

## Chapter

# Rethinking the Use of Antidepressants to Treat Alcohol Use Disorders and Depression Comorbidity: The Role of Neurogenesis

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## Abstract

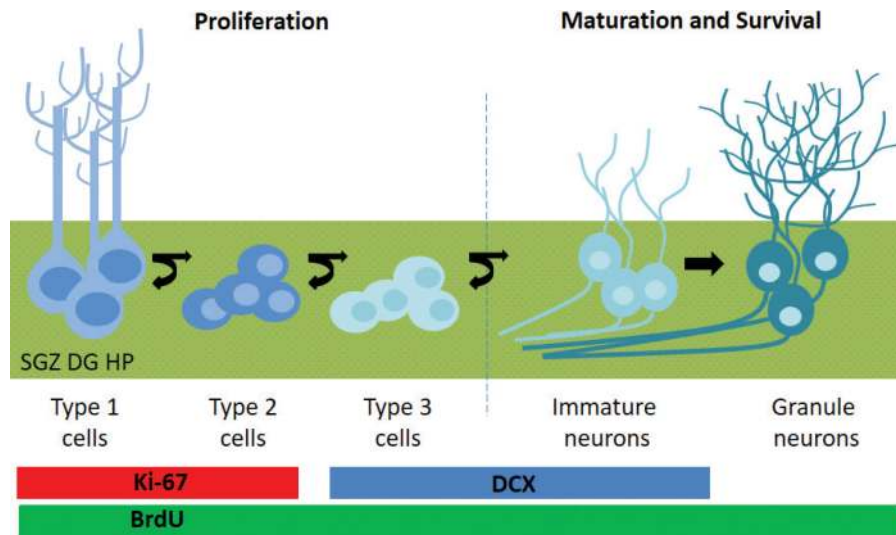
Patients with alcohol use disorders (AUDs) are frequently treated with antidepressant drugs (ADs), but clinical evidence of their efficacy is contradictory. Considering that ADs are thought to produce their therapeutic effects partially by increasing hippocampal plasticity and neurogenesis (HN), and that both AUDs and depression share a potential for the disruption of these neuroplastic processes, one could reasonably wonder whether the poor efficacy of AD treatment could be explained by the inability of these drugs to exert their proper action in patients suffering from AUD or depression. In order to further clarify this question, this chapter aims to examine available data regarding the effect of ADs on behavioral and HN alterations related to alcohol abstinence, as a key period in which the treatment would be implemented and in which their potential effects on alcohol-related problems remain under controversy.

**Keywords:** alcohol use disorders (AUDs), antidepressants (ADs), hippocampal neurogenesis (HN), depression, comorbidity, alcohol withdrawal

## 1. Introduction

AUD is a chronic relapsing brain disease characterized by the presence of various symptoms, such as physically hazardous alcohol drinking, tolerance, withdrawal, or craving related to alcohol consumption, whereas MD is a psychiatric disorder characterized by low mood, anhedonia, insomnia, low motivation, apathy, and feelings of guilt, among other symptoms [1]. Epidemiological studies have shown a strong relationship between alcohol use disorders (AUDs) and depression. Indeed, the prevalence of current or lifetime alcohol problems in depression is estimated around 16% and 30%, respectively [2].

Adult hippocampal neurogenesis (HN) is a complex multistep process by which neural progenitor cells (NPCs) divide throughout life and give rise to new functional neurons in restricted regions of the adult mammalian brain (**Figure 1**, and also described in [3]). The dentate gyrus of the hippocampus is one of the brain areas that respond to stimuli through multiple mechanisms that allow the proliferation,



**Figure 1.** Schematic representation of the stages of adult hippocampal neurogenesis in the subgranular zone of the dentate gyrus and the main immunolabeling techniques used in the cited studies.

maturation, and integration of new generated neurons in this structure, an event that appears to regulate and improve impaired cognition and mood in various disorders [4]. Both AUDs and depression have shown to compromise HN processes [5, 6]. The HN theory of depression sustains that depression results from impaired adult HN, and, therefore, its restoration leads to recovery [7]. Direct causality of HN alterations in the pathogenesis of depression seems unlikely [8], but the clinical relevance of hippocampal newly generated neurons in depression continues to be the object of study [9]. In addition, HN and plasticity processes have been proposed as a possible common neurobiological mechanism underlying alcohol withdrawal and depression [10]. In fact, HN has been proposed to significantly contribute to alcoholic pathology, although the mechanisms of alcohol-induced alterations in HN are not completely understood [6]. In this sense, there is strong evidence in animal models that alcoholic neuropathology is at least partially due to an attenuation of adult HN induced by intoxication, a state that could be reversed by spontaneous reactive HN processes during abstinence [11]. In this regard, authors have proposed that while suppression of hippocampal neurogenic proliferation appears to be a factor of comorbid vulnerability, enhancing HN into the neural circuits affected by drug may contribute to recovery [12, 13].

Antidepressants (ADs), mainly selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are the primary pharmacological treatment indicated for depression-diagnosed patients [14]. Concurrently, evidence of monoamine alterations in AUDs has encouraged the investigation of drugs that act on the serotonin system to treat alcohol abuse [15]. Only a few drugs with clear evidence but modest effects are approved for treatment of AUDs, as naltrexone and acamprosate, although given certain clinical circumstances, substance use disorders may require specific treatment; thus, off-label medications like ADs are also frequently prescribed, mainly in AUD depressed patients [16]. At first, the monoamine theory of depression is based on the fact that brain monoamine systems appear to regulate mood and traditional ADs, such as SSRI, and selectively increase monoamine signaling in neural pathways related to mood regulation [17]. Later, at the beginning of the century, different results supported the hypothesis that ADs might affect mood by increasing adult HN [18]. At the same time, numerous studies have led to propose that ADs can influence HN by serotonin modulation and that HN may be related to AD effects (reviewed in [19]). In agreement, postmortem studies have reported

that ADs augment NPC numbers [20, 21] and restore mature hippocampal neural population and dentate gyrus volume of depressed patients [22, 23]. These human data reflect the neurogenic potential of ADs previously reported in animals [24]. In this respect, animal studies have led to suggest that, while not causally involved in the onset of depression, HN has been related to the ability of chronic monoaminergic ADs to achieve recovery [8]. Recent studies have reopened the debate about the functional implication of adult HN in humans (see [25]), highlighting the need to further study the generation of new neurons in the adult human hippocampus. This also implies to characterize the role of HN in depression and AUDs [4, 6] and the extent to which it participates in recovery in the treatment with ADs [26].

## **2. Alcohol use disorders and depression**

Data from AUD patients have led to the proposal that the effective components of withdrawal, such as dysphoria and depressed mood, create a motivational drive that leads to compulsive ethanol drinking behavior even after long periods of abstinence [27]. Subsequent findings promoted the hypothesis that drugs of abuse elicit pronounced euphoria followed by a negative emotional state that can disrupt homeostasis, considered key to the etiology and maintenance of the pathophysiology of addiction [28].

### **2.1 Clinical and preclinical evidence of AUD contribution to depressive symptomatology**

Authors have considered whether there may be a causal relationship between AUDs and depression and whether one of the disorders can lead to the appearance of the other. Thus, numerous studies reveal ample evidence of the risk of depression resulting from AUDs [29]. Moreover, problematic patterns of alcohol consumption are related to depressive symptomatology, both in adult and adolescent populations [30, 31]. In an attempt to simplify the complexities of the relation between AUDs and depression, a classification of depression as primary or secondary according to whether it developed before or after the onset of the AUD was proposed. The term independent (ID) was used for a depression that began before the onset of alcohol dependence or during sustained (at least 4 weeks) abstinence, while depressive syndromes occurring only during a period of active alcohol dependence were labeled as substance-induced (SID) [32]. However, some of the depressive symptoms classified as ID could actually be substance-induced, as SID appears not to be a stable diagnosis, with about one quarter of patients initially labeled with SID meeting criteria for ID within the next 12 months [33]. Thus, SID would be considered a self-limiting condition that would tend to remit with abstinence, while ID would require specific depression treatment [32]. After receiving treatment for alcohol consumption, those with SID would show better depression outcomes and reduce their drinking more than those with ID [32]. Also, and further supporting a causal role of alcohol consumption in depression, reducing its consumption would improve the outcomes for both types of depression [34]. In the same sense, some authors have proposed that reducing hazardous drinking can improve depressive symptoms, but continued hazardous use slows recovery for psychiatric patients [35].

