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ARTICLE

Increased alcohol consumption in rats after subchronic antidepressant treatment

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Abstract

The use of antidepressants for alcoholism in humans has been a matter of controversy in recent years. Despite the existence of an important co-morbidity for depression and alcoholism, some studies suggest that the use of antidepressants could worsen the prognosis of alcoholism. However, there is a lack of studies in animal models exploring this phenomenon. In the present study, we show how the 15-d treatment with fluoxetine (10 mg/kg) or venlafaxine (50 mg/kg) affected alcohol deprivation effect (ADE) and subsequent alcohol consumption. Initially, fluoxetine reduced ADE and venlafaxine did not affect it. However, in the following days, both antidepressants increased alcohol consumption, an effect that was found to last at least 5 wk. Fluoxetine treatment was shown to cause a locomotor sensitized response to a challenge dose of amphetamine (0.5 mg/kg), indicating the presence of a supersensitive dopaminergic transmission. In summary, antidepressant treatment may increase alcohol consumption in rats after a period of alcohol deprivation and this could be related to alterations in the reward circuitry. This finding confirms in an animal model previous reports in humans that may limit the use of antidepressants for alcoholism.

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Introduction

The prescription of antidepressants is currently in expansion and, in some developed countries, use can reach 10% of the population (Ufer et al., 2007; Olfson and Marcus, 2009). Depression is closely related to alcohol consumption, since 15.4% of patients diagnosed with depression met the criteria for alcohol dependence (Kessler et al., 1996). Conversely, around 80% of alcoholics would complain of depressive symptoms at some time in their lives and in >30% of those cases the criteria for major depressive disorder were fulfilled (Regier et al., 1990; Kessler et al., 1996). Antidepressants are thus commonly used in alcohol users to treat co-morbid depression and they have also been considered as a potential treatment for alcoholism itself (Torrens et al., 2005). However, little information is available on antidepressant long-term use and its possible side-effects (Preskorn, 1994; Furukawa et al., 2007).

Selective serotonin reuptake inhibitors (SSRIs) and mixed serotonin–norepinephrine reuptake inhibitors (SNRIs) are two of the main classes of commonly used antidepressant drugs (ADs). Research into the use of SSRIs to treat patients with alcohol dependence has been underway for the past 15 yr, yielding an overall low efficacy and conflicting results (Torrens et al., 2005). Several independent studies have demonstrated that treatment with various SSRIs, including fluoxetine, actually worsened the prognosis and increased drinking relative to placebo in certain groups of patients (Chick et al., 2004; Dundon et al., 2004; Kranzler et al., 2006). However, this paradoxical effect has not been experimentally addressed to date.

Clinical investigations into the effectiveness of SSRIs to reduce alcohol consumption stemming from animal studies consistently demonstrate reductions in alcohol

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consumption after the administration of a variety of agonists of the serotonin receptors (Naranjo et al., 1986; Higley et al., 1998). Most of these studies assess only acute effects of SSRIs, offering little insight into the conflicting clinical data. In fact, the scarcity of studies assessing the possible influences of long-term antidepressant use on addictive conducts, in general, and alcohol consumption in particular, has already been noted by some (Fava, 1994; Medawar, 1997; Ashton and Young, 1999; Robinson and Berridge, 2000; Dean, 2002). However, and although the concern about the addictive potential of antidepressants has prompted an interesting debate (Medawar, 1997; Haddad, 1999; Dean, 2002), the possibility that antidepressant treatment might increase susceptibility to alcoholism has been largely overlooked.

Given the impossibility of assessing the consequences that treatment with all the different SSRIs or SNRIs could have on alcohol self-administration, we chose two of them. Fluoxetine and venlafaxine were selected because of their high prescription rates (see, for example, Depont et al., 2003) and because their rates of elimination represent two opposite extremes and their comparison could add some important information regarding the role of this variable in the observed effects (Perry, 2007). Also, their mechanisms of action differ in that while fluoxetine inhibits the serotonin transporter, as traditional SSRIs, venlafaxine adds to this effect its ability to block the norepinephrine transporter, therefore being included in the SNRIs (Andrews et al., 1996).

