TREATMENT

Dose–Response Effect of Baclofen in Reducing Daily Alcohol Intake in Alcohol Dependence: Secondary Analysis of a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract — Aims: To explore the effect of baclofen in a dose of 20 mg three times per day, compared with the already studied dose of 10 mg three times per day, in the treatment of alcohol dependence. Methods: We present a secondary analysis of a 12-week double-blind, placebo-controlled, randomized clinical trial with two doses of baclofen, specifically 10 mg t.i.d. and 20 mg t.i.d. Out of 94 subjects consecutively screened, 42 were randomized into the study. Fourteen of the 42 patients were randomly allocated to placebo, 14 to the group treated with baclofen 10 mg t.i.d. (B10 mg) and 14 to the group treated with baclofen 20 mg t.i.d. (B20 mg). Results: Compared with patients allocated to placebo, patients allocated to the B10 mg group had a 53% reduction in the number of drinks per day (P < 0.0001) and patients allocated to the B20 mg group had a 68% reduction in the number of drinks per day (P < 0.0001), with respect to the number of drinks per day during the 28 days before randomization. The effect of baclofen 20 mg t.i.d. was greater than that of baclofen 10 mg t.i.d. (P = 0.0214, Wald test) showing a dose-effect relationship. Both doses of baclofen were well tolerated. Conclusion: This is provisional evidence of a dose–response effect for baclofen in the treatment of alcohol dependence.

INTRODUCTION

Alcohol dependence afflicts nearly 10% of the population, both in the USA and in Europe, and causes serious morbidity and mortality (U.S. Department of Health and Human Services, 2000). Treatment of alcohol dependence consists of psychological, social and pharmaceutical interventions (Addolorato et al., 2005; Swift and Leggio, 2009). Only a few medications are approved in the USA and in Europe for this indication and their efficacy is less than optimal. In the last two decades, several further medications, including baclofen, have been tested and/or are under investigation as new pharmacotherapies for alcohol dependence.

Baclofen is a γ-aminobutyric acid (GABA) B-receptor agonist and at present is approved to treat spasticity. Preclinical experiments have demonstrated that administration of baclofen in alcohol-preferring rats affects several alcohol-seeking behaviours: acquisition and maintenance of alcohol-drinking behaviour, alcohol intake after a period of alcohol abstinence (relapse-like drinking), oral self-administration of alcohol and also modifies motivational cues for alcohol (reviewed by Colombo et al., 2004; Maccioni and Colombo, 2009).

Human studies with alcohol-dependent patients have shown the safety and the efficacy of baclofen as a pharmacotherapy for alcohol dependence. The ability of baclofen (10 mg t.i.d.) to reduce alcohol craving and intake and promote alcohol abstinence in alcohol-dependent individuals was observed in open-label studies (Addolorato et al., 2000; Flannery et al., 2004) as well as in other clinical studies where baclofen (10 mg t.i.d.) was administered open-label (Leggio et al., 2008a,b).

A 4-week double-blind, placebo-controlled, randomized clinical trial with 39 alcohol-dependent subjects assigned to receive baclofen (10 mg t.i.d.) or placebo showed a significantly higher percentage of subjects achieving and maintaining total alcohol abstinence in the baclofen group, compared with the placebo group (Addolorato et al., 2002). Similarly, there was a significant reduction in alcohol craving scores in the baclofen group compared with placebo. These findings were confirmed in a larger 12-week randomized clinical trial with baclofen (10 mg t.i.d.) vs. placebo, which enrolled a more severe population, alcohol-dependent patients with liver cirrhosis (Addolorato et al., 2007). Consistent with the previous observation, this study showed a significant effect of baclofen, compared with placebo, in reducing alcohol consumption and craving and in promoting total alcohol abstinence. In contrast, another 12-week randomized clinical trial with baclofen reported no significant differences in heavy drinking and craving between baclofen and placebo (Garbutt et al., 2010). It has been highlighted how the latter trial enrolled a less severe population of alcoholics than previous studies with baclofen (Flannery and Garbutt, 2008; Leggio et al., 2010). The difference in severity has been suggested as a possible explanation of the differences in outcomes between the last study and the previous ones (Flannery and Garbutt, 2008; Garbutt, 2009; Garbutt et al., 2010; Leggio et al., 2010).

