Journal of Psychoactive Drugs

ISSN: 0279-1072 (Print) 2159-9777 (Online) Journal homepage: https://www.tandfonline.com/loi/ujpd20

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To cite this article: Maurizio Coppola & Raffaella Mondola (2018) Impulsivity in Alcohol-Dependent Patients with and without ADHD: The Role of Atomoxetine, Journal of Psychoactive Drugs, 50:4, 361-366, DOI: 10.1080/02791072.2018.1471247

To link to this article: https://doi.org/10.1080/02791072.2018.1471247

JOURNAL OF PSYCHOACTIVE DRUGS
2018, VOL. 50, NO. 4, 361–366
https://doi.org/10.1080/02791072.2018.1471247

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Impulsivity in Alcohol-Dependent Patients with and without ADHD: The Role of Atomoxetine

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of hyperactivity, inattention, and impulsivity. As shown in the literature, this disorder is frequently associated with alcohol and drug abuse. Patients affected by ADHD show high levels of impulsivity and sensation seeking. These characteristics can significantly increase the risk of alcohol abuse, which is itself a clinical condition associated with high levels of impulsivity. Clinical studies suggest that atomoxetine is effective and safe in patients affected by both ADHD and alcohol dependence; however, information focused specifically on impulsivity is very limited. In an open-label study, we evaluated the difference in impulsivity level between alcohol-dependent patients with and without a diagnosis of ADHD. Furthermore, we hypothesized that, in patients with ADHD, atomoxetine could reduce the impulsivity trait.

ARTICLE HISTORY
Received 2 July 2017
Accepted 22 January 2018

KEYWORDS
ADHD; alcoholism; atomoxetine; comorbidity; impulsivity

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of hyperactivity, inattention, and impulsivity. As shown in the literature, this disorder is frequently associated with alcohol and drug misuse and abuse (Blum et al. 2014; Harstad and Levy 2014). Although ADHD was once considered a childhood disorder, long-term follow-up studies have demonstrated that symptoms persist in adulthood in 40–60% of cases (Hinshaw et al. 2012; Klein et al. 2012; Barkley et al. 2002; Hechtman 1999). In adults, the diagnosis of ADHD is frequently more complicated than in children because some symptoms can change in terms of intensity, clinical characteristics, and modality of presentation (Volkow and Swanson 2013). Moreover, in adults the diagnosis of ADHD is further complicated by both psychiatric comorbidities and substance abuse (Volkow and Swanson 2013). Generally, symptoms of hyperactivity decrease more than symptoms of inattention, but they are substituted by hyperactivity-like symptoms such as restlessness, anxiety, and irritability (Wender 1998). Furthermore, symptoms of inattention may be manifested as difficulties in carrying out tasks, producing important consequences in various aspects of life, including work, affective relations, and social activities (Faraone, Biederman, and Mick 2006). Adults affected by ADHD show high levels of impulsivity and sensation seeking (Ballon, Brunault, and Cortese 2015; Dalbudak et al. 2015). These characteristics can significantly increase the risk of alcohol abuse, which is itself a clinical condition associated with high levels of impulsivity (Courtney et al. 2012).

The pharmacotherapy approved for the treatment of ADHD includes stimulant and nonstimulant medications (Volkow and Swanson 2013). The only nonstimulant approved for treating adult ADHD is atomoxetine (Volkow and Swanson 2013). This medicine is a blocker of norepinephrine transporters enhancing noradrenergic transmission in the brain and dopaminergic transmission in the frontal cortex (Volkow and Swanson 2013). Atomoxetine increases by threefold extracellular norepinephrine and dopamine concentrations in the prefrontal cortex, and this effect appears to be related to the activity of ADHD symptoms (Garnock-Jones and Keating 2009). Clinical studies suggest that atomoxetine is effective and safe in patients affected by both ADHD and substance abuse (Adler et al. 2009; Wilens et al. 2008); however, clinical evidence focused specifically on impulsivity is limited. In a three-month, double-blind, placebo-controlled study performed in patients affected by both ADHD and alcohol dependence, Wilens and colleagues have shown that atomoxetine induced a clinically significant improvement in ADHD symptoms, but had an inconsistent effect on drinking behavior (Wilens et al. 2008). In a post-hoc exploratory subgroup analysis, Wilens and colleagues have shown that ADHD symptoms' improvement was significantly correlated with the

