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Effect of modafinil on impulsivity and relapse in alcohol dependent patients: A randomized, placebo-controlled trial

Leen Joos, Anna E. Goudriaan, Lianne Schmaal, Erik Fransen, Wim van den Brink, Bernard G.C. Sabbe, Geert Dom

Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Belgium
Amsterdam Institute for Addiction Research, Academic Medical Centre, University of Amsterdam, Department of Psychiatry, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
Arkin, Mental Health Care, P.O. Box 75848, 1070 AV Amsterdam, The Netherlands
StatUA, Center for Statistics, University of Antwerp, Prinsestraat 13, B-2000 Antwerpen, Belgium
Psychiatric Centre Alexian Brothers, Provinciesteenweg 408, B-2530 Boechout, Belgium

Received 24 May 2012; received in revised form 30 August 2012; accepted 5 October 2012

KEYWORDS
Alcohol dependence; Modafinil; Relapse; Response inhibition; State impulsivity; Impulse control

Abstract
Poor impulse control plays an important role in the development, course and relapse of substance use disorders. Therefore, improving impulse control may represent a promising approach in the treatment of alcohol dependence. This study aimed to test the effect of modafinil on impulse control and alcohol use in alcohol dependent patients (ADP) in a randomized, double-blind, placebo-controlled trial. Eighty-three abstinent ADP were randomized to 10 weeks modafinil (300 mg/d) or placebo. Alcohol use was quantified using the timeline follow-back method and was assessed until 6 months after treatment discontinuation. Impulsivity was assessed using self-report questionnaires (Barratt Impulsiveness Scale; State Impulsivity questionnaire) and neurocognitive tasks (Stop Signal Task; Delay Discounting Task) administered before, during and after treatment. Modafinil significantly improved self-report measures of state impulsivity, but had no effect on percentage of abstinent days or percentage of heavy drinking days, nor on the behavioral measures of impulsivity. However, subgroup analysis revealed that modafinil prolonged the time to relapse (p = .022) and tended to increase the percentage of abstinent days (p = .066) in ADP with poor response inhibition at baseline, whereas modafinil increased the percentage of heavy drinking days (p = .003) and reduced the percentage of abstinent days (p = .002) in patients with better baseline response inhibition. Overall results do not favor the use of modafinil in order to reduce relapse or relapse severity in ADP, and
1. Introduction

There is growing evidence that impulsive behavior plays an important role in the development, course and relapse of alcohol dependence (for review see De Wit, 2009; Verdejo-Garcia et al., 2008). Alcohol dependent patients (ADP) are characterized by higher levels of self-reported impulsivity, a faster discounting of delayed rewards and diminished response inhibition compared to healthy controls (Bjork et al., 2004; Dom et al., 2006; Von Diemen et al., 2008). Furthermore, these characteristics are important predictors of treatment outcome and relapse into alcohol use (Bowden-Jones et al., 2005; MacKillop and Kahler, 2009; Muller et al., 2008; Rubio et al., 2008). Nevertheless, to date, the reduction of craving has been the major focus of medication development for alcohol dependence, e.g. acamprosate and naltrexone. However, these treatment approaches have been moderately successful at best and relapse after treatment is the rule rather than the exception. Therefore, reducing impulsive behavior is a needed new treatment approach in alcohol dependence.