All studies reported above tested baclofen at the dose of 10 mg t.i.d. However, anecdotal reports have hypothesized the ability of high doses of baclofen (up to 140 and 270 mg/day) to reduce alcohol craving and consumption (Ameisen, 2005; Bucknam, 2007). Moreover, baclofen at the dose of 20 mg t.i.d. has been already tested in other addictions, i.e. cocaine dependence (Kahn et al., 2009; Shoptaw et al., 2003).

Thus, we planned a 12-week clinical trial to test two doses of baclofen, specifically 10 mg t.i.d. and 20 mg t.i.d. Initially, this study was planned as a multi-site, double-blind, placebo-controlled, randomized trial, named International Baclofen Interventional Study (IBIS) and involving sites in Europe and
in Australia. However, out of five centers that initially agreed to participate, only three joined the study, specifically our site at Catholic University of Rome (Italy) and sites located in Austria and Australia. However, in the Austrian and Australian sites, there was a large loss at follow-up of subjects and unavailability of all outcome measures at all time points. These factors led to the decision of not analysing the Australian and Austrian datasets because of intractable methodological limitations (Carpenter and Kenward, 2007; Piantadosi, 2005). Thus, statistical analysis was conducted only on the Italian data set. The main outcomes of this primary analysis were heavy drinking days (HDD), abstinent days (AD) and craving score. The secondary outcomes were time to first lapse and time to first relapse. Analysis of these pre-defined outcome measures did not show significant difference between groups, possibly related to the lack of statistical power (i.e. no differences were found in HDD or in AD for baclofen 10 mg t.i.d. v. placebo, or for baclofen 20 mg t.i.d. v. placebo). Nor were there significant differences in HDD or in AD between the baclofen groups. No significant modification of HDD in relation to time nor in relation to interaction treatment time was found. A more detailed description of the planned outcomes is reported elsewhere (Addolorato and Leggio, 2010). Here, we report the results of a secondary analysis, which was also conducted only on the Italian sample of 42 patients. Specifically, while the planned outcome was based on the reduction of heavy drinking, this post hoc analysis used the number of drinks per day across the entire study period as the outcome variable.

PATIENTS AND METHODS

Patients

Ninety-four alcohol-dependent patients referred to the Alcohol Treatment Unit of our Institute of Internal Medicine (‘Agostino Gemelli’ Hospital, Catholic University of Rome, Italy) were assessed for eligibility between January 2006 and December 2007. Table 1 shows inclusion and exclusion criteria. The study protocol was approved by the Ethics Committee of the ‘Agostino Gemelli’ Hospital of the Catholic University of Rome (Italy), where the study was conducted. All participants provided written informed consent. The trial was registered in the European Clinical Trials Database (EudraCT Number: 2006-000713-37).

Methods

We performed a 12-week, three-arm parallel, double-blind, randomized clinical trial with two doses of baclofen (10 mg t.i.d. or 20 mg t.i.d.) or placebo. Participants were screened (Week 00 visit) and, if eligible they were randomized (Week 01 visit). Randomized participants were seen as outpatients in our hospital every week during the first month (Week 02, 03 and 04 visits), and then every other week during the rest of the trial (Week 06, 08, 10 and 12 visits). Four weeks after the last medication dose, a follow-up visit (Week 16) was performed.