### **2.2 Preclinical evidence of the contribution of alcohol to depressive-like behavior**

Animal studies might overcome the limitations of the clinical studies, allowing to obtain not only correlative information but also contributing data that would

allow a larger approach to the possible underlying causes in the relation of the AUD and depression. Several preclinical studies have assessed behavioral alterations during acute withdrawal and/or protracted abstinence in different animal models of alcohol abuse [36–47]. Studies used rodents as experimental animals, and the majority used the AUD model of chronic intermittent ethanol (CIE) vapor exposure. Behavioral analysis was carried out from a few hours (less than 24 hours) to several days or weeks after the last alcohol consumption, using the forced swimming test (FST) the most frequently used paradigm for this purpose. FST allows detecting responses toward an inescapable stress in animals based on the measurement of the time they remain immobile rather than displaying active strategies, akin to responses that would be impaired in depression. This response has been commonly described in the literature as depressive-like behavior. Affective alterations induced by alcohol were generally detected once alcohol exposure ceased, regardless of the animal model used, with few exceptions. It is interesting to note that studies evaluating both acute and chronic abstinence found occurrence of depressive-like behavior in both experimental periods although mostly after prolonged abstinence, which may indicate that the negative affective state as a consequence of abstinence, especially when maintained for prolonged periods, might be a risk factor for displaying depressive-like behavior, analogous to the way in which depression manifests itself in abstinent AUD patients.

### **2.3 Depression contributes to the risk of alcohol relapse**

As previously mentioned, a negative affective state is not only a consequence of consumption but also could represent a maintenance factor for the addiction cycle [28]. In coherence, the “self-medication” theory postulates that the desire to avoid or alleviate preexisting or abstinence-related aversive states is a determining factor of excessive drug use and relapse [48]. Relapse is one of the most complicated components of drug addiction and involves a complex interaction of drug-associated cues that respond to multiple biological, psychiatric, psychological, and psychosocial factors which may precipitate the restoration of consumption [49, 50]. Therefore, one of the main goals in treating substance abuse is to preserve abstinence.

### **2.4 Clinical evidence of depressive symptomatology contributing to the risk of alcohol relapse**

Clinical data strongly support the relevance of negative emotionality in protracted abstinence and relapse. Thus, for example, a higher prevalence of depressed mood has been observed in AUD patients who relapsed [51]. Depression-related low motivation has been shown to precipitate alcohol relapse, while improvements contributed to greater abstinence [52–55]. In fact, those studies have emphasized the need to treat depression to preserve abstinence and improve outcome of patients with AUD. We mentioned before that the AUD can contribute to an ID or a SID. Thus, some authors wonder whether transient symptomatology (SID) would affect consumption in the same way as the observed ID in prolonged abstinence. In this sense, it has been suggested that while affective dysregulation in protracted abstinence is likely to be of immediate relevance for relapse to excessive alcohol use, the link between the early withdrawal phenomena and subsequent affective alterations remains unclear. However, other authors have concluded that both categories should be taken into account as factors that would precipitate relapse. Specifically, SID has been associated with a shorter time for the first alcohol consumption after discharge, while ID, in addition, predicted relapse to alcohol dependence. Interestingly, ID prior to the AUD did not predict outcomes for patients [56].

## **2.5 Preclinical evidence of depressive-like behavior contributing to the risk of alcohol relapse**

Results from clinical studies underline the need to understand possible underlying factors that contribute to the mutual negative influence of both pathologies. In this sense, animal models of AUD and depression offer the possibility of elucidating potential factors involved in the development of dual disorders [57]. Despite the prevalent comorbidity between depression and AUDs, direct evidence of causality of co-occurrence of the two pathologies is still scarce. Thus, Riga et al. [58] used a combination of models of depression and AUD through social defeat and alcohol self-administration and reported that a persistent depressive-like state led to profound alcohol reward-related changes, exaggerating the incentive salience of alcohol and facilitating cue-induced relapse to alcohol seeking. In addition, Lee et al. [47] reported higher alcohol self-administration behavior in mice which exhibited depressive-like behavior in prolonged abstinence as consequence of alcohol self-administration. It is interesting to note that this condition only occurred in animals that were exposed to alcohol during their adolescence and not in those in which the first exposure took place during adulthood, and that did not show alcohol-related affective alterations. Animal studies would show that affective alterations that persist in prolonged abstinence, regardless of whether they were related or not with alcohol exposure, would increase self-administration behavior under alcohol re-exposition.

## **3. Alcohol use disorders and hippocampal neurogenesis deterioration**

Years ago, the proposal arose that alcohol abuse might exert its negative effect in the human brain through an induction of neuronal loss on the hippocampus. In agreement, animal models of chronic alcohol exposure have shown consistently that alcohol is toxic to hippocampal neurons, inducing cell loss. Subsequent studies have led to suggest that alcohol may result in hippocampal pathology and deterioration through effects on adult HN (see [6]).

### **3.1 Clinical evidence of AUDs contributing to hippocampal neurogenesis deterioration**

The lack of techniques to assess adult HN *in vivo* in AUD patients limits the available information in this regard essentially to postmortem or neuroimaging studies. To date, we have only found one study that has shown that alcohol would have a negative effect on HN in humans [59]. Authors reported reduced numbers of three biomarkers representing different stages of the HN process: Ki67, as marker for cell proliferation, the sex determining region Y-box (Sox2) as stem/progenitor cell marker, and doublecortin (DCX) as marker of neural maturation in the dentate gyrus in subjects with ongoing alcohol abuse. These results converge with previous findings in human with a history of drug abuse [60]. Otherwise, neuroimaging studies allow the detection that alcohol abuse could also impair hippocampal volume. Indeed, some studies have revealed decreases in hippocampal volume in AUD patients, although these changes have been shown to revert with abstinence (reviewed in [61]). There is also evidence of impairment in hippocampus-related functions as consequence of problematic alcohol consumption, effects that, similarly to those found in volumetric studies, could improve with abstinence [62].

### **3.2 Preclinical evidence of alcohol contributing to hippocampal neurogenesis deterioration**

Animal studies are useful to compensate for the limited clinical evidence in AUD patients. In fact, the most consistent evidence of alcohol-induced hippocampal impairment due to, in part, its action on HN comes from preclinical studies. In addition, the different immunolabeling techniques allow us to differentiate the stages of adult animal HN, as proliferation, maturation, migration, and survival of newly generated cells. Obtaining samples throughout different stages offers detailed information on how these processes are altered along the addictive cycle, which constitutes a great advantage over the limitations of postmortem studies in humans. The majority of *in vivo* studies have shown that alcohol intoxication leads to an overall decrease in HN through alcohol's effects on cell proliferation and survival [63], while those HN parameters show heterogeneous results when assessed throughout abstinence. Several animal studies have evaluated HN parameters along acute withdrawal and/or protracted abstinence in different AUD models. Studies mainly analyzed parameters of HN at different times throughout abstinence and reported increases, decreases, and mixed results in HN-related parameters [64–79]. Studies were mainly in rodents (except [72], done in nonhuman primates). A large part of the studies used a 4-day binge model or self-administration protocols, whereas few authors used the CIE vapor exposure model. Different immunolabeling techniques have been used to assess HN in animals, mainly the thymidine analogue bromodeoxyuridine (BrdU), which is incorporated into dividing cells and allows monitoring of newly generated neurons in the adult brain. Main relevant aspects of results from those studies are analyzed in detail in the conclusion.