In that respect, modafinil is a promising compound. Modafinil (2-[(diphenylmethyl) sulfinyl] acetamide) is a wakefulness-promoting drug that is currently approved for the treatment of narcolepsy, but is also used for its cognitive enhancement (for review see Joos et al., 2010; Minzenberg and Carter, 2008). Modafinil improved symptoms of hyperactivity and impulsivity in children with ADHD (Biederman et al., 2005; Kahbazi et al., 2009; Swanson et al., 2006) and improved response inhibition in healthy individuals (Turner et al., 2003), adults with ADHD (Turner et al., 2004a), methamphetamine dependent individuals (Dean et al., 2011). A remarkable finding is that differences in baseline impulsivity levels may moderate the effect of modafinil on response inhibition. For example, Zack and Poulos (2009) reported an improvement in response inhibition (Stop Signal Task (SST)) in pathological gamblers who display high levels of self-reported baseline impulsivity (Eysenck Impulsivity Questionnaire), whereas no effect or even worsening of response inhibition occurred in their low impulsive counterparts. A similar effect was found in rats with high and low baseline levels of response inhibition (SST) (Eagle et al., 2007). Finally, modafinil demonstrated promising treatment effects in cocaine and methamphetamine dependent patients with significant more negative urine samples (Dackis et al., 2005; Shearer et al., 2009), longer periods of abstinence (Dackis et al., 2005; Anderson et al., 2009), a reduction of substance use (Hart et al., 2008; Shearer et al., 2009) and less craving (Hart et al., 2008; Anderson et al., 2009).

In summary, these results indicate that modafinil has the potential to reduce impulsive behavior and to reduce relapse rates in substance dependent patients although these effects might only occur in specific subgroups. Modafinil may therefore be a promising candidate for alcohol dependence treatment. However, so far no clinical trials have been conducted in ADP. Therefore we conducted a randomized double-blind placebo-controlled trial with modafinil in treatment seeking ADP. We hypothesized that a 10-wk treatment with modafinil in ADP would (1) reduce relapse and relapse severity during treatment and after treatment discontinuation, and (2) reduce impulsivity. Furthermore, it is hypothesized that treatment effects are mediated by reductions in impulsive behavior, i.e. participants whose impulsivity levels improved during treatment are expected to have a better outcome than patients without improvements in impulsivity. Finally, subgroups with high impulsivity at baseline are expected to benefit more from modafinil for alcohol dependence treatment than subgroups with low baseline impulsivity.

2. Experimental procedures

2.1. Participants

Study participants were treatment seeking ADP, meeting the following inclusion criteria: current DSM-IV diagnosis of alcohol dependence, age between 18 and 60 years and inclusion in the cognitive behavioral treatment program after detoxification. Exclusion criteria were: current DSM-IV dependence on substances other than alcohol (except for nicotine and cannabis); current use of psychoactive medications (except sleep medication with a maximum half-life of 8 h); current use of anti-alcohol medication (acamprosate, naltrexone, disulfiram); history of psychotic disorder; current mood or anxiety disorder; IQ below 75; amnesic disorders, neurological disorders or lifetime history of head injury with loss of consciousness (> 5 min); severe somatic disorders; color blindness; being on an active low-calorie diet (< 1000 cal/d); hypersensitivity for modafinil and/or lactose; and for women, being pregnant or breastfeeding. In addition, women were informed that combined intake of modafinil and estradiol may reduce the efficacy of estradiol, and were instructed to use supplementary contraception during the trial.

2.2. Design

2.2.1. Recruitment and screening

Each consecutive patient, admitted to one of 2 addiction treatment centers in Belgium, was invited to participate. Both treatment centers offer a similar behaviorally orientated treatment program within a residential and/or a day care setting. Enrollment occurred from October 2009 through July 2011; the study was completed in March 2012. Patients were screened for eligibility by examination of medical and psychiatric history, laboratory tests (blood chemistry, liver function tests, urinalysis) and an electrocardiogram.

All subjects gave written informed consent. The trial was approved by the medical ethics committee of the Antwerp University Hospital (Belgium), and was registered at the Dutch Trial Register (NTR1736; <www.trialregister.nl>).

2.2.2. Randomization

A stratified, permuted block randomization was used with gender as the only stratum and blocks contained random sizes of 2, 4 or
6 allocations for males, and 2 or 4 allocations for females. Personnel, not associated with the wards involved in the study, generated the allocation sequence by using ‘Random Allocation Software’ (Saghaei, 2004) and assigned the patients to one of the 2 treatment groups. Only these persons and the involved pharmacists were aware of the medication assignment. Group allocation was blind for both the participants and the researchers or care providers, who enrolled, treated, or assessed the patients.

