

Review

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Review

Psilocybin in Alcohol Use Disorder Maintains Abstinence Efficacy: A Scoping Review

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Abstract

Alcohol use disorder is a psychiatric condition characterized by excessive alcohol consumption. The drugs that are used to treat it often fail to prevent relapse. At the same time, psilocybin is increasingly being investigated for the treatment of various substance use disorder. This review aims to evaluate the results of the most recent clinical trials assessing psilocybin as a treatment for alcohol use disorder. According to these trials, psilocybin seems to reduce craving but its effect on overall alcohol consumption is less clear. There is no doubt that future trials would benefit from larger sample sizes and standardized tests.

Keywords: psilocybin; alcohol use disorder; clinical trials

Introduction

Alcohol use disorder (AUD) is a psychiatric condition characterized by excessive alcohol consumption. Patients are often caught in a cycle of abstinence (no alcohol at all) and relapse (defined as the consumption of at least 1 standard unit, i.e. 1 SU, corresponding to 14 g of ethanol). They also frequently experience heavy drinking days (at least 5 SU daily for men and 4 SU for women).[1]

In addition to psychotherapeutic intervention, AUD is treated by naltrexone or acamprosate. However, these drugs often fail to prevent relapse. Moreover, they may cause numerous adverse effects, such as somnolence. It is therefore crucial to consider alternative treatments.[2]

At the same time, psychedelics are increasingly being investigated for the treatment of various substance use disorders, since the involved mechanisms should be able to potentialize psychotherapy.[3] More precisely, psilocybin is a molecule that acts on the serotonin 5-HT_{2A} receptor among others. Although psilocybin has been prohibited in the United States of America for decades, the US Food and Drug Administration has recently designated it as breakthrough therapy.[4] It therefore makes sense to test psilocybin on patients suffering from AUD, as it could represent a more efficient and reliable treatment than those currently used.[5]

Psychedelics are very well known molecules that have been used for millennia for medical or recreational purposes. The magic mushrooms from which psychedelics are extracted were traditionally absorbed by South-American peoples. This triggered the interest of Europeans at the end of the 19. Century. In 1998, Dr. Heffter finally discovered a psychedelic active substance and named it mescaline.[6]

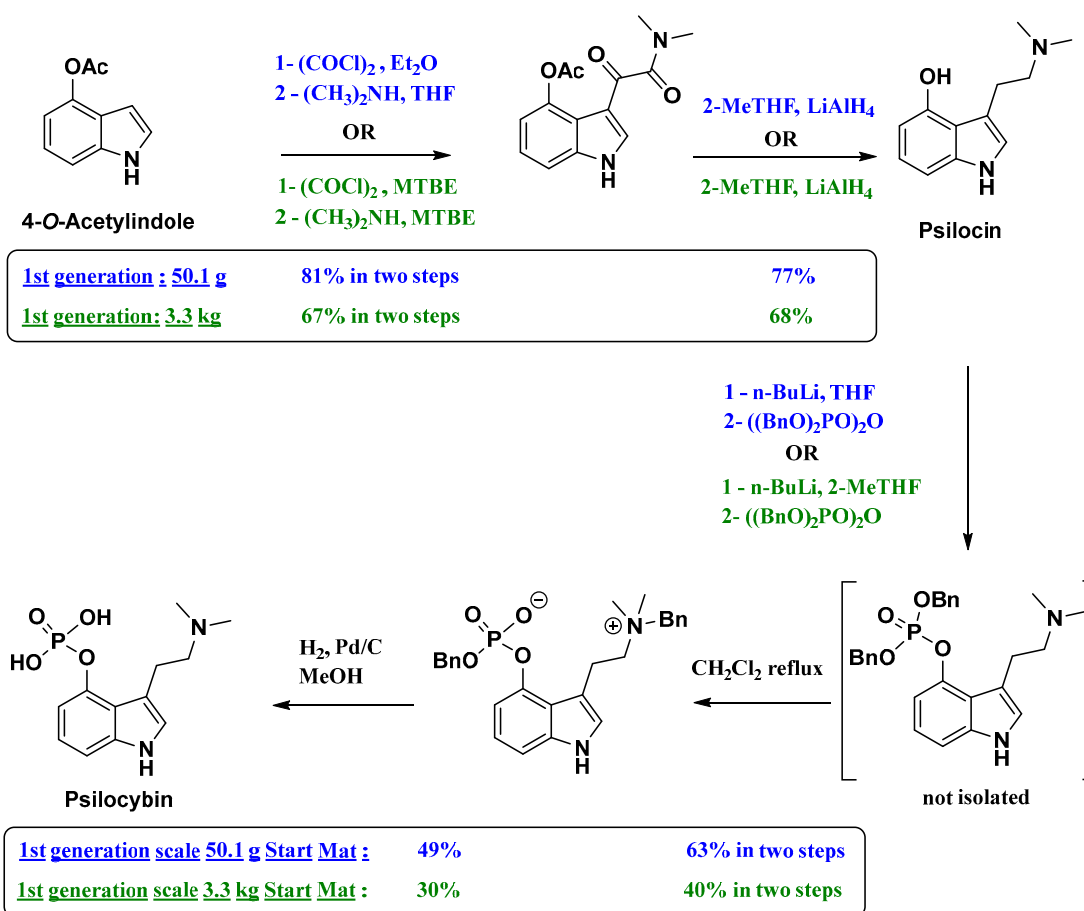
The effects of such molecules were then analysed as psychosis-like. Interestingly, psychedelics were not yet used as pharmaceutical agents, but they were rather viewed as tools to better understand the basis for psychiatric disorders. The powerful therapeutical potential of psychedelics became much more tangible when lysergic acid diethylamide (LSD) was discovered in 1943.[7]