### **3.3 Hippocampal neurogenesis deterioration contributes to the risk of alcohol relapse**

Hippocampus is essential in consolidation of stimuli previously paired with drug intake, and authors have proposed that alcohol produces strong deficits in hippocampus-dependent learning and memory and attenuates hippocampal plasticity during withdrawal, which may motivate attempts to self-medicate resulting in relapse and maintenance of drug use [80]. In this sense, one way by which impaired HN could contribute to addiction would be by disrupting learning and memory and by inducing negative affective states, both factors increasing susceptibility to relapse [81]. On the other hand, research during the last decade has shown that it is possible to disrupt alcohol-induced cues and that this has a lasting impact in reducing the tendency to seek drugs and to relapse [82]. In this regard, authors have suggested that although there are a host of plastic changes that occur with abstinence, one way that the hippocampus may recover in abstinence is through the repopulation of the dentate gyrus by adult HN [6].

### **3.4 Clinical evidence of hippocampal neurogenesis deterioration contributes to the risk of alcohol relapse**

In the same way as in the previous sections, human studies provide indirect indicators of the role of HN, such as the volume and functionality of the hippocampus. In this regard, clinical studies found that deficits in hippocampal volume in AUD patients compared with healthy controls normalize over an abstinence period of 2 weeks [83] and that hippocampal volume did not constitute a predictive factor for relapse risk in abstinent alcoholics [84]. On the other hand, it has been observed that the hippocampal-dependent functions could continue to be altered even in prolonged abstinence [62], which could be a factor that, as other authors propose,

would alter cognitive aspects linked to the risk of relapse [80]. Information from clinical studies shows that the course of the AUD would be related to the functionality of the hippocampus and not so much with alterations in its structure. Unfortunately, like the previous section, we are faced with a lack of clinical evidence in this regard, since we do not have information on the role that newly generated neurons in the hippocampus would play on the learning and memory processes involved in prevent relapse.

### **3.5 Preclinical evidence of hippocampal neurogenesis deterioration contributes to the risk of alcohol relapse**

Numerous animal studies have led to suggest that low neurogenic states could regulate the addictive behavior, assuming a factor of addiction or comorbid vulnerability [12]. Specifically, animal models of drug addiction studies have led to propose that adult HN appears to be important for the maintenance of hippocampal neuroplasticity, such that reducing HN during abstinence may increase the vulnerability to relapse, while enhancing HN during abstinence may help reduce the risk of relapse [22]. Among the studies cited that assessed HN parameters, only one study [78] analyzed the levels of alcohol consumption after the period of abstinence. Thus, they reported augmented alcohol self-administration after 4 weeks of abstinence in animals that showed reduced HN at the end of the experiment as consequence of a combination of self-administration and vapor exposures to alcohol (dependent animals) compared to animals that showed no reductions in HN who did not receive exposure to vaporized alcohol (nondependent animals). Some results from [78] suggest that the observed reactive HN effect does not have an implication in recovery. On the contrary, animals that showed this reactive effect and lower levels of survival of newly generated neurons ended up showing higher alcohol consumption during relapse. Main implications of these findings are analyzed in the conclusion.

## **4. AD treatment in alcohol use disorders, depression, and hippocampal neurogenesis**

Several studies have led to the suggestion that reversing depressive symptomatology [54] and HN deterioration [21] could be a therapeutical option in cases of comorbidity between AUDs and depression. Given the potential of ADs to improve affective symptoms and promote HN, it is reasonable to assume that such treatment would benefit AUD patients. The following sections attempt to clarify these aspects.

### **4.1 Clinical evidence of antidepressant treatment improves depressive symptomatology and hippocampal neurogenesis deterioration**

Meta-analysis and reviews that integrate results of clinical studies in which patients with AUD and depression were treated with ADs show drug-dependent and inconclusive results. Some findings showed that SSRIs adequately treat depressive symptomatology in individuals with AUD and depression [85–87], while others showed that SSRIs were not more effective than placebo in treating comorbid patients [88, 89]. In relation, it has also been seen that SSRIs would not show greater effects than TCAs [90]. In fact, results from different studies using TCAs seem to converge in its effectiveness in alleviating depressive symptomatology [88, 91]. This may present differences in the response to a treatment for

depression in alcohol-dependent participants depending on the different types of depression, as a stronger effect of ADs was found in ID than in SID patients [32]. The most recent meta-analysis available concerning the efficacy of AD treatment in these patients shows a modest effect in some outcomes of depression [92]. However, most authors point out the need for more studies with similar outcome measures, well-defined sample designs, adequate doses, and duration of treatment so that the integration of studies can reach conclusions with a high quality of evidence [87, 90, 92], and some of them emphasize the need to evaluate possible alternative ADs, as, for example, nonselective or partial agonist-reuptake inhibitors [93, 94]. On the other hand, as seen in the introduction, ADs have shown to potentially increase HN in depressed patients [20, 21]. Unfortunately, no evidence of AD-related HN effect has been described in AUD patients.

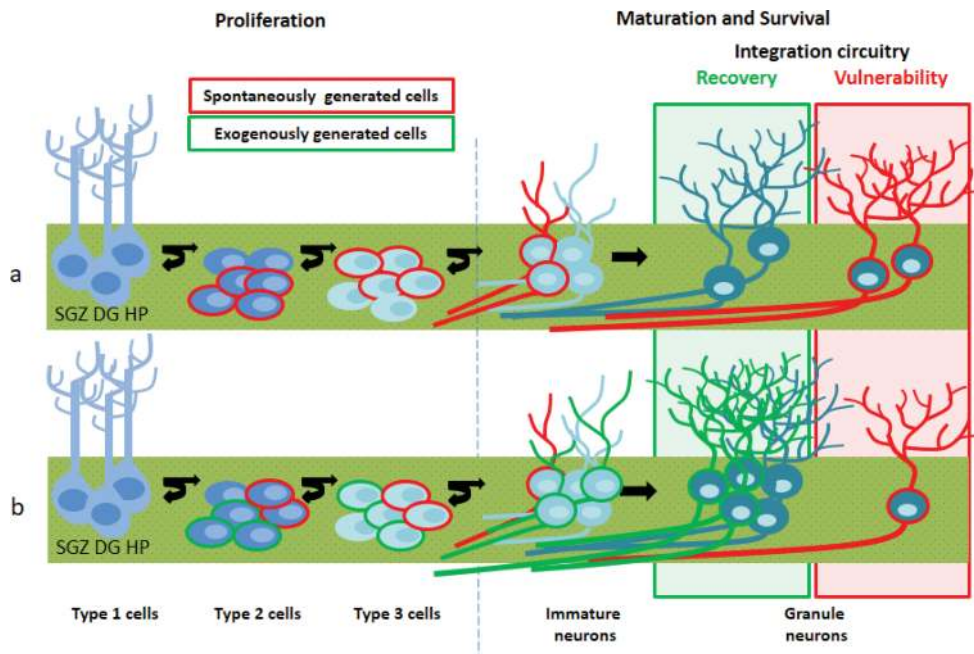
#### **4.2 Preclinical evidence of antidepressant treatment improves depressive-like behavior and hippocampal neurogenesis deterioration in alcohol exposure and abstinence**