After a brief pre-screening, participants were scheduled for a more comprehensive screening visit. At the screening visit, diagnosis of alcohol dependence was performed according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-TR criteria (American Psychiatric Association, 2000). Other major Axis I psychiatric disorders including other substance dependence (except nicotine dependence) were exclusion criteria (diagnosed using the Mini International Neuropsychiatric Interview (Sheehan et al., 1999). Relevant medical history was recorded and physical examination was performed. The number of standard drinks consumed by each patient in the 28-day period before the screening visit was recorded using the Timeline Follow Back

### Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range 18–60 years (inclusive)</td>
<td>Clinically significant medical disease that might interfere with the evaluation of the study medication or that might represent a safety concern</td>
</tr>
<tr>
<td>Diagnosis of alcohol dependence according to DSM IV-TR</td>
<td>Clinical significant psychiatric illness including any psychotic disorders, bipolar disorder, severe depression, suicidal ideation, substance use disorders other than alcohol and nicotine dependence or cannabis abuse</td>
</tr>
<tr>
<td>Alcohol intake of at least 2 HDDa per week on average and an average overall consumption of 21 drinks per week or more for men and 14 drinks per week or more for women in the 4 weeks before enrolment</td>
<td>Abstinence from alcohol for &gt;10 days prior to randomization day</td>
</tr>
<tr>
<td>Ability to understand and sign written informed consent</td>
<td>Concurrent use of psychotropic medication, including antidepressant, mood stabilizers, antipsychotics, anxiolytics or hypnotics</td>
</tr>
<tr>
<td>Ability to refrain from drinking for at least 3 days prior to randomization day</td>
<td>Concurrent use of anticonvulsants, insulin or oral hypoglycaemics</td>
</tr>
<tr>
<td>Desire to achieve abstinence or to greatly reduce alcohol consumption</td>
<td>AST and/or ALT levels &gt;3 times of UNL, or bilirubin and/or creatinine greater than UNL</td>
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<tr>
<td>Evidence of a stable residence</td>
<td>Urine drug screen positive for substance of abuse other than cannabis</td>
</tr>
<tr>
<td>Presence of a referred family able to assist with drug administration and monitoring</td>
<td>Pregnant women and women of childbearing potential who did not practise a medical acceptable form of birth control</td>
</tr>
<tr>
<td>Frosted glass (adherence monitoring)</td>
<td>Breastfeeding women</td>
</tr>
</tbody>
</table>

*Concurrent use of anticonvulsants, insulin or oral hypoglycaemics |

aHDD is an overall intake of five or more drinks per day for men and of four or more drinks per day for women.
(TLFB) method (Sobell et al., 1988). The TLFB was administered by trained investigators.

Blood and urine laboratory tests included complete blood count, mean cell volume, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyl-transferase, chemistry and urinalysis for microscopic examination and drug screen. For women, a urine pregnancy test UbHCG (urine beta human chorionic gonadotrophin) was performed at screening and during treatment Weeks 4, 8 and 12.

Individuals meeting inclusion/exclusion criteria were scheduled for the initial treatment visit (Week 1 visit) within 1 week. Subjects were asked to abstain from drinking alcohol at least for 3 days prior to the initial treatment visit. Subjects who had significant withdrawal symptoms [diagnosed according to the Clinical Institute Withdrawal Assessment for Alcohol-revised scale (Sullivan et al., 1989)] were treated with diazepam, but patients who required >10 days of treatment with benzodiazepines were excluded. Thus, patients started the study after at least 3 and no >10 days of abstinence from alcohol.

At the baseline visit and at all subsequent visits, a blood alcohol concentration <5 mg/dl was required. Otherwise, the visit was rescheduled. At the baseline visit, patients were randomized to one of the three treatment conditions (placebo or baclofen 10 mg t.i.d. or baclofen 20 mg t.i.d.). Eligible patients were allocated to one of the treatment groups according to a computer-generated randomization list produced by the pharmacist who prepared the drug and the placebo. Participants and investigators were unaware of treatment assignment. To maintain masking, an independent colleague, who did not have any further role in the study, concealed the randomization codes in a safe box. For the duration of the study (including also the 4 weeks of follow-up), this colleague could be contacted at any time to break the blind in case of emergency. Placebo and baclofen were prepared by a local compounding pharmacy, which had already prepared medication for our other double-blind studies. Placebo, baclofen 10 mg and baclofen 20 mg tablets were identical in size, colour, shape and taste. In the baclofen 10 mg t.i.d. group, the drug was administered at a dose of 5 mg t.i.d. for the first 3 days, 10 mg t.i.d. on Days 4–81 and finally 5 mg t.i.d. for the last 3 days; patients of the baclofen 20 mg t.i.d. group took a dose of 5 mg t.i.d. for the first 3 days, a dose of 10 mg t.i.d. on Days 4–7, a dose of 20 mg t.i.d. on Days 8–77, a dose of 10 mg t.i.d. on Days 78–81 and finally, a dose of 5 mg t.i.d. for the last 3 days.