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reduction in alcohol craving. Furthermore, they showed that relapse to alcohol abuse was significantly correlated with the worsening of most ADHD symptoms in the placebo group, but not in the atomoxetine group (Wilens et al. 2011). In another post-hoc analysis, Adler and colleagues compared the safety of atomoxetine treatment in adult ADHD patients with and without alcohol dependence, showing substantial safety of atomoxetine in both groups. Finally, Benegal and colleagues have evaluated the efficacy of atomoxetine as adjunctive treatment in patients affected by substance use disorders and externalizing symptoms (e.g., ADHD symptoms, conduct disorders, temperamental traits), showing a potential role of atomoxetine in the treatment of early onset alcohol and other drug dependence (Benegal et al. 2016).

These studies evaluated the efficacy of atomoxetine in the treatment of ADHD symptoms in alcoholics and/or in the treatment of drinking behavior, but no study has evaluated the efficacy of atomoxetine in reducing trait impulsivity as a specific dimension. Considering that ADHD and alcohol dependence can be linked to the same neurobiological mechanisms, in particular those involved in the Reward Deficiency Syndrome, it is important to investigate the clinical differences and reciprocal influences in order to better target the pharmacological treatment. The Reward Deficiency Syndrome describes a group of addictive, compulsive and impulsive disorders, including alcoholism, attention deficit disorder, drug abuse and food bingeing, pathological gaming, Internet addiction and sex addiction, having common genetic and neurobiological mechanisms (Blum et al. 2014). In particular, both hypodopaminergic trait/state and the DRD2 A1 allele variant were hypothesized as risk factors for drug and alcohol abuse, impulsive behaviors, and vulnerability to relapses (Blum, Febo, and Badgaiyan 2016).

Due to its pharmacological activity, atomoxetine can be considered a potential alternative for the treatment of impulsivity in both disorders; however, it is necessary to know what characteristics of impulsivity may be treated with this medicine. Impulsivity is a multifaceted and multidimensional construct involving several types of cognitive and behavioral expressions. Impulsivity influences important aspects of alcohol use escalation and desistance in a clinically relevant fashion with respect to developmental risk periods for alcohol use, dependence and alcohol habits, including binge drinking. Impulsivity represents an independent predictor of a mortality risk among individuals seeking help for alcohol-related problems. The treatment of impulsivity should be considered a key point in the treatment of alcoholism in order to reduce morbidity and mortality (Blonigen et al. 2011; Potenza and De Wit 2010). In an open-label study, we evaluated the difference in impulsivity level between alcohol-dependent patients with and without a diagnosis of ADHD. We hypothesized that, in patients with ADHD, atomoxetine could reduce the impulsivity trait.

Methods

Our work was an observational, 12-week, open-label uncontrolled study, carried out from January to June 2016. A total of 92 alcohol-dependent patients were recruited from outpatient facilities in the Addiction Treatment Unit of Alba, Italy. Inclusion criteria were: (1) a diagnosis of alcohol dependence in accordance with the DSM IV criteria as assessed by Mini-International Neuropsychiatric Interview Plus 5.0.0 (MINI) (Sheehan et al. 1998); (2) a diagnosis of ADHD in accordance with the DSM IV criteria as assessed by both MINI (Sheehan et al. 1998) and Diagnostic Interview for ADHD in adults (DIVA 2.0) (Ramos-Quiroga et al. 2016); (3) absence of a diagnosis of other drug dependence, apart from alcohol, in accordance with the DSM IV criteria as assessed by MINI (Sheehan et al. 1998); (4) no current comorbidity with severe medical conditions including alcohol-related brain diseases; (5) at least 18 years of age. Patients were allowed to continue any psychopharmacological treatment started before inclusion (valproic acid, carbolithium, olanzapine, citalopran, and lorazepam). All patients started psychotherapy in association with the pharmacological treatment.