Studies in animals have suggested that the ability of AD treatment to affect HN would be linked to its behavioral therapeutic effects [8]. In fact, authors reported that increasing HN has been demonstrated to be necessary and sufficient to reduce depressive-like behavior in animals [95]. On the contrary, other authors have concluded that, although ADs promote HN, this would not be a critical event for their mood-reciprocating actions [96]. In the same direction, authors have proposed that the therapeutic effect of the AD would not be determined exclusively by an increase in the number of newly generated neurons but rather in the way in which those neurons are functionally incorporated into hippocampal preexisting circuits that would be linked to recovery [97]. Few animal studies evaluated the efficacy of an AD treatment (desipramine, imipramine, and amitifadine) in a model of alcohol exposure. Studies from Getachew et al. [36, 43] found that subchronic desipramine and imipramine treatment reversed depression-like behavior and anxiety in rodents under acute withdrawal conditions. Similarly, Warnock et al. [39] reported that two different doses of acute amitifadine reversed the abstinence-induced increased immobility in the FST. Finally, Stevenson et al. [37] reported that subchronic desipramine reverted depression-like behavior and restored HN parameters, both aspects impaired under protracted abstinence conditions in mice. Similarly, other studies have tested the efficacy of AD-like drugs as 7,8-DHF, a trkB agonist [40]; trichostatin A, a histone deacetylase inhibitor [76]; rolipram, a phosphodiesterase-4 inhibitor [45]; or ketamine, a N-methyl-D-aspartate receptor antagonist [42, 46], reporting that those treatments also restored the HN parameters and/or the behavioral alterations impaired by the exposure and abstinence to alcohol. In addition, non-pharmacological conditions, as wheel running or natural extracts, induced similar patterns of recovery in HN parameters [65, 77] and in depressive-like behavior [45, 50] in rodents exposed and abstinent of alcohol. This data, in conjunction with previous studies that used ADs, would suggest that if a treatment had protective effects on the HN function, it could also reflect its therapeutic effect on affective disturbances in alcohol exposed animals. Nevertheless, the causality of this relationship needs to be further elucidated. **Figure 2** illustrates the possible state and role of HN during alcohol withdrawal.

#### **4.3 Clinical evidence of antidepressant treatment improves depressive and alcohol use disorder outcome**

Although ADs are not among the first-line treatment options in AUD, they are among the additional alternative treatments available, mainly when comorbid





**Figure 2.**

(a) Schematic representation of the adult HN along alcohol withdrawal and abstinence. Spontaneous burst in cell proliferation is followed by a lower survivability and aberrant patterns of cell migration and integration of the newly generated neurons which could contribute to vulnerability related circuitry. (b) Exogenously induced cell proliferation (by physical exercise or proneurogenic treatment as ADs) could prevent the consolidation of neural circuitry involved in vulnerability, promoting survivability and integration of the newly generated neurons into neural pathways of recovery.

conditions are present [16]. In this regard, authors have proposed that AD treatment could ameliorate alcohol consumption [98], possibly by improving depressive symptoms [99]. Some of the aforementioned studies and meta-analysis evaluated alcohol-related outcomes in AUD depressed patients [87, 90, 92], showing a modest or no efficacy of AD treatment in alleviating some aspects linked to alcohol consumption. Recent conclusions show that ADs increased the number of participants abstaining during the trials and reduced the number of drinks per drinking day, while no differences were reported between ADs and placebo in other relevant outcomes of the AUD [92]. In addition to the mentioned low overall effectiveness, it is important to mention that some studies reported even poorer drinking outcomes in AUD patients treated with SSRIs compared to those treated with placebo [100–102]. In this line, studies have reported clinical cases where treatment with SSRIs appears to be the cause of increased frequency of intoxication by alcohol and new onset of alcohol-related problems [103–105]. Finally, patients who actively drink suffering of comorbid anxiety and AUD have also shown that they may increase alcohol consumption under treatment with SSRIs [106].

#### 4.4 Preclinical evidence of antidepressant treatment improves alcohol relapse

Preclinical data concerning the effectiveness of pharmacological treatments in AUDs is still scarce [107]. Animal studies that evaluate the effect of different AD treatments on preventing alcohol consumption report reduction in alcohol intake after an acute drug dose or under short-term relapse conditions [108]. Nonetheless, taking in mind that the evaluation of the effectiveness of conventional AD treatment should be done considering the delay in its therapeutic effects, studies should go beyond short-term evaluations, assessing long-term

consequences of treatment in animal models that better mimic AUD patient conditions [109]. Thus, unlike studies using acute treatments, authors that evaluated chronic and subchronic escitalopram, sertraline, paroxetine, fluoxetine (SSRIs), and duloxetine, dual serotonin/norepinephrine reuptake inhibitor (SNRI) treatments found that, along the treatment period, animals showed lower alcohol intake levels, but cessation of treatment produced a restoration of basal alcohol consumption [110–112]. Ho et al. [110] also found an augmentation in alcohol intake in depressed animals once treatment with escitalopram ceased. Interestingly, authors also found the same effect in animals under combination of AD (escitalopram) and anti-relapse (acamprosate) treatments. Related to that, subchronic treatment with different ADs (SSRIs and SNRIs) has been demonstrated to augment alcohol consumption in animal models of alcohol deprivation, which were treated along abstinence and re-exposed to alcohol self-administration once AD treatment ended [113, 114].

## **5. Conclusions**

Translating evidence from preclinical studies to clinical practice still creates a major challenge in development of new pharmacological treatments in AUDs. The first thing we must point out is the lack of animal studies that have evaluated the effectiveness of the AD treatment in alcohol exposure and abstinence. In this sense, it is important to highlight the numerous studies in animals that evaluate the alcohol exposure and abstinence impact on affective and HN parameters compared to the scarce studies that try to reverse such effects by testing appropriate ADs. In addition, strong criteria are needed when evaluating treatments in AUD animal models, highlighting the use of self-administration procedures and the evaluation of dependence by observing abstinence and relapse behavior. In this sense, animal studies evaluating HN alterations were mainly used as short periods (4 days) of forced alcohol exposition, while prolonged self-administration or CIE models, which better represent important aspects of alcohol consumption patterns in AUD patients, were used to a lesser extent.

One of the most direct methodological limitations when comparing clinical and preclinical studies is determined by the period in which the AD treatment begins. Preclinical studies would indicate that animals can display different affective responses to ADs according to the moment it is administered. In addition, AD cessation could have negative repercussions in alcohol consumption and relapse. While these effects should be further clarified in future studies, clinical trials should take these relevant aspects into account.

The debate about the implication of the new neurons generated in the hippocampus as a consequence of alcohol abstinence continues to be an object of interest. Despite alcohol-induced HN impairments that mainly persist along abstinence, some studies have shown increases in parameters of neural proliferation in animals mainly along early withdrawal periods. First, the possible role of this HN re-establishment effect as factor of recovery was considered, but later studies would even point to opposing hypotheses. In this regard, other findings led to the question whether neurons born during this reactive neurogenic process survive or properly integrate into the existing hippocampal circuitry to provide beneficial effects on hippocampal function and recovery. An early increase in neuronal proliferation induced by abstinence, followed by a reduction in survival in prolonged abstinence, appears to result in an increase in alcohol self-administration. Thus, this apparent AD-induced dual role of HN and the consequent changes in addictive behavior should be elucidated.

To resume, preclinical evidence strongly supports that alcohol consumption and abstinence lead to negative affective states and alterations in HN, some of which may persist in prolonged abstinence. Although affective alterations related to alcohol have been evaluated, there is limited data available concerning the alcohol-induced HN deterioration in clinical patients. Both alcohol-induced depression and changes in HN could be relevant to promote relapse, exacerbating the addictive cycle, although additional studies should clarify this complex interaction. Conventional ADs have been proposed to alleviate affective alterations possibly by promoting HN; thus AUD depressed patients could benefit from its effects. Unfortunately, clinical trials still face several limitations in order to draw reliable conclusions in this regard. Moreover, preclinical studies should bear in mind important methodological aspects onward when translating information regarding the efficacy of AD treatment into AUD patients.