LSD, together with psilocybin, began to be prescribed as part of the treatment of mood or alcohol use disorders. When associated with psychotherapy, these drugs were promising good results. However, the prohibitive legislature held science to a standstill. It was only after 1990 that psychedelics were studied again. Nowadays, they may become valuable tools in the treatment of various psychiatric disease, such as depression or AUD.[8]

First of all, synthetic pathways to psilocybin will be summarised. Then, this review aims to evaluate the results of the most recent clinical trials assessing psilocybin as a treatment for AUD. Ongoing trials will also be discussed and insights will be provided into the next steps of clinical research.[9]

Synthetic Pathways to Psilocybin

There are several ways to obtain psilocybin, including extraction and synthesis. Given the relatively low levels present in various sources, particularly mushrooms of the *Psilocybe* family, extraction is an inappropriate method to implement, particularly in terms of biodisponibility and analytic procedure for medical use.[10] In order to obtain sufficient quantities to carry out all biological studies, chemical synthesis of the compound appears to be a good alternative.[11] There are also various clinical studies to be conducted depending on the desired action, which in our case is the effect on alcohol dependence. These clinical studies consume a considerable amount of product, as the appropriate dosage must be measured to obtain the required therapeutic effect. Pharmacokinetics studies and bioavailability based on the absorption processes of the two compounds, the prodrug (psilocybin) and its active ingredient (psilocin), should also be considered. They therefore need to be obtained through a method that is applicable on a large scale, inexpensive, compatible with industrial processes, and, even better to limit the purification steps that generate the most atomic loss for sustainability reasons. Two years ago, we reviewed the various synthetic routes to psilocybin and its active precursor, psilocin[12]. However, here we will focus our description on Hofmann's initial method from 1959 for the pharmaceutical industry[13–15], a process that has improved considerably since then. It starts with a properly functionalized indole nucleus, to which the dimethylethylamine chain is incorporated in three steps, and then the six-membered aromatic center is functionalized. Following this work, improvements were made at the experimental level by Nichols et al.[16] at the end of the last century to achieve more efficient conditions. Shirota et al.[17] then made further improvements to enable the synthesis to be scaled up to the gram level. Currently, the most effective method for obtaining these compounds is that described in 2020 by Sherwood et al.[18,19], which allows work on a several hundred grams scale. It is easy to implement, can be carried out using commercially available products, and uses sustainable purification methods (Scheme 1). In fact, no purification by chromatographic column is used. The method is so effective that purification is achieved by simple filtration and/or recrystallization, yielding the desired products with very good yields compared to other methods. For the first generation, although reliable and easily scalable from milligram to kilogram batches, this chemical synthesis approach requires large amounts of solvents. The method had to be adapted in terms of solvents in some steps (Scheme 1). A second generation[19] was developed to avoid the use of tetra-benzyl pyrophosphate (TBPP), which is far too expensive to work with in very large quantities. The latter was effectively replaced by phosphorus oxychloride (POCl₃), resulting in 1.2 kg of psilocybin from 6.9 kg of 4-*O*-acetylindole. It should be noted that an interesting biocatalytic approach was proposed by some of the same authors in 2020[20], allowing the compounds to be obtained with higher yields and in a more sustainable manner. This method, starting from 4-hydroxytryptamine, does not require the use of palladium. However, in this case, studies still need to be conducted for large-scale production.



