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,

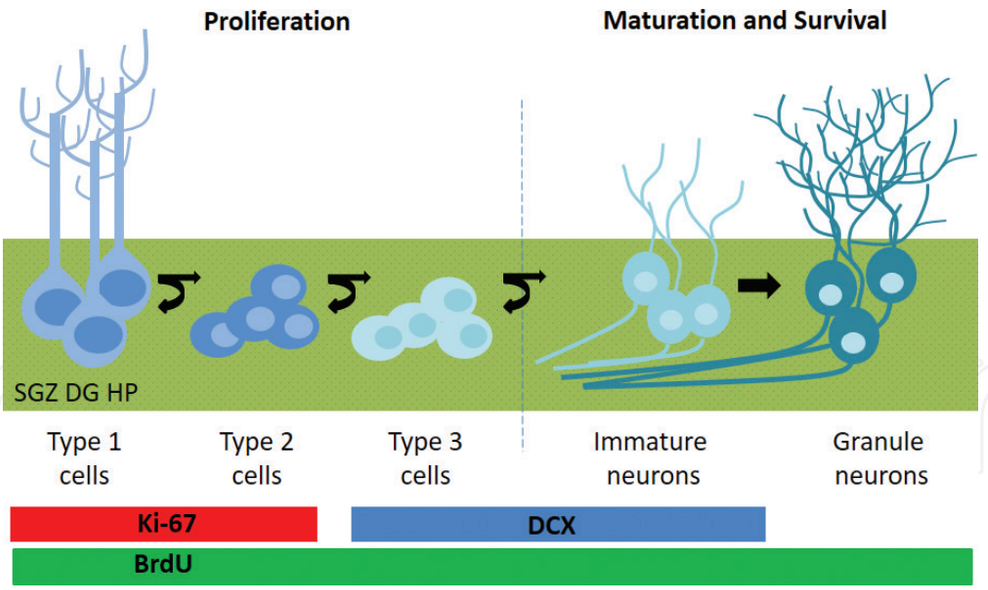

Figure 1.
Schematic representation of the stages of adult hippocampal neurogenesis in the subgranular zone of the dentate gyrus and the main immunolabeling techniques used in the cited studies.

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-rectifying 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 NH 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

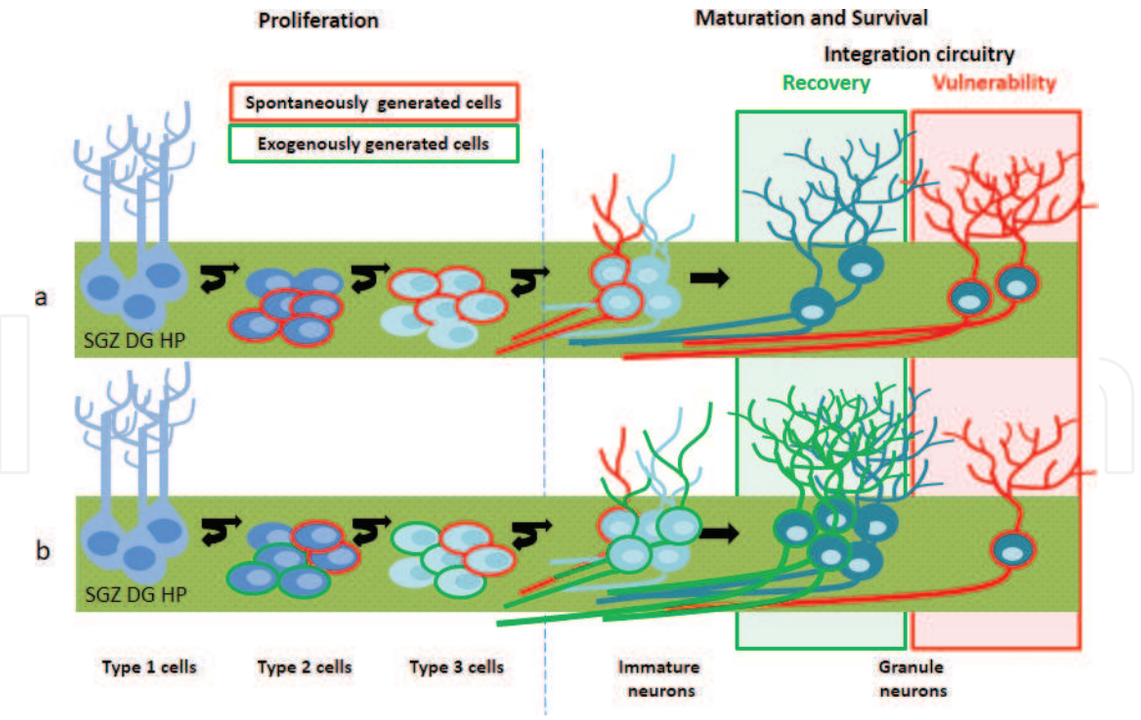

Figure 2.
(a) Schematic representation of the adult HN along alcohol withdrawal and abstinence. Spontaneous burst in cell proliferation is followed by a lower survivability and aberrant patterns of cell migration and integration of the newly generated neurons which could contribute to vulnerability related 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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