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## **Conflict of interest**

The authors declare no conflict of interest.


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## References

- [1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 5. Washington, DC: American Psychiatric Association; 2013
- [2] Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: A systematic review. *The American Journal of Medicine*. 2005;**118**(4):330-341. DOI: 10.1016/j.amjmed.2005.01.007
- [3] Balu DT, Lucki I. Adult hippocampal neurogenesis: Regulation, functional implications, and contribution to disease pathology. *Neuroscience and Biobehavioral Reviews*. 2008;**33**(3):232-252. DOI: 10.1016/j.neubiorev.2008.08.007
- [4] Baptista P, Andrade JP. Adult hippocampal neurogenesis: Regulation and possible functional and clinical correlates. *Frontiers in Neuroanatomy*. 2018;**12**:44. DOI: 10.3389/fnana.2018.00044
- [5] Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci*. 2007 Sep;**10**(9):1110-1115. DOI: 10.1038/nn1969
- [6] Olsufka RA, Peng H, Newton JS, Nixon K. Alcohol effects on adult neural stem cells—A novel mechanism of neurotoxicity and recovery in alcohol use disorders. In: Rasmussen TP, editor. *Stem Cells in Birth Defects Research and Developmental Toxicology*. Hoboken, NJ: Wiley; 2018. DOI: 10.1002/9781119283249.ch8
- [7] Jacobs BL, van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: A novel theory of depression. *Molecular Psychiatry*. 2000;**5**:262-269
- [8] Tanti A, Belzung C. Hippocampal neurogenesis: A biomarker for depression or antidepressant effects? Methodological considerations and perspectives for future research. *Cell and Tissue Research*. 2013;**354**(1):203-219. DOI: 10.1007/s00441-013-1612-z
- [9] Peng L, Bonaguidi MA. Function and dysfunction of adult hippocampal neurogenesis in regeneration and disease. *The American Journal of Pathology*. 2018 Jan;**188**(1):23-28. DOI: 10.1016/j.ajpath.2017.09.004
- [10] Renoir T, Pang TY, Lanfumey L. Drug withdrawal-induced depression: Serotonergic and plasticity changes in animal models. *Neuroscience & Biobehavioral Reviews*. 2012;**36**(1):696-726. DOI: 10.1016/j.neubiorev.2011.10.003
- [11] Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol and Alcoholism*. 2009;**44**(2):115-127. DOI: 10.1093/alcalc/agn079
- [12] Chambers RA. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. *Drug and Alcohol Dependence*. 2013;**130**(1-3):1-12. DOI: 10.1016/j.drugalcdep.2012.12.005
- [13] Mandyam CD, Koob GF. The addicted brain craves new neurons: Putative role for adult-born progenitors in promoting recovery. *Trends in Neurosciences*. 2012;**35**(4):250-260. DOI: 10.1016/j.tins.2011.12.005
- [14] Abbing-Karahagopian V, Huerta C, Souverein PC, de Abajo F, Leufkens HGM, Slattery J, et al. Antidepressant prescribing in five European countries: Application of common definitions to assess the prevalence, clinical observations, and methodological implications. *European Journal of Clinical Pharmacology*. 2014;**70**(7):849-857. DOI: 10.1007/s00228-014-1676-z

- [15] Marcinkiewicz CA, Lowery-Gionta EG, Kash TL. Serotonin's complex role in alcoholism: Implications for treatment and future research. *Alcoholism, Clinical and Experimental Research*. 2016 Jun;**40**(6):1192-1201. DOI: 10.1111/acer.13076
- [16] Soyka M, Müller CA. Pharmacotherapy of alcoholism—An update on approved and off-label medications. *Expert Opinion on Pharmacotherapy*. 2017;**18**(12):1187-1199. DOI: 10.1080/14656566.2017.1349098
- [17] Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 1995 Fall;**7**(4):524-533; discussion 523-4
- [18] Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology*. 2001;**25**(6):836-844
- [19] Mahar I, Bambico FR, Mechawar N, Nobrega JN. Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. *Neuroscience and Biobehavioral Reviews*. 2014;**38**:173-192. DOI: 10.1016/j.neubiorev.2013.11.009
- [20] Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, Mann JJ, et al. Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology*. 2009;**34**(11):2376-2389. DOI: 10.1038/npp.2009.75
- [21] Boldrini M, Hen R, Underwood MD, Rosoklija GB, Dwork AJ, Mann JJ, et al. Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. *Biological Psychiatry*. 2012;**72**(7):562-571. DOI: 10.1016/j.biopsych.2012.04.024
- [22] Boldrini M, Butt TH, Santiago AN, Tamir H, Dwork AJ, Rosoklija GB, et al. Benzodiazepines and the potential trophic effect of antidepressants on dentate gyrus cells in mood disorders. *The International Journal of Neuropsychopharmacology*. 2014;**17**(12):1923-1933. DOI: 10.1017/s1461145714000844
- [23] Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H, et al. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. *Neuropsychopharmacology*. 2013 May;**38**(6):1068-1077. DOI: 10.1038/npp.2013.5
- [24] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *The Journal of Neuroscience*. 2000;**20**(24):9104-9110
- [25] Kempermann G, Gage FH, Aigner L, Song H, Curtis MA, Thuret S, et al. Human adult neurogenesis: Evidence and remaining questions. *Cell Stem Cell*. 2018;**23**(1):25-30. DOI: 10.1016/j.stem.2018.04.004
- [26] Eliwa H, Belzung C, Surget A. Adult hippocampal neurogenesis: Is it the alpha and omega of antidepressant action? *Biochemical Pharmacology*. 2017;**141**:86-99. DOI: 10.1016/j.bcp.2017.08.005
- [27] Hershon HI. Alcohol withdrawal symptoms and drinking behavior. *Journal of Studies on Alcohol*. 1977;**38**(5):953-971
- [28] Koob GF. The dark side of emotion: The addiction perspective. *European Journal of Pharmacology*. 2015;**753**:73-87. DOI: 10.1016/j.ejphar.2014.11.044