2.2.3. Medication
Modafinil 100 mg immediate release tablets and matching placebos were manufactured by TioFarma, Oud-Beijerland (The Netherlands). The study medication was administered as a single morning dose and was slowly titrated: day 1–4: 100 mg/d; day 5–8: 200 mg/d; day 9–70; 300 mg/d. Blood pressure, pulse and temperature were monitored daily at the start, and weekly when the parameters and the medication dosage were stable. In case of adverse effects the treatment dose was reduced by 100 mg at a time. After 10 weeks, the study medication was discontinued without taper.

2.3. Assessments
2.3.1. Clinical characteristics
Sociodemographic characteristics were collected with an interview. Intelligence was measured with the Dutch version of the National Adult Reading Test (NLV; Schmand et al., 1992). The presence of alcohol, substance use and other psychiatric disorders was assessed with the M.I.N.I.-plus International Neuropsychiatric Interview (Van Vliet and De Beurs, 2007).

2.3.2. Primary outcome variables
2.3.2.1. Alcohol use. Alcohol use in the 30 days before admission until 6 months after treatment was quantified with the Time Line Follow Back method (TLFB; Sobell and Sobell, 1992; Sobell et al., 1996). The calendar was filled in by the patients, while receiving assistance from the researcher who asked questions regarding personal events and habits to improve the participants recall strategy. The amount of alcohol consumed was converted into standard alcohol drinks containing approximately 10 g alcohol per drink (Lemmens, 1994). Given previous positive treatment effects of modafinil on number of abstinent days in substance dependent patients (Anderson et al., 2009; Dackis et al., 2005; Shearer et al., 2008), percentage abstinent days from alcohol was used as a first primary outcome measure. Second, percentage heavy drinking days was used as primary outcome variable, incorporating both frequency and intensity of alcohol use. A heavy drinking day was defined by 5 or more standard drinks for men, and 4 or more for women (Anton et al., 2006).

2.3.2.2. Impulsivity. The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was used to measure trait impulsivity; the State Impulsivity questionnaire (STIMP; Wingrove and Bond, 1997) was used to measure state impulsivity or impulsive mood at the moment the questionnaire was filled in. As the BIS-11 measures impulsive personality traits over an extended time period, the BIS-11 was only administered at baseline because no changes over time were expected. Hence this indicator of impulsivity could not be used as an outcome measure.

Behavioral impulsivity, i.e. response inhibition and impulsive decision making, was measured with a Stop Signal Task (SST; Eagle et al., 2008) and a Delay Discounting Task (DDT; Wittmann et al., 2007) respectively (see the Supplementary material for more details). The dependent variable of the SST is the Stop Signal Reaction Time (SSRT), with higher SSRT’s reflecting poorer response inhibition. For the DDT, the k-value was used as dependent variable, with higher k-values corresponding to a steeper discounting of future rewards and thus to higher levels of impulsiveness.

2.3.3. Secondary outcome variables
Key secondary outcome measures were mean alcohol use, time to relapse to heavy drinking and time to relapse, regardless of the quantity. Results of these and other secondary measures are presented in the Supplementary material, as well as information and results regarding adverse events, abuse potential and compliance.

2.4. Procedure
Assessments took place at 5 time points (see Figure 1). In case patients terminated their inpatient or day care treatment before completing the medication trial, patients were able to continue their medication intake at home, provided that testing during medication was completed. During inpatient stay medication was administered under supervision, in all other cases medication compliance was measured by means of self-report and pill count of returned containers. Patients who participated from home were screened on alcohol and drug use with breath and urine analysis before each testing. Inpatients were regularly screened on drug and alcohol use during their standard treatment. Finally, patients received remuneration for their participation: 40 euro after completing T2, 25 euro after FU1 and 35 euro after FU2.