During the study period, in addition to the study medication, all subjects received brief psychological therapy designed for the treatment of alcohol-dependent patients (BRENDA; Starosta et al., 2006) from trained staff. During the study, BRENDA was employed at each visit for nine sessions of ~30 min. Participants were also encouraged to attend Alcoholics Anonymous.

At each visit, drinking was recorded using TLFB; concomitant medications, adverse events and general clinical and psychiatric status were recorded. Patients’ interview and pill counts were used to assess compliance with the study medication.

**Statistical analysis**

Continuous variables are reported as medians, interquartile range (IQR) and minimum and maximum values because of skewed distributions. The IQR was calculated as the difference between the 75th and 25th percentiles. Categorical variables are reported as the number or percentage of subjects with the characteristic of interest. The efficacy of baclofen 20 mg and baclofen 10 mg vs. placebo was evaluated using a random-effect negative binomial regression model accounting for over dispersion (Hilbe, 2007; Horton et al., 2007). The outcome variable was the number of drinks per day evaluated by TLFB, and the predictors were treatment (1 = placebo; 2 = baclofen 10 mg; 3 = baclofen 20 mg), time of the study (0 = pre-randomization period; 1 = after-randomization period) and a time × treatment interaction, which was the main predictor of interest (time × treatment = 2 for the effect of baclofen 10 mg vs. placebo during the study and time × treatment = 3 for the effect of baclofen 20 mg vs. placebo during the study). Effect sizes are given as incidence rate ratios and 95% confidence intervals. The data of the patients who dropped out from the study were not discarded but modelled using maximum likelihood principles (Schafer and Graham, 2002). Statistical analysis was performed using STATA version 11.1 (StatCorp, College Station, TX, USA).

**RESULTS**

Out of 94 subjects consecutively screened, 42 satisfied inclusion criteria and were randomized into the study. These 42 patients had a median (IQR) age of 44 (13) years (range 23–60 years). Out of the 42 subjects randomized, 76% were males. Table 2 shows study participants’ baseline demographic characteristics. Fourteen of the 42 patients were randomly allocated to placebo, 14 to baclofen 10 mg t.i.d. (B10 mg) and 14 to baclofen 20 mg t.i.d. (B20 mg). Six patients in the placebo group dropped out from the study at Days 28, 35, 35, 49, 56 and 84; two patients in the B10 mg group dropped out at Days 49 and 70; and two patients in the B20 mg dropped out at Days 56 and 84. All the ten dropped-out patients were lost to follow-up, i.e. they missed three or more consecutive visits.

Figure 1A–C show the profile plots of drink consumption in the three study groups. Table 3 reports the incidence rate ratios obtained from negative binomial regression to test the efficacy of baclofen vs. placebo. Compared with the patients allocated to placebo, those allocated to B10 mg obtained a 53% reduction in the number of drinks per day ($P < 0.0001$) and patients allocated into the B20 mg group obtained a 68% reduction in the number of drinks per day ($P < 0.0001$), with respect to the number of drinks per day during the

<table>
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<tr>
<th>Table 2. Baseline characteristics of study participants</th>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Education (&lt;13 years)</td>
</tr>
<tr>
<td>Employed</td>
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</tbody>
</table>

Data represent number of patients (and percentage) or median (IQR).
28 days before randomization. The effect of baclofen 20 mg t.i.d. was greater than that of baclofen 10 mg t.i.d. ($P = 0.0214$, Wald test), showing a dose–effect relationship. Table 4 reports the average number of drinks per day before and after the randomization as estimated by the negative binomial regression.