- [29] Conner KR, Pinquart M, Gamble SA. Meta-analysis of depression and substance use among individuals with alcohol use disorders. *Journal of Substance Abuse Treatment*. 2009;**37**(2):127-137. DOI: 10.1016/j.josat.2008.11.007
- [30] Brennan PL, SooHoo S, Lemke S, Schutte KK. Alcohol use predicts 10-year depressive symptom trajectories in the health and retirement study. *Journal of Aging and Health*. 2016;**28**(5):911-932. DOI: 10.1177/0898264315615837
- [31] Skogen JC, Knudsen AK, Hysing M, Wold B, Sivertsen B. Trajectories of alcohol use and association with symptoms of depression from early to late adolescence: The Norwegian Longitudinal Health Behaviour Study. *Drug and Alcohol Review*. 2016;**35**(3):307-316. DOI: 10.1111/dar.12350
- [32] Foulds JA, Adamson SJ, Boden JM, Williman JA, Mulder RT. Depression in patients with alcohol use disorders: Systematic review and meta-analysis of outcomes for independent and substance-induced disorders. *Journal of Affective Disorders*. 2015;**185**:47-59. DOI: 10.1016/j.jad.2015.06.024
- [33] Brown RA, Ramsey SE, Kahler CW, Palm KM, Monti PM, Abrams D, et al. A randomized controlled trial of cognitive-behavioral treatment for depression versus relaxation training for alcohol-dependent individuals with elevated depressive symptoms. *Journal of Studies on Alcohol and Drugs*. 2011;**72**:286. DOI: 10.15288/jasad.2011.72.286
- [34] Foulds JA, Douglas Sellman J, Adamson SJ, Boden JM, Mulder RT, Joyce PR. Depression outcome in alcohol dependent patients: An evaluation of the role of independent and substance-induced depression and other predictors. *Journal of Affective Disorders*. 2015;**174**:503-510. DOI: 10.1016/j.jad.2014.11.052
- [35] Bahorik AL, Leibowitz A, Sterling SA, Travis A, Weisner C, Satre DD. The role of hazardous drinking reductions in predicting depression and anxiety symptom improvement among psychiatry patients: A longitudinal study. *Journal of Affective Disorders*. 2016;**206**:169-173. DOI: 10.1016/j.jad.2016.07.039
- [36] Getachew B, Hauser SR, Taylor RE, Tizabi Y. Desipramine blocks alcohol-induced anxiety- and depressive-like behaviors in two rat strains. *Pharmacology, Biochemistry, and Behavior*. 2008;**91**:97-103. DOI: 10.1016/j.pbb.2008.06.016
- [37] Stevenson JR, Schroeder JP, Nixon K, Besheer J, Crews FT, Hodge CW. Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. *Neuropsychopharmacology*. 2009;**34**:1209-1222. DOI: 10.1038/npp.2008.90
- [38] Ehlers CL, Liu W, Wills DN, Crews FT. Periadolescent ethanol vapor exposure persistently reduces measures of hippocampal neurogenesis that are associated with behavioral outcomes in adulthood. *Neuroscience*. 2013;**244**:1-15. DOI: 10.1016/j.neuroscience.2013.03.058
- [39] Warnock KT, Yang ARST, Yi HS, June HL, Kelly T, Basile AS, et al. Amitifadine, a triple monoamine uptake inhibitor, reduces binge drinking and negative affect in an animal model of co-occurring alcoholism and depression symptomatology. *Pharmacology Biochemistry and Behavior*. 2012;**103**(1):111-118. DOI: 10.1016/j.pbb.2012.07.014
- [40] Briones TL, Woods J. Chronic binge-like alcohol consumption in adolescence causes depression-like symptoms

- possibly mediated by the effects of BDNF on neurogenesis. *Neuroscience*. 2013;**254**:324-334. DOI: 10.1016/j.neuroscience.2013.09.031
- [41] Pang TY, Renoir T, Du X, Lawrence AJ, Hannan AJ. Depression-related behaviours displayed by female C57BL/6J mice during abstinence from chronic ethanol consumption are rescued by wheel-running. *The European Journal of Neuroscience*. 2013;**37**(11):1803-1810. DOI: 10.1111/ejn.12195
- [42] Holleran KM, Wilson HH, Fetterly TL, et al. Ketamine and MAG lipase inhibitor-dependent reversal of evolving depressive-like behavior during forced abstinence from alcohol drinking. *Neuropsychopharmacology*. 2016;**41**(8):2062-2071. DOI: 10.1038/npp.2016.3
- [43] Getachew B, Hauser SR, Csoka AB11, Taylor RE, Tizabi Y. Role of cortical alpha-2 adrenoceptors in alcohol withdrawal-induced depression and tricyclic antidepressants. *Drug and Alcohol Dependence*. 2017;**175**:133-139. DOI: 10.1016/j.drugalcdep.2017.03.004
- [44] Kim HJ, Park SD, Lee RM, Lee BH, Choi SH, Hwang SH, et al. Gintonin attenuates depressive-like behaviors associated with alcohol withdrawal in mice. *Journal of Affective Disorders*. 2017;**215**:23-29. DOI: 10.1016/j.jad.2017.03.026
- [45] Gong MF, Wen RT, Xu Y, Pan JC, Fei N, Zhou YM, et al. Attenuation of ethanol abstinence-induced anxiety- and depressive-like behavior by the phosphodiesterase-4 inhibitor rolipram in rodents. *Psychopharmacology*. 2017;**234**(20):3143-3151. DOI: 10.1007/s00213-017-4697-3
- [46] Vranjkovic O, Winkler G, Winder DG. Ketamine administration during a critical period after forced ethanol abstinence inhibits the development of time-dependent affective disturbances. *Neuropsychopharmacology*. 2018 Aug;**43**(9):1915-1923. DOI: 10.1038/s41386-018-0102-0
- [47] Lee KM, Coehlo MA, Solton NR, Szumlinski KK. Negative affect and excessive alcohol intake incubate during protracted withdrawal from binge-drinking in adolescent, but not adult mice. *Frontiers in Psychology*. 2017;**8**:1128. DOI: 10.3389/fpsyg.2017.01128
- [48] Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: A self-medication hypothesis. *Neuropsychopharmacology*. 1998;**18**(3):135-174
- [49] Durazzo TC, Meyerhoff DJ. Psychiatric, demographic, and brain morphological predictors of relapse after treatment for an alcohol use disorder. *Alcoholism, Clinical and Experimental Research*. 2016;**41**(1):107. DOI: 116. 10.1111/acer.13267
- [50] Milton AL, Everitt BJ. The psychological and neurochemical mechanisms of drug memory reconsolidation: Implications for the treatment of addiction. *The European Journal of Neuroscience*. 2010;**31**(12):2308-2319. DOI: 10.1111/j.1460-9568.2010.07249.x
- [51] Strowig AB. Relapse determinants reported by men treated for alcohol addiction: The prominence of depressed mood. *Journal of Substance Abuse Treatment*. 2000 Dec;**19**(4):469-474
- [52] Cengiz C, Devci A, Yapici A. Effects of depression on treatment motivation in male alcohol dependence. *Noro Psikiyatri Arsivi*. 2015;**52**(4): 412-416. DOI: 10.5152/npa.2015.9859
- [53] Holzhauer CG, Gamble SA. Depressive symptoms mediate the relationship between changes in

emotion regulation during treatment and abstinence among women with alcohol use disorders. *Psychology of Addictive Behaviors*. 2017;**31**(3): 284-294. DOI: 10.1037/adb0000274

[54] Suter M, Strik W, Moggi F. Depressive symptoms as a predictor of alcohol relapse after residential treatment programs for alcohol use disorder. *Journal of Substance Abuse Treatment*. 2011;**41**(3):225-232. DOI: 10.1016/j.jsat.2011.03.005

[55] Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? *Addiction Biology*. 2010;**15**(2):169-184. DOI: 10.1111/j.1369-1600.2009.00194.x

[56] Samet S, Fenton MC, Nunes E, Greenstein E, Aharonovich E, Hasin D. Effects of independent and substance-induced major depressive disorder on remission and relapse of alcohol, cocaine and heroin dependence. *Addiction*. 2012;**108**(1):115-123. DOI: 10.1111/j.1360-0443.2012.04010.x

[57] Ng E, Browne CJ, Samsom JN, AHC W. Depression and substance use comorbidity: What we have learned from animal studies. *The American Journal of Drug and Alcohol Abuse*. 2017;**43**(4):456-474. DOI: 10.1080/00952990.2016.1183020

[58] Riga D, Schmitz LJ, van der Harst JE, van Mourik Y, Hoogendijk WJ, Smit AB, et al. A sustained depressive state promotes a guanfacine reversible susceptibility to alcohol seeking in rats. *Neuropsychopharmacology*. 2014;**39**(5):1115-1124. DOI: 10.1038/npp.2013.311

[59] Le Maître TW, Dhanabalan G, Bogdanovic N, Alkass K, Druid H. Effects of alcohol abuse on proliferating cells, stem/progenitor cells, and immature neurons in

the adult human hippocampus. *Neuropsychopharmacology*. 2018;**43**(4):690-699. DOI: 10.1038/npp.2017.251