2.5. Statistical analyses
Our sample size was based on a previous reported trial with modafinil for cocaine dependence (Dackis et al., 2005). Initially, we attempted to collect 100 participants, which would allow us to...
detect a standardized effect size of minimal $d=.70$ for our main analyses with 80% power (calculated with G*Power (Buchner et al., 1997) and based on independent 2-tailed sample $t$-test analysis with alpha $=.010$ after Bonferroni correction for multiple comparisons (see below)). However, due to time and practical considerations, the trial ended with 83 randomized patients, resulting in a reduced power of 70% to find group differences in the primary outcome measures in the total sample.

Primarily, data from patients with a positive urine drug screen (MOD: $n=3$; PLAC: $n=1$) and patients who reported the regular use (> 3 months) of anti-alcohol medication during follow-up (MOD: $n=2$; PLAC: $n=1$) were excluded from analysis for the time points involved. Student $t$-tests and chi-square tests were used to compare baseline functioning and abstinence rates between groups. To correct for a positively skewed distribution of the outcome variable of the DDT ($k$-value) the natural logarithmic transformation was used: $LN(k+.001)$.

Mixed-effects repeated-measures analyses with random intercepts, were conducted to analyze the treatment effect of modafinil compared to placebo. When entering one of the alcohol use variables as dependent variable, $T0$ was entered as covariate in order to obtain a linear model. Survival analyses based on the log-rank (Kaplan-Meier) statistic were used to examine between group differences in time to drop-out and relapse to (heavy) drinking.

Subgroups were created according to the median of the total BIS-11 scores, total STIMP scores, SSRT’s and $LN(k)$-values. These subgroup variables were entered into the mixed model, resulting in a 3-way interaction model. Given the randomized control design, the main effect of treatment is constrained to equal zero. Therefore, it is allowed to fit a 3-way interaction model omitting a main effect of treatment and the 2-way interaction Treatment X Baseline Impulsivity (Fitzmaurice et al., 2004; pp. 126–127) in order not to jeopardize the power of the study. Subsequently, the meaning of each significant 3-way interaction was explored by analyzing a 2-way Time X Treatment interaction in each subgroup.

To correct for multiple comparisons, a Bonferroni correction was applied to the main analyses and to the subgroup analyses on the primary outcome variables, setting the significance level at $p<.01$ (.05/5) and $p<.0025$ (.05/20), respectively. For analyses on secondary outcomes (see the Supplementary material) the significance level was set at $p<.05$. Analyses were performed on SPSS 16.0.

3. Results

3.1. Participants flow

Of the 706 patients who were consecutively admitted to the treatment centers, 593 patients of those did not meet inclusion criteria and 30 eligible patients declined to participate. The remaining 83 eligible patients were eventually randomized to the modafinil ($n=41$) or the placebo ($n=42$) group. Their mean age was 41.8 years ($SD=9.4$ years) and most of them were males (85.5%) and inpatients (87.9%). The participants flow is presented in Figure 2. Overall, drop-out occurred equally within the modafinil ($n=17$; 41.5%) and the placebo group ($n=15$; 33.4%) ($\chi^2 = 29$, $p = .591$), and no significant difference was observed between groups with regard to time to drop-out (log-rank (Kaplan-Meier): $\chi^2 = .54$, $p = .544$).

3.2. Baseline characteristics

There were no significant differences between the modafinil-group (MOD) and the placebo-group (PLAC) with regard to all baseline characteristics (see Table 1 for means and standard deviations).

![Figure 2](image-url) Study participant flow diagram.

AD: Anti-Depressants; T1: testing during treatment; T2: testing after treatment; FU1: follow-up interview after 3 months counted from the end of treatment; FU2: follow-up interview after 6 months counted from the end of treatment.
3.3. Efficacy of modafinil

3.3.1. Abstinence rates

At the end of the treatment period (T2), 54.2% patients were completely abstinent in the modafinil group, against 42.8% in the placebo-group ($\chi^2 = .66, p = .416$). At FU2, the abstinence rates were 29.2% in the modafinil group and 14.8% in the placebo group ($\chi^2 = 1.55, p = .214$).