In order to assess the possible long-term effects of a treatment with these SSRIs and SNRIs on alcohol consumption in a context of alcohol relapse after a period of abstinence, we selected a model based on the alcohol deprivation effect (ADE: Sinclair and Senter, 1967; Griebel et al., 2002). This model refers to a transient increase in alcohol consumption found after periods of forced abstinence. We based our design on a protocol previously used to study the effect of other pharmacological interventions (i.e. exposure to alcohol vapours) in alcohol relapse assessed by measuring alterations in the expression of the ADE and subsequent alcohol consumption rates (Roberts et al., 2000).

Additionally, we tested the effects of both drugs on amphetamine-induced locomotor sensitization. The existence of functional neuroadaptions in dopaminergic transmission induced by the antidepressant treatment might be a relevant factor in the explanation of the observed enhancements in alcohol consumption (Blum et al., 2009). This research could have implications for the understanding of the effects of long-term antidepressant use in the context of addiction.

Experimental procedures

Animals

We used 60 adult male Wistar rats (10 per group; Harlan, Spain) weighing 150–200 g at the beginning of the experiment and 400–500 g at the time of AD treatment. During treatment with both ADs, the animals were housed individually on a reverse 12-h light/dark cycle (lights on 12:00 hours) and constant temperature (23±1 °C). Standard food and tap water were available *ad libitum* in the home cage. The animals were allowed to acclimatize to the housing facilities for 2 wk before the beginning of the alcohol self-administration protocol.

All procedures were conducted in strict adherence to the principles of laboratory animal care (National Research Council, Neuroscience CoGftUoAi, Research B, 2003) and the European Community Council Directive (86/609/EEC) and were approved by the Ethical Committee of the University Complutense of Madrid. Special care was taken to minimize the suffering and number of animals necessary to achieve our research goals.

Drugs

Fluoxetine was obtained from Eli Lilly (Spain). A fresh fluoxetine solution was prepared daily (before injection) by dissolving fluoxetine HCl in the vehicle (0.9% saline). Fluoxetine was injected (10 mg/kg i.p.) in a volume of 2 ml/kg. This dose was chosen based on the literature reporting antidepressant effects of fluoxetine (Ciulla et al., 2007; Marcussen et al., 2008; Brenes and Fornaguera, 2009). Venlafaxine HCl was obtained from Normon S.A. (Spain) and administered in the same way at a dose of 50 mg/kg. The fluoxetine/venlafaxine 1:5 dose proportion is usually reported in clinical practice, with a maximal level dose of 80 mg/kg.d and 275 mg/kg.d for fluoxetine and venlafaxine respectively (Clerc et al., 1994; da-Silva et al., 1999). Alcohol solution was prepared daily as a 10% alcohol w/v solution from 99% ethanol. Amphetamine was obtained from Sigma-Aldrich (Spain) and administered i.p. to the animals prior to the locomotor sensitization test, in a dose of 0.5 mg/kg.

Alcohol self-administration and relapse model

We used an alcohol relapse model based on the ADE, which is considered to have good predictive validity in relation to alcohol consumption. Considering that drugs that are used to treat mental disorders are best studied in animal models of the disorder (Russell et al., 2005; Soeters et al., 2008), our subjects were raised according to a passive model of depression

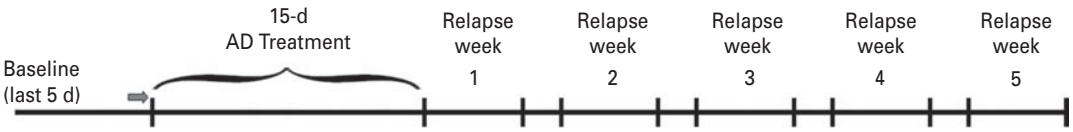

Fig. 1. Timeline of the experiment. AD, Antidepressant drug.