[60] Bayer R, Franke H, Ficker C, Richter M, Lessig R, Büttner A, et al. Alterations of neuronal precursor cells in stages of human adult neurogenesis in heroin addicts. *Drug and Alcohol Dependence*. 2015;**156**:139-149. DOI: 10.1016/j.drugalcdep.2015.09.005

[61] Wilson S, Bair JL, Thomas KM, Iacono WG. Problematic alcohol use and reduced hippocampal volume: A meta-analytic review. *Psychological Medicine*. 2017;**47**(13):2288-2301. DOI: 10.1017/S0033291717000721

[62] Staples MC, Mandym CD. Thinking after drinking: Impaired hippocampal-dependent cognition in human alcoholics and animal models of alcohol dependence. *Frontiers in Psychiatry*. 2016;**7**:162. DOI: 10.3389/fpsy.2016.00162

[63] Xu C, Loh HH, Law PY. Effects of addictive drugs on adult neural stem/progenitor cells. *Cellular and Molecular Life Sciences*. 2015;**73**(2):327-348. DOI: 10.1007/s00018-015-2067-z

[64] Nixon K, Kim DH, Potts EN, He J, Crews FT. Distinct cell proliferation events during abstinence after alcohol dependence: Microglia proliferation precedes neurogenesis. *Neurobiology of Disease*. 2008;**31**(2):218-229. DOI: 10.1016/j.nbd.2008.04.009

[65] Maynard ME, Leasure JL. Exercise enhances hippocampal recovery following binge ethanol exposure. *PLoS ONE*. 2013;**8**(9):e76644. DOI: 10.1371/journal.pone.0076644

[66] McClain JA, Morris SA, Marshall SA, Nixon K. Ectopic hippocampal neurogenesis in adolescent male rats following alcohol dependence.



Addiction Biology. 2013;**19**(4):687-699.  
DOI: 10.1111/adb.12075

2010;**107**(24):11104-11109. DOI:  
10.1073/pnas.0912810107

[67] Nickell CRG, Peng H, Hayes DM, Chen KY, McClain JA, Nixon K. Type 2 neural progenitor cell activation drives reactive neurogenesis after binge-like alcohol exposure in adolescent male rats. *Frontiers in Psychiatry*. 2017;**8**:283. DOI: 10.3389/fpsy.2017.00283

[73] Broadwater MA, Liu W, Crews FT, Spear LP. Persistent loss of hippocampal neurogenesis and increased cell death following adolescent, but not adult chronic ethanol exposure. *Developmental Neuroscience*. 2014;**36**(3-4):297-305. DOI: 10.1159/000362874

[68] Hayes DM, Nickell CG, Chen KY, McClain JA, Heath MM, Deeny MA, et al. Activation of neural stem cells from quiescence drives reactive hippocampal neurogenesis after alcohol dependence. *Neuropharmacology*. 2018;**133**:276-288. DOI: 10.1016/j.neuropharm.2018.01.032

[74] Vetreno RP, Crews FT. Binge ethanol exposure during adolescence leads to a persistent loss of neurogenesis in the dorsal and ventral hippocampus that is associated with impaired adult cognitive functioning. *Frontiers in Neuroscience*. 2015;**9**:35. DOI: 10.3389/fnins.2015.00035

[69] Hansson AC, Nixon K, Rimondini R, et al. Long-term suppression of forebrain neurogenesis and loss of neuronal progenitor cells following prolonged alcohol dependence in rats. *The International Journal of Neuropsychopharmacology*. 2010;**13**(5):583-593. DOI: 10.1017/S1461145710000246

[75] Morris SA, Eaves DW, Smith AR, Nixon K. Alcohol inhibition of neurogenesis: A mechanism of hippocampal neurodegeneration in an adolescent alcohol abuse model. *Hippocampus*. 2010;**20**(5):596-607. DOI: 10.1002/hipo.20665

[70] Crews FT, Mdzinarishvili A, Kim D, He J, Nixon K. Neurogenesis in adolescent brain is potently inhibited by ethanol. *Neuroscience*. 2006;**137**(2):437-445. DOI: 10.1016/j.neuroscience.2005.08.090

[76] Sakharkar AJ, Vetreno RP, Zhang H, Kokare DM, Crews FT, Pandey SC. A role for histone acetylation mechanisms in adolescent alcohol exposure-induced deficits in hippocampal brain-derived neurotrophic factor expression and neurogenesis markers in adulthood. *Brain Structure and Function*. 2016;**221**(9):4691-4703. DOI: 10.1007/s00429-016-1196-y

[71] Richardson HN, Chan SH, Crawford EF, Lee YK, Funk CK, Koob GF, et al. Permanent impairment of birth and survival of cortical and hippocampal proliferating cells following excessive drinking during alcohol dependence. *Neurobiology of Disease*. 2009;**36**(1):1-10. DOI: 10.1016/j.nbd.2009.05.021

[77] Vetreno RP, Lawrimore CJ, Rowsey PJ, Crews FT. Persistent adult neuroimmune activation and loss of hippocampal neurogenesis following adolescent ethanol exposure: Blockade by exercise and the anti-inflammatory drug indomethacin. *Frontiers in Neuroscience*. 2018;**12**. DOI: 10.3389/fnins.2018.00200

[72] Taffe MA, Kotzebue RW, Crean RD, Crawford EF, Edwards S, Mandyam CD. Long-lasting reduction in hippocampal neurogenesis by alcohol consumption in adolescent nonhuman primates. *Proceedings of the National Academy of Sciences*.

[78] Somkuwar SS, Fannon MJ, Staples MC, Zamora-Martinez ER, Navarro AI, Kim A, et al. Alcohol

dependence-induced regulation of the proliferation and survival of adult brain progenitors is associated with altered BDNF-TrkB signaling. *Brain Structure & Function*. 2016;**221**(9):4319-4335. DOI: 10.1007/s00429-015-1163-z

[79] Liu W, Crews FT. Persistent decreases in adult subventricular and hippocampal neurogenesis following adolescent intermittent ethanol exposure. *Frontiers in Behavioral Neuroscience*. 2017;**11**:151. DOI: 10.3389/fnbeh.2017.00151

[80] Kutlu MG, Gould TJ. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: Contributions to development and maintenance of addiction. *Learning & Memory*. 2016;**23**(10):515-533. DOI: 10.1101/lm.042192.116

[81] Canales JJ. Deficient plasticity in the hippocampus and the spiral of addiction: Focus on adult neurogenesis. *Current Topics in Behavioral Neurosciences*. 2013;**15**:293-312. DOI: 10.1007/7854\_2012\_230

[82] Cui C, Noronha A, Warren K, Koob GF, Sinha R, Thakkar M, et al. Brain pathways to recovery from alcohol dependence. *Alcohol (Fayetteville, N.Y.)*. 2015;**49**(5):435-452. DOI: 10.1016/j.alcohol.2015.04.006

[83] Kühn S, Charlet K, Schubert F, Kiefer F, Zimmermann P, Heinz A, et al. Plasticity of hippocampal subfield volume cornu ammonis 2+3 over the course of withdrawal in patients with alcohol dependence. *JAMA Psychiatry*. 2014;**71**(7):806-811. DOI: 10.1001/jamapsychiatry.2014.352

[84] Gross CM, Spiegelhalter K, Mercak J, Feige B, Langosch JM. Predictability of alcohol relapse by hippocampal volumetry and psychometric variables. *Psychiatry Research*. 2013;**212**(1):14-18. DOI: 10.1016/j.psychres.2012.09.011

[85] Danovitch I, Steiner AJ, Kazdan A, Goldenberg M, Haglund M, Mirocha J, et al. Analysis of patient-reported outcomes of quality of life and functioning before and after treatment of major depressive disorder comorbid with alcohol use disorders. *Journal of Addiction Medicine*. 2017;**11**(1):47-54. DOI: 10.1097/adm.0000000000000268

[86] Davis LL, Wisniewski SR, Howland RH, Trivedi MH, Husain MM, Fava M, et al. Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? An analysis of the STAR\*D level one treatment outcomes. *Drug and Alcohol Dependence*. 2010;**107**(2-3):161-170. DOI: 10.1016/j.drugalcdep.2009.10.003

[87] Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. *JAMA*. 2004;**291**(15):1887-1896. DOI: 10.1001/jama.291.15.1887

[88] Iovieno N, Tedeschini E, Bentley KH, Evins AE, Papakostas GI. Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: A meta-analysis of placebo-controlled randomized trials. *The Journal of Clinical Psychiatry*. 2011;**72**(8):1144-1151. DOI: 10.4088/JCP.10m06217

[89] Zhou X, Qin B, Del Giovane C, Pan J, Gentile S, Liu Y, et al. Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders: A systematic review and meta-analysis. *Addiction*. 2015;**110**(1):38-48. DOI: 10.1111/add.12698.10

[90] Torrens M, Fonseca F, Mateu G, Farré M. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug and Alcohol Dependence*.