3.3.2. Primary outcome measures

3.3.2.1. Alcohol use. Percentage abstinent days and percentage heavy drinking days changed over time, with a decrease of abstinent days ($b = -1.03, t(101.2) = -3.312, p = .756$) or percentage heavy drinking days ($b = -1.46, t(101.0) = 1.597, p = .113$) (see Figs. S1 and S2 in the Supplementary material).

3.3.2.2. Impulsivity. A significant (Bonferroni: $p < .01$) time by treatment interaction was found for the total STIMP scores ($b = -6.2, t(124.1) = -3.413, p = .001$), indicating that patients reported less state impulsivity during and after treatment with modafinil compared to placebo (see Figure 3). In addition, the SSRT improved over time ($b = -10.45, t(127.1) = -2.749, p = .007$), but no significant time by treatment interaction was found ($b = 3.15$).

### Table 1  Baseline characteristics of the modafinil and the placebo group with $p$-values.

<table>
<thead>
<tr>
<th></th>
<th>Modafinil mean (SD or %)</th>
<th>Placebo mean (SD or %)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>41</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42.0 (9.8)</td>
<td>41.6 (9.2)</td>
<td>.838</td>
</tr>
<tr>
<td>% Males</td>
<td>85.4%</td>
<td>85.7%</td>
<td>.964</td>
</tr>
<tr>
<td>% Married/co-habiting</td>
<td>24.4%</td>
<td>26.2%</td>
<td>.936</td>
</tr>
<tr>
<td>Intelligence (NART)</td>
<td>102.8 (9.4)</td>
<td>103.2 (8.0)</td>
<td>.821</td>
</tr>
<tr>
<td>Days abstinent before testing</td>
<td>21.1 (19.4)</td>
<td>34.5 (87.6)</td>
<td>.343</td>
</tr>
<tr>
<td><strong>Alcohol and substance use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset of heavy drinking</td>
<td>27.6 (10.9)</td>
<td>30.1 (11.0)</td>
<td>.282</td>
</tr>
<tr>
<td>Years of heavy drinking</td>
<td>11.8 (7.8)</td>
<td>9.6 (7.8)</td>
<td>.198</td>
</tr>
<tr>
<td>% Non-smokers</td>
<td>14.6%</td>
<td>11.9%</td>
<td>.714</td>
</tr>
<tr>
<td>Substances used:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only alcohol</td>
<td>62.5%</td>
<td>73.8%</td>
<td>.477</td>
</tr>
<tr>
<td>Alcohol+cannabis</td>
<td>20.0%</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Alcohol+other drugs/poly</td>
<td>17.5%</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Percentage heavy drinking days</td>
<td>57.2% (37.2)</td>
<td>47.7% (35.2)</td>
<td>.247</td>
</tr>
<tr>
<td>Percentage days abstinent</td>
<td>42.0% (38.3)</td>
<td>45.4% (35.8)</td>
<td>.676</td>
</tr>
<tr>
<td>Mean use</td>
<td>13.5 (14.4)</td>
<td>10.3 (12.3)</td>
<td>.280</td>
</tr>
<tr>
<td>Withdrawal (SAWS total score)</td>
<td>6.5 (5.7)</td>
<td>5.7 (4.6)</td>
<td>.525</td>
</tr>
</tbody>
</table>

**BIS-11:** Barratt Impulsiveness Scale; **DDT:** Delay Discounting Task; **NART:** National Adult Reading Test; **PANAS:** Positive and Negative Affect Scale; **SAWS:** Short Alcohol Withdrawal Scale; **SSRT:** Stop Signal Reaction Time; **STIMP:** State Impulsivity Scale.