based on isolation, which is considered to have greater aetiological validity than those based on lesions or monoamine depletion (Willner, 1991; Barrot et al., 2005; Deussing, 2006). In accordance with this, our subjects were single-housed from adolescence up to the time of the experiment. Those subjects were then trained to lever-press for alcohol self-administration and, after they had reached a steady level of self-administration, they were withdrawn from alcohol self-administration sessions and then treated with the two drugs (fluoxetine and venlafaxine) for 15 d. After 24 h, alcohol self-administration sessions were re-introduced and changes in the patterns of alcohol consumption were monitored in this drug-free state.

Specifically, animals were trained to self-administer alcohol in operant chambers (Letica, LE 850 model; Panlab, Spain) enclosed in sound-attenuating boxes and fitted with an exhaust fan. The chambers were equipped with two retractable levers (one being the active lever and the other being the inactive lever), located on either side of a drinking dipper. The side of the active lever was counterbalanced between sessions to avoid development of location preferences. Pressing the active lever resulted in the delivery of 0.1 ml solution, which was presented to the animal followed by a 2.5 s time out, while pressing the inactive lever had no consequences. All the alcohol operant sessions lasted 30 min/d over a 5 d/wk (Monday to Friday) schedule for the entire study. The number of responses and dipper presentations in both levers was registered automatically by computer software. Animals were weighed daily before the alcohol self-administration sessions. Training was carried out using a modification of the traditional saccharine fading procedure (Samson et al., 1999) described in Alen et al. (2009). During the first 3 d training, the animals received 0.2% saccharin solution in the dipper to facilitate the acquisition of lever pressing. Thereafter, the following sequence on a fixed ratio 1 schedule was used: 0.16% saccharine and 2% alcohol for three sessions; 0.12% saccharine and 4% alcohol for three sessions; 0.08% saccharine and 6% alcohol for four sessions; 0.04% saccharine and 8% alcohol for four sessions; 0.02% saccharine plus 10% alcohol; finally, 10% alcohol alone for the rest of sessions. The experiments began once a relatively constant level of alcohol consumption had been reached, following a period of at least 6 wk access to alcohol (10% w/v). Then the 30 animals were randomly assigned to one of three experimental groups (1. vehicle; 2. 50.0 mg/kg venlafaxine; 3. 10.0 mg/kg fluoxetine) and treated for 15 d with the corresponding drug and dose or saline vehicle. After that, animals were left to rest for a period of 24 h and then the daily 30 min alcohol (EtOH) self-administration sessions were reintroduced and monitored in this drug-free state. See Fig. 1 for a schematic representation of the experimental procedure.

Behavioural sensitization experiment

In a parallel experiment, the two above-mentioned experimental conditions plus their vehicle control group were reproduced in another set of animals to establish their potential for inducing motor sensitization to the effects of amphetamine, which could shed some light on the explanation of the observed effects.

Animals for the behavioural sensitization experiment were trained for alcohol and injected with the previously described doses of fluoxetine, venlafaxine or vehicle for a period of 15 d, similar to the alcohol self-administration experiment. After each injection, the animals were activity-monitored for 30 min, after which they were returned to their home cages. The amphetamine challenge (0.5 mg/kg i.p.) was administered on the 16th day, for all three groups and differences in locomotor activity between the experimental groups were monitored for the 30 min post-injection interval. The locomotor sensitization phase, as well as the testing phase, was carried out keeping the context constant for each animal (i.e. always using the same chamber for each animal).

Behavioural testing took place in activity-monitoring chambers (35 × 35 cm) equipped with eight photocells evenly distributed in two rows of four at 5 and 10 cm from the floor. The number of times each photo beam was broken was registered by a computer program devised for this purpose and used as a general index of locomotor activity.