2005;78(1):1-22. DOI: 10.1016/j.drugalcdep.2004.09.004

[91] Cornelius J, Chung T, Douaihy A, Kirisci L, Gance J, Kmiec J, et al. A review of the literature of mirtazapine in co-occurring depression and an alcohol use disorder. *Journal of Addictive Behaviors, Therapy & Rehabilitation*. 2016;5(4):159. DOI: 10.4172/2324-9005.1000159

[92] Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database of Systematic Reviews*. 2018;4. Art. No.: CD008581. DOI: 10.1002/14651858.CD008581.pub2

[93] Nunes EV, Levin FR. Treatment of co-occurring depression and substance dependence: Using meta-analysis to guide clinical recommendations. *Psychiatric Annals*. 2008;38(11)

[94] Belmer A, Patkar OL, Pitman KM, Bartlett SE. Serotonergic neuroplasticity in alcohol addiction. *Brain Plasticity*. 2016;1(2):177-206. DOI: 10.3233/BPL-150022

[95] Hill AS, Sahay A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors. *Neuropsychopharmacology*. 2015;40(10):2368-2378. DOI: 10.1038/npp.2015.85

[96] Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Molecular Psychiatry*. 2009;14(8):764-773. DOI: 10.1038/mp.2008.119

[97] Mateus-Pinheiro A, Pinto L, Bessa JM, Morais M, Alves ND, Monteiro S, et al. Sustained remission from depressive-like

behavior depends on hippocampal neurogenesis. *Translational Psychiatry*. 2013;3(1):e210. DOI: 10.1038/tp.2012.141

[98] Graham K, Massak A. Alcohol consumption and the use of antidepressants. *CMAJ*. 2007;176(5):633-637. DOI: 10.1503/cmaj.060446

[99] Mann K. Pharmacotherapy of alcohol dependence: A review of the clinical data. *CNS Drugs*. 2004;18(8):485-504. DOI: 10.2165/00023210-200418080-00002

[100] Charney DA, Heath LM, Zikos E, Palacios-Boix J, Gill KJ. Poorer drinking outcomes with citalopram treatment for alcohol dependence: A randomized, double-blind, placebo-controlled trial. *Alcoholism, Clinical and Experimental Research*. 2015;39(9):1756-1765. DOI: 10.1111/acer.12802

[101] Chick J, Aschauer H, Hornik K. Efficacy of fluvoxamine in preventing relapse in alcohol dependence: A one-year, double-blind, placebo-controlled multicentre study with analysis by typology. *Drug and Alcohol Dependence*. 2004;74(1):61-70. DOI: 10.1016/j.drugalcdep.2003.11.012

[102] Dundon W, Lynch KG, Pettinati HM, Lipkin C. Treatment outcomes in type A and B alcohol dependence 6 months after serotonergic pharmacotherapy. *Alcoholism: Clinical and Experimental Research*. 2004;28:1065-1073. DOI: 10.1097/01.alc.0000130974.50563.04

[103] Atigari OV, Kelly AM, Jabeen Q, Healy D. New onset alcohol dependence linked to treatment with selective serotonin reuptake inhibitors. *The International Journal of Risk & Safety in Medicine*. 2013;25(105-109). DOI: 10.3233/JRS-130586

- [104] Brookwell L, Hogana C, Healya D, Manginb D. Ninety-three cases of alcohol dependence following SSRI treatment. *The International Journal of Risk & Safety in Medicine*. 2014;**26**: 99-107. DOI: 10.3233/JRS-140616
- [105] Menkes DB, Herxheimer A. Interaction between antidepressants and alcohol: Signal amplification by multiple case reports. *The International Journal of Risk & Safety in Medicine*. 2014;**26**(3):163-170. DOI: 10.3233/JRS-140632
- [106] Gimeno C, Dorado ML, Roncero C, Szerman N, Vega P, Balanzá-Martínez V, et al. Treatment of comorbid alcohol dependence and anxiety disorder: Review of the scientific evidence and recommendations for treatment. *Frontiers in Psychiatry*. 2017;**8**:173. DOI: 10.3389/fpsy.2017.00173
- [107] Barajaz AM, Kliethermes CL. An assessment of the utilization of the preclinical rodent model literature in clinical trials of putative therapeutics for the treatment of alcohol use disorders. *Drug and Alcohol Dependence*. 2017;**181**:77-84. DOI: 10.1016/j.drugalcdep.2017.09.022
- [108] Simon O'Brien E, Legastelois R, Houchi H, Vilpoux C, Alaux-Cantin S, Pierrefiche O, et al. Fluoxetine, desipramine, and the dual antidepressant milnacipran reduce alcohol self-administration and/or relapse in dependent rats. *Neuropsychopharmacology*. 2011;**36**: 1518-1530. DOI: 10.1038/npp.2011.37
- [109] Bell RL, Hauser SR, Liang T, Sari Y, Maldonado-Devincci A, Rodd ZA. Rat animal models for screening medications to treat alcohol use disorders. *Neuropharmacology*. 2017;**122**:201-243. DOI: 10.1016/j.neuropharm.2017.02.004
- [110] Ho AMC, Qiu Y, Jia YF, Aguiar FS, Hinton DJ, Karpyak VM, et al. Combined effects of acamprosate and escitalopram on ethanol consumption in mice. *Alcoholism, Clinical and Experimental Research*. 2016;**40**(7):1531-1539. DOI: 10.1111/acer.13099
- [111] Gulley JM, McNamara C, Barbera TJ, Ritz MC, George FR. Selective serotonin reuptake inhibitors: Effects of chronic treatment on ethanol-reinforced behavior in mice. *Alcohol*. 1995;**12**(3):177-181. DOI: 10.1016/0741-8329(94)00079-s
- [112] Skelly MJ, Weiner JL. Chronic treatment with prazosin or duloxetine lessens concurrent anxiety-like behavior and alcohol intake: Evidence of disrupted noradrenergic signaling in anxiety-related alcohol use. *Brain and Behavior*. 2014;**4**(4):468-483. DOI: 10.1002/brb3.230
- [113] Alén F, Orio L, Gorriti MA, de Heras RG, Ramírez-López MT, Pozo MA, et al. Increased alcohol consumption in rats after subchronic antidepressant treatment. *The International Journal of Neuropsychopharmacology*. 2013;**16**:1809-1818. DOI: 10.1017/s1461145713000217
- [114] Alén F, Serrano A, Gorriti MÁ, Pavón FJ, Orio L, de Heras RG, et al. The administration of atomoxetine during alcohol deprivation induces a time-limited increase in alcohol consumption after relapse. *The International Journal of Neuropsychopharmacology*. 2014;**17**(11):1905-1910. DOI: 10.1017/s146114571400087x