Patients diagnosed as ADHD received treatment with atomoxetine at 80 mg/day (in the first week, all patients assumed 40 mg/day), according to the clinical criterion and within the technical data limits. The treatment started after baseline assessment and the observation was continued for 12 weeks. During all 12 weeks, each patient was clinically evaluated every two weeks, while a psychodiagnostic assessment was performed at baseline (V0), after eight weeks (V1), and after 12 weeks (V2).

Impulsivity was assessed by Barratt Impulsiveness Scale (BIS-11), a questionnaire designed to assess the personality/behavioral construct of impulsiveness in three areas: attentional impulsivity, motor impulsivity, and nonplanning impulsivity (Patton, Stanford, and Barratt 1995). Hazardous and harmful alcohol consumption was assessed by both the Alcohol Use Disorder Identification Test (AUDIT) (normal score up to 7) (Babor, Higgins-Biddle, and Monteiro 2001) and blood Carboxy Deficient Transferrin concentration (CDT). Axis I comorbidities were assessed using the MINI, while the Structured Interview for Diagnostic and

Statistical Manual of Mental Disorders, Fourth Edition, Personality Disorders (SIDP-IV), was used to assess personality disorders (Zimmerman 1994). The presence of binge drinking was evaluated with the following question: "Over the past 2 weeks, how many occasions have you had to consume 5 (male)/4 (female) or more drinks in a row?" Response codes were: (1) none; (2) once; (3) twice; (4) three or more (three or more was considered heavy binge drinking) (Courtney and Polich, 2009). Considering the mechanism of action of atomoxetine, we used the Antidepressant Side-Effects Checklist (ASEC) to evaluate the presence of adverse side-effects (Uher et al. 2009).

During the first visit, a blood sample was taken from all patients to measure the CDT plasma concentration. Each patient was tested with an electrocardiogram before starting the treatment with atomoxetine, while blood pressure was assessed every two weeks after starting the medicine. Data were analyzed using Social Science Statistics (http://www.socscistatistics.com/).

Sociodemographic and clinical characteristics were reported as mean and standard deviation (SD) or percentage (%). Alcohol-dependent patients without ADHD were included in group number 1 (GN1), while those with ADHD were included in group number 2 (GN2). Categorical variables were examined using the chi-square test, while the continuous variables were examined using the t-test for normally distributed data or Mann-Whitney's U test for non-normally distributed data. Correlation between BIS-11 scores and sociodemographic data, AUDIT scores, and CDT plasma concentration was evaluated using the Pearson's correlation coefficient for normally distributed data and Kendall's Tau-b bivariate correlation coefficient for non-normally distributed data. An ANOVA for repeated measurements was performed to evaluate the correlation among BIS-11 total scores at V0, V1, V2, AUDIT total score and CDT value in alcohol-dependent patients with ADHD after treatment with atomoxetine. Normal or non-normal distribution of variables was evaluated using the Shapiro-Wilk's test. A statistical correction was used for the multiple subanalyses presented. A p-value of 0.05 was fixed as level of significance. The study was conducted in accordance with the Declaration of Helsinki and it was approved by the ASLCN2 Local Ethics Committee as part of the study with the following code number: ASLCN2/SerD1. All patients included in the study provided a written informed consent.

Results

Ninety-two alcohol-dependent patients, 70 males and 22 females with a mean age of 47.7 years (SD = 11.2; range 21–71), were included in the study. GN1 included 82 patients, 65 males and 17 females with a mean age of 48.9 years (SD = 10.9; range 21–71), while GN2 included 10 patients, 5 males and 5 females with a mean age of 37.4 years (SD = 7.5; range 25–46). Patients with ADHD were treated with 40 mg per day of atomoxetine for one week, then 80 mg per day for the other 11 weeks. All patients completed the study and no significant side-effects were reported. In the first two weeks, four patients reported mild nausea and four patients reported experiencing goosebumps. Statistical analysis of sociodemographic characteristics (Table 1) showed no difference between groups in terms of educational levels and employment, while we observed significant differences in age (p = 0.0017), sex (p = 0.04), and marital status (p < 0.001). No difference between groups was found in the prevalence of mood and personality disorders (Table 1), while patients with ADHD showed more frequent binge drinking than patients without ADHD (p = 0.02). No difference between groups was found in AUDIT total score and CDT value (Table 1). A significant difference in BIS-11 total score was found between patients with and without ADHD (p < 0.001). Analyzing data for BIS-11 subscales, we found significant differences between groups in motor impulsivity (p = 0.030) and nonplanning impulsivity (p < 0.001), but we found no difference in attentional impulsivity (Table 1).

