hobbies, for instance sport. He felt agomelatine to be less effective than zolpidem had been, but in the dosage of 75 mg it ensured him a sufficiently restful and satisfactory sleep.

After twelve weeks of agomelatine treatment (the last 5 weeks with 75 mg/day), the PSQI global score dropped from 14 to 7. The patient reported on having lost some body weight due to increased sports activity. Importantly, he did not notice any decline of libido or sexual functioning (erectility, capacity for orgasm) during therapy. The control of his liver enzymes after three, six, and twelve weeks revealed no hepatotoxic effect of agomelatine despite the high daily dose of 75 mg. The patient expressed the wish to continue treatment in our department in the manner described.

## DISCUSSION

Based on its mechanism of action at melatonin receptors, agomelatine appears to be a promising alternative off-label medication for the treatment of sleep disturbances in AD patients. Moreover, due to its positive side-effect profile (in particular, no weight gain and no impairment of sexual functions), it holds out the prospective of becoming a valuable asset in the pharmacological repertoire of sleep medicine. However, considering the possibly adverse effects of agomelatine on liver functions (the risk of liver damage is increased in AD patients, anyhow) the use of this substance in AD patients may be controversial. The reported case demonstrates severe AD-associated sleep disturbances to be a heavy burden for the patients affected. The available pharmacological options for a long-term treatment are either contraindicated due to their abuse potential (hypnotics) or badly tolerated due to their adverse side-effects on bodyweight and sexual functions (antipsychotics, antidepressants, anticonvulsants).

Thus, agomelatine appears to be a treatment option for a subgroup of AD patients. This assumption has been corroborated by the successful treatment of our patient. However, we recommend the off-label use of agomelatine for the treatment of AD-associated sleep disturbances only if the following criteria are met: (I) The patient is well-known and considered to be reliable, is regularly attending an outpatient department or private practice, and is informed in detail of the drug's potential liver toxicity and the necessity of instantly discontinuing the treatment in case of a relapse into alcohol consumption. (II) Before starting treatment any impairment of liver function must be diagnosed, while under treatment the liver function has to be checked regularly by monitoring the liver transaminases in the plasma. (III) Agomelatine is only prescribed in small units.

Based on premarketing phase-I-data documenting high doses of agomelatine (up to 800 mg/day) to be tolerated well, we decided to increase the daily dosage in the present case to 75 mg/day, notwithstanding the maximum dosage of 50 mg/day recommended by the manufacturer. The increase beyond 50 mg/day may be indicated in patients whose deranged sleeping patterns fail to respond to agomelatine in lower doses.

## CONCLUSIONS

The present retrospective data suggest that agomelatine might become a future treatment option for insomnia in alcohol-dependent patients. The increase beyond 50 mg/day may be indicated in patients whose deranged sleeping patterns fail to respond to agomelatine in lower doses.

***Acknowledgements:*** None.

***Conflict of interest :*** None to declare.

## References

1. *Brower KJ: Insomnia, alcoholism and relapse. Sleep Med Rev 2003; 7:523-539.*
2. *Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF: Insomnia, self-medication, and relapse to alcoholism. Am J Psychiatry 2001; 158:399-404.*
3. *Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practive and research. Psychiatry Res 1989; 28:193-213.*
4. *De Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ: Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov 2010; 9:628-642.*
5. *European Medicines Agency: Valdoxan: Product Characteristics. EMA, 2012.*
6. *Kasper S, Hamon M: Beyond the monoaminergic hypothesis: agomelatine, a new antidepressant with an innovative mechanism of action. World J Biol Psychiatry 2009; 10:117-126.*
7. *Kuhlwein E, Hauger RL, Irwin MR: Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. Biol Psychiatry 2003; 54:1437-1443.*
8. *Montejo AL, Prieto N, Terleira A: Better sexual acceptability of agomelatine (25 and 50 mg) compared with paroxetine (20 mg) in healthy male volunteers. An 8-week, placebo-controlled study using the PESEXDQ-SALSEX scale. J Psychopharmacol 2010; 24:111-120.*
9. *Olie JP, Kasper S: Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. Int J Neuropsychopharmacol 2007; 10:661-673.*
10. *Papakostas GI: Tolerability of modern antidepressants. J Clin Psychiatry 2008; 69:Suppl E1:8-13.*

*Correspondence:*

*Martin Grosshans, MD*
*Department of Addictive Behavior and Addiction Medicine*
*Central Institute of Mental Health Mannheim, University of Heidelberg*
*68159 Mannheim, Germany*
*E-mail: martin.grosshans@zi-mannheim.de*