*a*30 days before admission.
Figure 4  Time × treatment (modafinil vs. placebo) interaction based on MMRM for percentage abstinent days in subgroups of alcohol dependent patients with poor baseline response inhibition (n = 30, sample at T2; SSRT > 233.22) versus alcohol dependent patients with good baseline response inhibition (n = 22, sample at T2; SSRT < 233.22), adjusted for baseline percentage abstinent days and with error bars representing standard errors. T2: testing after treatment; FU1: follow-up interview after 3 months counted from the end of treatment; FU2: follow-up interview after 6 months counted from the end of treatment; MMRM: Mixed-model Repeated Measures analysis; SSRT: Stop Signal Reaction Time.

t(130.5) = .560, p = .576). Regarding DDT performance, neither a significant main effect of time (t(119.5) = −1.025, p = .307) nor a significant time by treatment interaction effect was found (t = .08, t(121.8) = .732, p = .466). Because there were no significant effects of modafinil on primary alcohol outcomes, performing mediation analyses was regarded redundant.

3.3.3. Subgroup analyses
Significant (Bonferroni: p < .002) 3-way interactions were only found for subgroups based on the split half of the SSRT (group median SSRT = 233.22). A significant 3-way interaction came forward for the primary outcome measures percentage abstinent days (b = 13.3, t(72.6) = 4.980, p < .001) and percentage heavy drinking days (b = 8.8, t(76.5) = −3.567, p = .001) as dependent variables, indicating that the effect of modafinil depends on the SSRT; ADP with good response inhibition at baseline experienced a faster decline in percentage abstinent days (b = −14.04, t(42.7) = −3.268, p = .002; see Figure 4) and a steeper increase in percentage heavy drinking days (b = 13.24, t(42.9) = 3.117, p = .003; see Figure S3) with modafinil compared to placebo. In contrast participants with a poor response inhibition at baseline tended to experience a slower decline in percentage abstinent days with modafinil compared to placebo (b = 8.24, t(58.7) = 1.871, p = .066) (see Figure 4), whereas no significant time by treatment interaction occurred in this subgroup for percentage heavy drinking days (b = −1.57, t(58.5) = −.448, p = .656; see Figure S3).

4. Discussion
This is the first randomized double-blind placebo-controlled trial with modafinil in a sample of alcohol dependent patients. Overall, the use of modafinil was well tolerated and no abuse potential of modafinil was reported. No significant main effects of modafinil were found for the primary alcohol outcome variables compared to placebo.

Despite these mainly negative results, the overall abstinence rates were higher in the modafinil compared to the placebo condition (T2: 54% vs. 42%; FU2: 29% vs. 15%). The reduced statistical power may have prevented these effects from becoming statistically significant. However, subgroup analysis revealed that modafinil seems to be especially beneficial in ADP with poor baseline response inhibition, whereas ADP with a good response inhibition at baseline rather experience detrimental effects of modafinil on their alcohol use. Comparable bidirectional effects of modafinil have already been published in single-dose administration studies (Dean et al., 2011; Eagle et al., 2007; Finke et al., 2010; Heinzerling et al., 2010; Kakehashi et al., 2010; Zack and Poulos, 2009). These findings may all fit the ‘inverted-U-shaped’ function proposed by Cools and D’Esposito (2011). This function supposes that the efficacy of a drug depends on basal dopamine levels. Studies so far indicate that modafinil directly binds to dopamine (DA) and noradrenaline (NA) transporters resulting in an increase of extracellular DA and NA in the neocortex (Minzenberg and Carter, 2008; Volkow et al., 2009). Therefore, ADP with a suboptimal (too little) baseline DA level might benefit from modafinil, whereas the opposite might be true for individuals on top of the inverted U curve. In addition, our results indicated that differences in baseline response inhibition but not delay discounting caused bidirectional effects of modafinil, which is consistent with previous reported results stating that both dimensions of impulsivity have distinct underlying neural correlates (Brooks et al., 2012; Paterson et al., 2011).