**DISCUSSION**

This analysis found that oral administration of baclofen, both at the dose of 10 mg t.i.d. and at that of 20 mg t.i.d., was significantly more effective than placebo in reducing daily alcohol intake, although previous analysis of HDD and AD in this rather small sample had not shown an effect of baclofen. In addition, the effect of baclofen 20 mg t.i.d. in reducing daily alcohol intake was significantly greater than that of baclofen 10 mg t.i.d., showing a dose–effect relationship. This study thus represents a preliminary demonstration of a baclofen dose–effect relationship in the treatment of alcoholic patients.

This study confirms previous studies (Addolorato et al., 2000, 2002, 2007; Flannery et al., 2004; Leggio et al., 2008a, b) showing an effect of baclofen on alcohol consumption in alcohol-dependent individuals. The effects of baclofen on alcohol consumption may depend on its ability to interfere with neuronal substrates mediating the reinforcing properties of ethanol throughout GABA$_B$ receptor stimulation. GABA$_B$ receptors located in the ventral tegmental area have been reported to control the activity of mesolimbic dopamine neurones, which are involved in the regulation of reinforcing

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**Table 3. Effect of baclofen on alcohol consumption**

<table>
<thead>
<tr>
<th>Incidence rate ratio (95% confidence intervals)</th>
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<tbody>
<tr>
<td>Baclofen 10 mg t.i.d.$^a$</td>
</tr>
<tr>
<td>Baclofen 20 mg t.i.d.$^a$</td>
</tr>
<tr>
<td>Start of trial (Day ≥ 28)</td>
</tr>
<tr>
<td>Baclofen 10 mg t.i.d. after start of the trial$^a$</td>
</tr>
<tr>
<td>Baclofen 20 mg t.i.d. after start of the trial$^a$</td>
</tr>
</tbody>
</table>

The outcome variable is the number of drinks per day, and placebo is the reference group for all comparisons. The effects of baclofen 10 mg t.i.d. and baclofen 20 mg t.i.d. after randomization are those of interest. Effects sizes were obtained from a negative binomial regression model accounting for over dispersion (see Statistical analysis for details).$^*$ vs. placebo $^a P < 0.001.$

**Table 4. Average number of drinks per day before and after randomization**

<table>
<thead>
<tr>
<th>Average number of drinks (95% confidence intervals)</th>
<th>Pre-randomization</th>
<th>Post-randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11.98 (9.05–14.91)</td>
<td>0.55 (0.40–0.70)</td>
</tr>
<tr>
<td>Baclofen 10 mg t.i.d.</td>
<td>13.91 (10.37–17.46)</td>
<td>0.30 (0.21–0.39)</td>
</tr>
<tr>
<td>Baclofen 20 mg t.i.d.</td>
<td>9.65 (7.30–12.01)</td>
<td>0.14 (0.09–0.19)</td>
</tr>
</tbody>
</table>

No serious or severe side effects leading to drug cessation were observed, and no patients discontinued treatment because of side effects. Side effects experienced are shown in Table 5. One patient randomized to 20 mg t.i.d. experienced drowsiness, weakness, fatigue and muscle pain, which disappeared after halving the dose. Side effects in other patients resolved spontaneously within 2 weeks of treatment. No patient reported euphoria or related pleasant effects caused by the drug. At drug discontinuation, no new side effects were observed.

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**Fig. 1. (A) Number of drinks per day in the placebo group. The outcome variable is the natural logarithm of the number of drinks consumed in a day and has 1 added to it to permit the calculation of a logarithm corresponding to 0. The vertical bar marks the start of the randomized study (Day 28). (B) Number of drinks per day in the baclofen 10 mg t.i.d. group. Legend as in (A). (C) Number of drinks per day in the baclofen 20 mg t.i.d. group. Legend as in (A).**
properties of addictive drugs, including alcohol (Colombo et al., 2004; Di Chiara, 1995; Koob et al., 1998; Weiss and Porrino, 2002).

The dose–response effect observed is consistent with previous preclinical and clinical observations. Pre-treatment with baclofen resulted in a dose-dependent suppression of extinction responding for alcohol in alcohol-prefering rats (Colombo et al., 2003), where extinction responding for alcohol was defined as the maximal number of lever responses reached by each rat in the absence of alcohol reinforcement. A dose-dependent decrease of ethanol self-administration has also been observed in alcohol-dependent rats treated with increasing doses of baclofen (Walker and Koob, 2007).