Table 1. Differences in sociodemographic and clinical characteristics and scales scores between alcohol-dependent patients with and without ADHD.

	GN1*	GN2**	p value
Age (Mean + SD°)	48.9 + 10.9	37.4 + 7.5	**0.0017**
Sex			**0.04**
Males	65	5	
Females	17	5	
Employment (in percentage)			0.2
Employed	67%	50%	
Unemployed	33%	50%	
Education (in years; mean + SD°)	9.9 + 2.7	7.2 + 2.5	0.052
Marital status			**<0.001**
single	18	6	
Life partner	64	4	
Bis-11^			
Total score (Mean + SD°)	80.4 + 9.8	99.3 + 7.1	**<0.001**
Attentional impulsivity (Mean + SD°)	27.1 + 3.4	26.3 + 4.5	0.49
Motor impulsivity (Mean + SD°)	25.7 + 6.1	32.1 + 6.4	**0.030**
Nonplanning impulsivity (Mean + SD°)	4.9 + 1.4	27.4 + 5.3	**<0.001**
AUDIT°° (Mean + SD°)	23.9 + 5.2	22.8 + 3.3	0.49
CDT°°°	2.8 + 2.9	1.6 + 0.8	0.19
Mood disorders	70.7%	70%	0.96
Personality disorders	26.8%	30%	0.83
Binge drinking	30.4%	80%	0.02

*Alcohol-dependent patients without ADHD
** Alcohol-dependent patients with ADHD
^ Barratt Impulsiveness Scale
° Standard deviation
°° Alcohol Use Disorder Identification Test
°°°Carboxy Deficient Transferrin

Table 2. Correlations between impulsivity and hazardous and harmful alcohol consumption.

	GN1*	GN2**
Bis-11^ vs AUDIT°°	0.7	0.77
Attentional impulsivity vs AUDIT	0.07	0.32
Motor impulsivity vs AUDIT	0.27	0.25
Nonplanning impulsivity vs AUDIT	0.61	0.95
Bis-11^ vs CDT°°°	0.42	0.23
Attentional impulsivity vs CDT	0.038	0.59
Motor impulsivity vs CDT	0.94	0.63
Nonplanning impulsivity vs CDT	0.71	0.038

*Alcohol-dependent patients without ADHD
** Alcohol-dependent patients with ADHD
^ Barratt Impulsiveness Scale
°° Alcohol Use Disorder Identification Test
°°°Carboxy Deficient Transferrin

Table 3. Correlation among BIS-11^ total score V0*, V1**, V2***, AUDIT°° total score and CDT°°° value in patients treated with atomoxetine.

V0 vs V1	$P < 0.05$
V0 vs V2	$P < 0.001$
V1 vs V2	$P = 0.05$
V1 vs AUDIT	$P < 0.001$
V2 vs AUDIT	$P < 0.001$
V1 vs CDT	$P < 0.001$
V2 vs CDT	$P < 0.001$

* Baseline
** After 8 weeks
*** After 12 weeks
^ Barratt Impulsiveness Scale
°° Alcohol Use Disorder Identification Test
°°°Carboxy Deficient Transferrin

No group difference was observed in the correlation between BIS-11 total score and AUDIT total score, as well as between BIS-11 total score and CDT value. However, when we evaluated our data for BIS-11 subscales, we observed a correlation between attentional impulsivity and CDT value ($p = 0.038$) in patients without ADHD, as well as a correlation between nonplanning impulsivity and CDT value in patients with ADHD ($p = 0.038$) (Table 2). On the whole, ANOVA analysis showed a positive association among BIS-11 total scores at V0, V1, V2, AUDIT total score and CDT value in patients affected by ADHD and treated with atomoxetine ($p < 0.001$). In particular, the BIS-11 total score was significantly modified from the treatment with atomoxetine at both 8 ($p < 0.05$) and 12 ($p = 0.001$) weeks (Table 3). This improvement was related to hazardous and harmful alcohol consumption, because our statistical assessment showed a positive correlation among BIS-11 total score after treatment with atomoxetine, AUDIT total score and CDT value (Table 3).