Data analysis

Alcohol self-administration in the whole experiment was analysed by means of a repeated measures

analysis of variance (ANOVA) of three factors [group (3: vehicle, venlafaxine or fluoxetine); days per week (5); weeks (5)]. The ADE effect for the first self-administration session was obtained comparing the base line scores (mean of the lever presses, which were reinforced with the EtOH presentation for the last 5 d before the forced abstinence) with the results of the first session by means of a Student's *t* test for paired groups. Further repeated measures ANOVAs were performed for each week independently and also for the first day of the week after the weekend pause for the four final weeks. The ADE in the next weeks was analysed by comparing the mean alcohol consumption rates in the last session of the previous week (Friday) and the first of the next (Monday) after the short deprivation period of the weekend. Differences between groups were further analysed using a repeated measures ANOVA for the four Mondays of the four cycles after the short weekend pause. Variations in weight were also analysed by a repeated measures ANOVA of two factors: days of treatment; weight.

The locomotor sensitization experiment was analysed by means of two one-way ANOVAs for mean locomotor activity during the whole drug treatment and locomotor activity during the amphetamine challenge, with treatment as the factor. All the analyses were performed using the SPSS for Windows statistical software, version 17.0.

Results

ADE effect, first day post-deprivation

Following the 15 d deprivation period, the rate of EtOH lever pressing on the first session was significantly higher (Fig. 2) when compared with the mean for the last 5 d before the deprivation, for the vehicle and the venlafaxine-treated groups ($t=2.41$ and $t=-2.64$; $p<0.05$). The fluoxetine group did not show an ADE effect on the first day ($t=1.53$; n.s.).

Daily ethanol self-administration in the first week of alcohol re-introduction

From the second day of the week, differences appeared between both groups treated with the antidepressants and the vehicle-treated group (Fig. 3).

Weekly ethanol self-administration

The general repeated measures ANOVA per days per weeks was statistically significant ($F=10,53$; $p<0.001$). Further *post hoc* analysis showed that animals in both

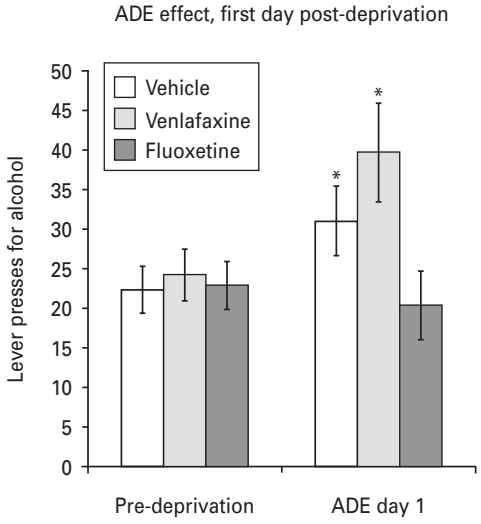

Fig. 2. Lever presses for alcohol during the first session post-deprivation in the three groups treated with vehicle, fluoxetine for 15 d (10 mg/kg.d) or venlafaxine (50 mg/kg.d) compared with the mean of alcohol consumption for the last 5 d before deprivation (left columns). As the graph shows, only the vehicle- and the venlafaxine-treated groups showed the presence of an alcohol deprivation effect (ADE). * $p<0.05$.

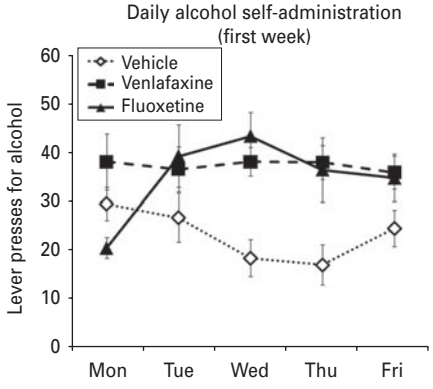

Fig. 3. Lever presses for alcohol in the first relapse week after the deprivation period, during which the three groups were treated with vehicle, fluoxetine (10 mg/kg.d) or venlafaxine (50 mg/kg.d) for 15 d. As can be seen, the differences between groups begin to emerge from the second day of the week.

treatments (venlafaxine and fluoxetine) drank significantly more alcohol than those in the control group ($p<0.005$ and $p<0.001$ respectively). Herein, we show the mean values per week for a clearer representation of the above-mentioned differences (Fig. 4).