In our previous studies, we selected the minimum therapeutic dose of 10 mg t.i.d. to avoid possible side effects (Addolorato et al., 2000, 2002). However, baclofen is used at higher doses to control spasticity (i.e. 80 mg/day). Moreover, recent studies with other addicted populations have used higher doses, such as 20 mg t.i.d. in cocaine-dependent individuals (Kahn et al., 2009; Shoptaw et al., 2003) and 20 mg q.i.d. in nicotine-dependent individuals (Franklin et al., 2009). Furthermore, anecdotal reports describe how high doses of baclofen (up to 140 and 270 mg/day) resulted in a marked decrease in alcohol intake and alcohol craving in patients not responding to lower doses (Ameisen, 2005; Bucknam, 2007).

Our previous trial showed a significant effect of baclofen 10mg t.i.d. in alcohol-dependent patients with liver cirrhosis. We can speculate that, for patients with liver disease [who were not recruited in the study of Garbutt et al. (2010) that had a negative result for 10 mg t.i.d.], a lower dose may be sufficient to show an effect of baclofen because some 15% of baclofen metabolism depends on the liver, while a higher dose is required when liver disease is not present.

The present study provides additional evidence of the safety of baclofen at the dose of 20 mg t.i.d. when administered to alcoholics. Notably, a recent human laboratory study showed the safety of baclofen (0, 40 and 80 mg) when co-administered with alcohol (Evans and Bisaga, 2009). Moreover, our study showed no evidence of potential addictive properties of baclofen when administered to an addictive population, such as alcohol-dependent individuals, as shown by the absence of a withdrawal syndrome and the lack of euphoric effects. This observation is consistent with the lack of potential addictive properties of baclofen at doses of 20mg t.i.d. and 20 mg q.i.d., when administered to individuals with cocaine dependence (Shoptaw et al., 2003; Kahn et al., 2009) and nicotine dependence (Franklin et al., 2009), respectively.

Finally, in the present study, there was a lower, although not statistically significant, number of drop outs in the two baclofen groups than in the placebo group. The safety of baclofen and its efficacy with respect to placebo can explain the lower number of drop outs in baclofen-treated patients, an observation consistent with previous pharmacological trials in psychiatric patients (Krupitsky et al., 1993) and with our previous baclofen alcohol studies (Addolorato et al., 2002, 2007).

Our study has limitations. First, the results reported here represent a secondary analysis conducted in a small sample. The main IBIS study was markedly underpowered and, as mentioned before, this led to the lack of the planned sample size able to show a possible medication effect on the planned outcomes (HDD, AD and craving score); specifically, results did not show significant differences in the primary outcomes measures. Nevertheless, this secondary analysis shows that there is an effect of baclofen on some drinking outcomes, with a dose–response effect, thus providing much needed data necessary for potential future large clinical trials. Secondly, the application of a ‘day-by-day’ model prevented us from analysing other outcomes such as HDD, AD, time to first lapse, time to first relapse, craving, anxiety and markers of alcohol abuse (i.e. AST, ALT) because these data were not available on a daily basis.

In conclusion, the present study provides further evidence that baclofen is an effective and safe pharmacotherapy for AD and provides the first evidence of a possible dose–response effect. Future large studies testing different doses of baclofen and targeting alcoholics with different degrees of severity of dependence should be performed to further investigate the role of baclofen in AD.

<table>
<thead>
<tr>
<th>Headache</th>
<th>Baclofen 10 mg t.i.d.</th>
<th>Baclofen 20 mg t.i.d.</th>
<th>Placebo t.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Tiredness</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>–</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Drowsiness, weakness, fatigue, muscle pain</td>
<td>–</td>
<td>1*</td>
<td>–</td>
</tr>
</tbody>
</table>

*These side effects disappeared after applying a half-dose reduction.


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Conflict of interest statement. The authors declare that they have no conflict of interest.

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