Discussion

In this observational open-label study, we investigated the levels of impulsivity in alcohol-dependent patients with and without ADHD. Furthermore, we assessed the effect of atomoxetine on impulsivity in patients with ADHD. Statistical analysis of sociodemographic characteristics suggests that alcohol-dependent patients with ADHD have more difficulty in holding a job and maintaining stable personal relationships than patients without ADHD. Furthermore, although p value for education is 0.052, it is near to the level of significance, suggesting that patients with ADHD achieve a lower level of education when compared with patients without ADHD. This information is in line with the neurodevelopmental etiology of ADHD worsening the socio-relational adaptation of patients. As shown by BIS-11 total score, both groups showed high levels of impulsivity; however, scores in patients with ADHD were significantly higher than in those without ADHD. In particular, when we analyzed data for BIS-11 subscales, the results were statistically significant for motor impulsivity and nonplanning impulsivity. On the whole, in patients with ADHD, hazardous and harmful alcohol consumption evaluated with AUDIT and CDT is positively correlated with impulsivity level. Furthermore, patients with ADHD more frequently experienced binge drinking as compared to patients without ADHD.

Overall, our results suggest that ADHD may influence the clinical characteristics of alcoholism in alcohol-dependent patients. On the other hand, alcohol consumption has compromised the attentional impulsivity in patients without ADHD and nonplanning impulsivity in patients with ADHD, suggesting that alcoholism may negatively influence some aspect of impulsivity in both groups.

The pharmacological treatment with atomoxetine in patients with ADHD produced a significant reduction in the levels of impulsivity, in accordance with information in the scientific literature (De Bruyckere et al. 2016). Atomoxetine is a nonstimulant medicine acting like a blocker of norepinephrine transporters. Unlike stimulant drugs, it is not associated with addictive potential because it does not increase the dopamine transmission in the brain reward area (Upadhyaya et al. 2013). This pharmacological characteristic is relevant in the treatment of ADHD in patients affected by alcohol and/or drug dependence because it reduces the risk of misuse. The clinical improvement found at both 8 and 12 weeks was not negatively influenced by higher alcohol consumption, suggesting that even alcohol-dependent patients may obtain benefit from the therapy. Atomoxetine did not induce significant side-effects and all patients completed the study, suggesting a good tolerability in alcohol-dependent patients. The reduction of impulsivity in alcohol-dependent patients represents a key

point in the treatment of alcoholism because impulsivity can influence numerous clinical aspects of this disorder, including age of onset, quantity and frequency of alcohol consumption, binge drinking behavior, and inhibitory control (Blonigen et al. 2011). Furthermore, impulsivity represents an important and independent mortality risk factor in alcohol-dependent patients. On the whole, reduction in impulsivity level could improve the outcomes and social costs, reducing both alcohol-related diseases and mortality (Blonigen et al. 2011).

According to our results, alcoholism and ADHD appear to be related by a mutual influence in which each disorder may affect the clinical characteristics of the other. In particular, ADHD can increase the levels of motor and nonplanning impulsivity, promoting immediate actions and ignoring the long-term consequences, while alcohol abuse can increase the nonplanning impulsivity in patients with ADHD, worsening the socio-relational adaptation. Pharmacological treatment with atomoxetine was well-tolerated and effective in reducing the impulsivity level, even in patients with significant alcohol consumption. This result may be particularly relevant for the clinical practice, especially during the treatment of severe alcoholics with a history of frequent relapses. These results should be considered in light of limitations. First, the study is not a controlled trial, but an open-label evaluation. Second, the study was performed in a single center. Third, the sample is very small. Fourth, the length of our work permitted us to consider only the short-term effects of atomoxetine. However, in the context of these limitations, our findings suggest that atomoxetine may be considered a potential choice in the treatment of ADHD in alcohol-dependent patients because of its therapeutic efficacy, safety, and absence of addictive potential.

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