Then, repeated measures ANOVA was carried out for the 5 d in each week and the next 4 wk, showing

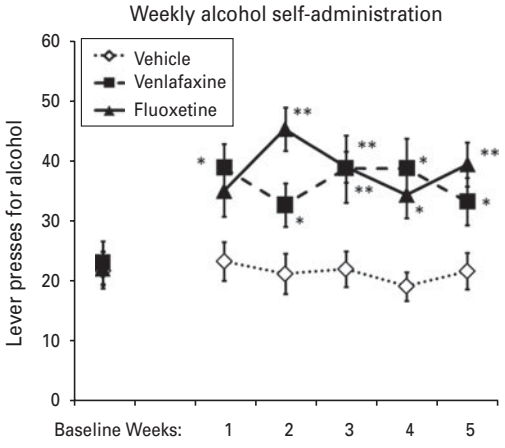

Fig. 4. Average weekly alcohol consumption in the groups treated for 15 d with vehicle, fluoxetine (10 mg/kg) or venlafaxine (50 mg/kg). Note that these results were obtained under drug-free conditions, while the treatments for each group were administered in the pause between baseline and relapse.

the constant presence of differences between both groups of animals treated with the antidepressants and the vehicle group. In the first week ($F_{2,29}$=4.79; p<0.05), Tukey's *post hoc* test showed the presence of significant differences between the vehicle group and the venlafaxine group (p<0.05). There were no significant differences between the fluoxetine group and the vehicle group (p<0.08). However, if the first day of relapse is not computed, we do observe significant differences ($F_{2,29}$=5.785; p<0.01) between the fluoxetine group and the vehicle group (p<0.05). In the second week ($F_{2,29}$=13.24; p<0.001), Tukey's test showed a significant difference between the fluoxetine group and the vehicle group (p<0.001) and also between the venlafaxine group and the vehicle group (p<0.05). In the third week ($F_{2,29}$=7.23; p<0.005.), Tukey's test showed significant differences between the fluoxetine and venlafaxine groups compared to the vehicle group (p<0.01). In the fourth week ($F_{2,29}$=8.13; p<0.005), Tukey´s test showed p<0.005 for the differences between the venlafaxine group and the vehicle group and p<0.05 for the fluoxetine and the vehicle groups. In the fifth and last week ($F_{1,29}$=7.2; p<0.005), Tukey's test showed p<0.05 for the differences between the venlafaxine group and the vehicle group and p<0.01 for the differences between the fluoxetine group and the vehicle group.

A repeated measures ANOVA analysis of EtOH self-administration scores on the first session after the weekend pauses showed the presence of effects of treatment: $F_{2,29}$=11.07; p<0.001. Tukey's analysis showed that the fluoxetine and the venlafaxine groups showed a higher ADE after the 2-d deprivations (p<0.001 and 0.005 respectively; see Table 1).

Effects of AD treatment on body weight

We also found that fluoxetine and venlafaxine treatment significantly reduced body weight during the 15-d treatment (repeated measures ANOVA; $F_{2,29}$= 9.53 and p<0.001). *Post hoc* analyses reveal a reduction in body weight after chronic fluoxetine treatment (p<0.001) and after chronic venlafaxine administration (p<0.05; data not shown).