Although patients treated with modafinil clearly felt less impulsive, modafinil did not improve impulsive behavior on the SST and DDT, also not in the subgroup of patients with poor baseline response inhibition. These findings are in contrast to previous reported results from Zack and Poulos (2009) and Eagle et al. (2007), and only a minority of the earlier studies reported the absence of an effect of modafinil on response inhibition (Turner et al., 2004b; Vansickle et al., 2008). This may suggest that the dosage of 300 mg/d was insufficient to exert an effect. However, earlier studies have shown that a higher dose (e.g. 400 mg/d) does not necessarily result in a better effect, but rather opposite effects (Randall et al., 2005; Sofuoglu et al., 2008).

Finally, some limitations of this trial must be noted. First, the sample size might have been too small to obtain significant effects of modafinil in this heterogeneous population of impulsive and less impulsive ADP. Previous research was mainly done in cocaine dependence (Dackis et al., 2011).
which is more consistently associated with high impulsivity levels than alcohol dependence (Kirby and Petry, 2004) and larger effect sizes in cocaine dependence may be related to a more homogenous effect of modafinil. In addition, due to the small sample size, this study was only able to detect large effects of modafinil on the various outcome measures, so more subtle positive treatment effects of modafinil could not be revealed. Second, strict exclusion criteria were applied and subsequently the study population had no psychiatric comorbidity and no toxic effects of other substances than alcohol, resulting in relatively low levels of impaired decision making and response inhibition (Benaiges et al., 2010; Dom et al., 2006; Kirby and Petry, 2004). Finally, reliability of treatment compliance may be questioned, as recordings of the number of missed pills solely relied on self-reports and pill count. However, during residential treatment (mean 63.0 days; SD=27.6) the medication was administered under supervision and therefore we assume that treatment adherence was sufficient.

In summary, although modafinil reduced self-reported state impulsivity, our results did not favor the general use of modafinil in order to prevent relapse or reduce relapse severity in ADP. However, promising effects of modafinil emerged in ADP with poor response inhibition at baseline. Further research within this subgroup is therefore highly recommended, whereas one should be cautious with the prescription of modafinil to a non-selected sample of ADP, as modafinil may exert detrimental effects in patients with low baseline impulsivity.

Role of funding source

Funding for this study was provided by the Netherlands Organization for Scientific Research, ZonMW (Grant 31160003). ZonMW had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit this paper for publication.

Contributors

L. Joos, L. Schmaal, Dr. A.E. Goudriaan, Prof. Dr. W. Van den Brink, Prof. Dr. B.G.C. Sabbe and Prof. Dr. G. Dom conceptualized the study and oversaw the data analyses. E. Fransen supported the data analysis that were carried out for this manuscript. L. Joos executed the study and wrote the first draft of the manuscript, with support of the co-authors. All authors contributed to and have approved the final manuscript.

Conflict of interest

Wim van den Brink is a consultant for Merck Serono (acipimox) and Lundbeck (nalmefene) and received speaker fees from Merck Serono, Lundbeck, Eli Lilly, Pfizer, and Schering-Plough. In addition, he received unrestricted grants for investigator initiated studies from Alkermes (naltrexone XR) and Neurosearch (tesofensine). Geert Dom has received speaker fees from Merck, Lundbeck, GlaxoSmithKline, Johnson & Johnson, and Astra Zeneca. All other authors have no conflict of interest to declare.

Acknowledgments

We thank the patients for their commitment and time and thank the participating hospitals: the Psychiatric Centre Brothers Alexians (Boechout, Belgium) and the Psychiatric Hospital Sint-Norbertus (Duffel, Belgium).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2012.10.004.

References


Dom, G., De Wilde, B., Hulstijn, W., van den Brink, W., Sabbe, B., 2006. Decision-making deficits in alcohol-dependent patients...