Effects of AD treatment on locomotor sensitization

One way ANOVA showed a general effect of AD treatment on locomotor sensitization after an amphetamine challenge ($F_{2,29}$=10.67 p<0.001; see Fig. 5;). *Post hoc* Tukey's test revealed significant differences between fluoxetine treatment for 15 d and both the vehicle group and the venlafaxine group (p<0.001 and 0.005, respectively). Locomotor activity after the drug treatment for 15 d was reduced significantly ($F_{2,29}$=14.19) in the fluoxetine group compared to the vehicle group (p<0.001) and the venlafaxine group (p<0.005), as revealed by Tukey's *post hoc* test.

Discussion

The main finding of this study is that both fluoxetine and venlafaxine, given during a period of abstinence from alcohol, at doses that usually show antidepressant properties, are able to alter the ADE and induce long-lasting increases in alcohol consumption in animals with an extended background of EtOH self-administration. It should be noted that the administration of fluoxetine and venlafaxine was limited to the 15-d period preceding relapse to alcohol and that all the subjects were in a drug-free state for the rest of the experiment. The subsequent enhancements in alcohol consumption lasted, however, for the 5 wk of the experiment showing no sign of decay, which attests their endurance. This relative endurance contrasts with the transient nature of the ADE, observed in the control animals that were not exposed to antidepressants, but vehicle treated, for the same period. In the case of fluoxetine, this particular drug schedule is capable of inducing locomotor sensitization to amphetamine, thus disclosing the presence of alterations in the reward circuitry, possibly responsible for the observed enhancements in alcohol consumption. Additionally, from the fourth day of treatment, a weight reduction was observed in the fluoxetine-treated animals with

Table 1. Mean lever-presses for alcohol±S.E.M. on the first day after the weekend deprivation period

Treatment	Week 2	Week 3	Week 4	Week 5	Different from vehicle
Fluoxetine	62.09±8.6	45.64±6.0	38.80±4.9	41.73±6.3	Yes ($p<0.001$)
Venlafaxine	32.09±4.4	45.17±3.3	43.50±2.4	30.67±4.7	Yes ($p<0.005$)
Vehicle	25.15±5.4	23.00±3.7	21.91±43.5	26.00±3.7	

A repeated measures analysis of variance of alcohol self-administration scores on the first session after the weekend pauses showed the presence of effects of treatment: $F_{2,29}=11.07$; $p<0.001$. Tukey's analysis showed that the fluoxetine and venlafaxine groups showed a higher alcohol deprivation effect after the 2-d deprivation ($p<0.001$ and 0.005 respectively) compared with the vehicle-treated group.

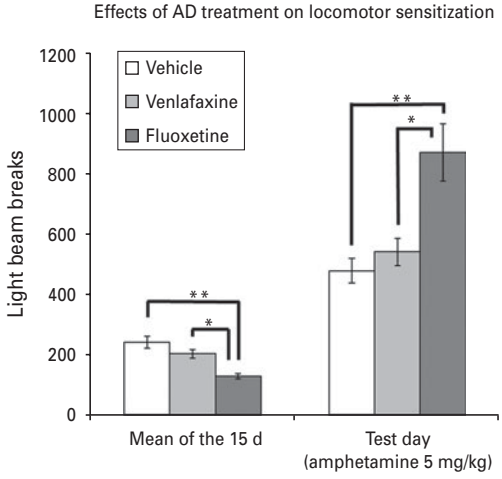

Fig. 5. Average locomotor activity as indexed by the number of light beam breaks during the 30 min after drug injection on each drug treatment (vehicle, 10 mg/kg fluoxetine or 50 mg/kg venlafaxine), compared with the same measure after the amphetamine challenge (0.5 mg/kg), 24 h after the last drug injection. The fluoxetine-treated group response to the amphetamine challenge was significantly different when compared to that of the other groups. AD, Antidepressant drug.

regard to the vehicle group and, to a lesser extent, with regard to the venlafaxine-treated group. Fluoxetine also reduced locomotor activity as observed after the treatment administration. In agreement with these findings, reductions in weight and locomotor activity after fluoxetine or venlafaxine were reported in previous studies (see Lin et al., 1999; Appolinario et al., 2004; Nemeroff and Thase, 2007).

Venlafaxine is known to have antidepressant-like effects in experimental animal models such as social interaction paradigms or the forced swimming test (Muth et al., 1986; Mitchell and Fletcher, 1993; Reneric and Lucki, 1998) and so is fluoxetine (Page et al., 1999; Rygula et al., 2006). Regarding alcohol, venlafaxine administration has been shown to partially attenuate the signs of ethanol withdrawal syndrome and fluoxetine appears to reduce ethanol self-administration in relapse to alcohol in rats (Sağlam et al., 2004; Simon O'Brien et al., 2011). Our finding that fluoxetine and venlafaxine treatment may potentiate alcohol relapse would appear paradoxical in this context. However, it should be noted that those studies either administered the drugs concurrently with alcohol consumption or did not consider alcohol consumption itself. In any case, published studies did not assess the possible long-term effects that these drugs could have on alcohol consumption.

Despite the initial enthusiasm prompted by the relationship between serotonergic dysfunction and alcoholism, as well as early data from basic research, the prescription of antidepressants in the treatment of alcoholism remains controversial. Their utility would be currently regarded as specific to reducing depressive symptoms, but having little impact on treating co-occurring alcohol dependence (Pettinati et al., 2000; Pettinati, 2004). Indeed, several authors reported that SSRI treatment actually worsened drinking among type B alcoholics, those with a more severe drinking problem (Chick et al., 2004; Dundon et al., 2004; Kranzler et al., 2006). Also, among some addict populations, the use of antidepressants, including SSRIs, appears to be associated with higher levels of polydrug use and greater probability of heroin overdose (Darke and Ross, 2000). Other reports suggest that chronic treatment with antidepressants, such as fluoxetine and venlafaxine, may cause alterations in the reward system. Such reports include the presence of an abstinence syndrome after SSRI treatment discontinuation (Coupland et al., 1996; Haddad, 1999; Levinson-Castiel et al., 2006), the development of tolerance (Rapport and Calabrese, 1993; Baldessarini et al., 2002), difficulties quitting this medication (Menecier et al., 1997) or even instances of abuse specifically involving venlafaxine or fluoxetine (Gross, 1996;

Ashton and Young, 1999; Sattar et al., 2003; Song et al., 2011). Indeed, some authors have suggested that these drugs could act, at least in certain cases, in a manner analogous to drugs of abuse, inducing some kind of neural sensitization that would enduringly alter the neural response to ulterior stimulation, i.e. by antidepressant treatment itself, stress, or other drugs (Fava, 1999; Robinson and Berridge, 2000; Raja, 2009).

The presence of psychomotor sensitization such as that found in our study is currently interpreted as evidence of the presence of hypersensitivity in the referred motivational circuitry (Robinson and Berridge, 2000). Thus, our finding is in agreement with previous studies reporting the ability of SSRIs to induce locomotor sensitization and to potentiate the responses to amphetamine (Nomikos et al., 1991; Collu et al., 1997; Sills et al., 2000). However, the absence of locomotor sensitization to amphetamine observed in the animals treated with venlafaxine would indicate that some mechanism other than the sensitization of the dopaminergic system could underlie the observed increases in alcohol consumption in the case of SNRIs. It should be noted, however, that the induction of sensitization would usually be considered to be necessary, but not sufficient, for the sensitization to be expressed in the form of increased locomotor activity in response to a test dose of amphetamine (DiFranza and Wellman, 2007).

Our divergent results in the locomotor sensitization test may be explained considering the different pharmacological mechanisms of both drugs. As mentioned earlier, fluoxetine inhibits the reuptake of serotonin, while venlafaxine does so for both serotonin and norepinephrine. Uncoupling between noradrenergic and serotonergic neurons has been proposed as a mechanism crucial for the development of locomotor sensitization and drug addiction (Tassin, 2008). According to this view, norepinephrine and serotonin, in the locus coeruleus and raphe nuclei, respectively, and also in the prefrontal cortex, mutually regulate each other. Drugs of abuse, such as opiates, amphetamine or alcohol, induce an imbalance between these two regulatory systems and this may eventually contribute to enduring addictive behaviour. However, venlafaxine and clorimipramine, both inhibiting serotonin and norepinephrine reuptake activity, fail to induce an imbalance between the two, as well as the consequent sensitized response of both these neurotransmitters; thus, preventing the development of locomotor sensitization (Lanteri et al., 2007). The absence of a sensitized locomotor response to the challenge dose of amphetamine in our experiment would be in agreement with this view. However, the increased alcohol consumption in the venlafaxine-treated group remains to be explained.

Serotonergic alterations could also participate in the observed increases in alcohol consumption as decreases in serotonergic function increase ethanol intake (see LeMarquand et al., 1994). Such decreases have been observed after SSRI discontinuation (Blier and Tremblay, 2006). The elimination rates of the two drugs could participate in this mechanism and it would be expected that a faster elimination rate would cause a more pronounced effect on the serotonergic system, eventually affecting alcohol consumption. However, this was not the case and the long half-life of fluoxetine (around 4–6 d for the drug and 16 d for its active metabolite *vs.* 5 h of venlafaxine and 11 h for its active metabolite) did not attenuate alcohol consumption rates in relapse compared to that of the venlafaxine-treated animals (Gilman et al., 1980; RxList Inc., 2013). According to this, at the time of testing for alcohol consumption, after AD treatment, fluoxetine could still be present in the organism of the animals treated with this drug, while venlafaxine would have already been eliminated. This could be an important factor explaining the reduced consumption of alcohol in the first moment in the fluoxetine-treated group (see Fig. 2), as the presence of this drug in the organism is reported to reduce alcohol self-administration in relapse (Le et al., 1999).

The main limitation of our study is the use of a single dose of each of the two drugs. Although carefully selected based on previous studies reporting antidepressant effects, the doses are clearly in the medium-to-high rank (De Vry et al., 1999; Page et al., 1999; Marcussen et al., 2008). Although this fact is obviously a limitation of our study, it is interesting to note that, for the treatment of addiction, and particularly alcoholism, several authors recommend the use of high doses (Ciraulo et al., 1988). Another limitation of the study may include the drug administration procedure. The route of antidepressant administration in this study was i.p., following other studies on the antidepressant effects of these drugs (Duncan et al., 1998; De Vry et al., 1999; Griebel et al., 2002), but whether the effects reported in this article hold for other administration routes remains to be explored in the future.

Our results are important for the understanding of the potential negative effects of SSRI/SNRI treatment on alcohol consumption and have particular relevance considering the current widespread use of SSRI/SNRIs, including their increasing use in adolescence and childhood, sometimes in conjunction with stimulant drugs (Bussing and Levin, 1993; Clavenna et al., 2007; Kurian et al., 2007). Indeed, adolescence is a period

that is considered a window of vulnerability to pharmacological events that can determine future associations with abused drugs (Laviola et al., 1999; Spear and Brake, 2004; Schramm-Sapyta et al., 2009).

In conclusion, our study shows that both SSRI- and SNRI-type 15-d antidepressant treatment is able to induce long-lasting increases in alcohol consumption when this drug is resumed. These results sum up the abundant data regarding the effects of commonly used SSRI, fluoxetine, and SNRI, venlafaxine, and seeks to fill some existing gaps in basic research in the field. Fluoxetine, but not venlafaxine, induced a sensitization to the locomotor response after an amphetamine challenge, suggesting hyperactivation of rewarding areas. Further studies are needed to ascertain the relevance of our findings and their possible repercussions for medical practice, as well as their physiological mechanisms.

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Statement of Interest

None.

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