Scheme 1. Sherwood's psilocin and psilocybin synthesis.

Objectives

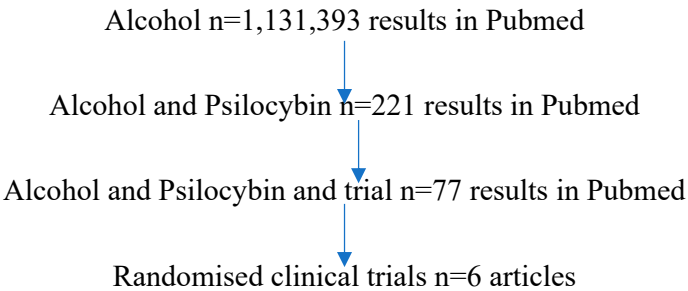
To address the gap between the need for an efficient treatment against AUD and the currently available medication, the present scoping review aimed to systematically map the clinical research on psilocybin as a treatment for AUD. In doing so, it sought to identify existing knowledge gaps in this field and provide insights to guide future clinical investigations.

Materials and Methods

Data Sources and Search Strategy

To identify potentially relevant documents, the bibliographic database Pubmed was searched between 2002 and June 2025. Any peer-reviewed journal articles were included if they were published between 2002 and June 2025 in the English language and if they described a randomised clinical trial focused specifically on psilocybin effect in the cure of AUD.

The initial PubMed search yielded over 1.1 million results for alcohol. Adding psilocybin reduced this number to 221. Further restriction to clinical trials resulted in 77 articles. Finally, only 6 randomized clinical trials met the inclusion criteria.



Scheme 2. : Screening method.

Next the database clinicaltrials.gov was searched up to June 2025 to identify ongoing clinical trials with similar features to those already stated.

Articles were excluded if they did not fit into the conceptual framework of the study.

Inclusion and Exclusion Criteria

Peer-reviewed journal articles were included if they were published before June 2025 in the English language, described a randomised clinical trial and focused specifically on psilocybin effect in the cure of AUD. Articles studying AUD in conjunction with another psychiatric disease were also included. Articles were excluded if they did not fit into the conceptual framework of the study. This study has not received any funding.

Results

Study Selection

In this exploratory study, we identified 77 articles in which a trial involving psilocybin and alcohol was described. A total of 6 articles were ultimately selected, as they were the only ones to report a randomised clinical trial.

Psilocybin and AUD

1. Psilocybin and alcohol consumption

One of the main methods to assess the evolution of AUD is alcohol consumption, which can be measured on different scales. Among these, the percentage of heavy drinking days (PHDD) is the most often used, thanks to its reliability. Since alcohol consumption is typically assessed through patients' self-reports, PHDD appears simpler than other scales such as percentage of drinking days (PDD) or mean drinks per day (DPD), which are more difficult to apply.[5] Indeed, patients find it hard to recall exactly how many drinks they had, or during how many days they consumed.

For an even more reliable method, the number of abstinence days can be considered. This measure is easy to report and can be validated by quantifying ethylglucuronide in biological samples.[2] However, it is important to note that the cost of this test remains the main source of concern for its implementation in routine practice.[21] Therefore, it is mostly used in research.

Unfortunately, each clinical trial has its own design which sometimes leads to opposite conclusions. For instance, Bogenschutz et al. shows a decrease in PHDD among patients treated with psilocybin compared to diphenhydramine.[5] However, other trials have not observed similar effects.[2,22] Besides, even Bogenschutz et al. did not find any significant difference in PDD. Interestingly, diphenhydramine is an antagonist of the histamine H₁ receptor, which makes the comparison with psilocybin more difficult.[23] Indeed the latter is a serotonin agonist.

If Bogenschutz' results are reliable, psilocybin could help the patients not to drink less frequently (PDD), but to experience heavy drinking less frequently (PHDD). The difference is important to note as it is not sufficient for patients suffering of AUD to stop their heavy drinking sessions. The ultimate goal is to solve any problematic pattern of alcohol use, as well as clinically significant impairment which are caused by it.[24]

Perhaps, the structural differences among these clinical trials are sufficient to account for these discrepancies. In this case, it would be legitimate to explore more sensible methods. Indeed, psilocybin may induce a mild decrease in alcohol consumption, such as PHDD would fail to account for it. As a matter of fact, even PDD and DPD may not be the best way to assess AUD.

It is interesting to note the method used by Luquiens et al., which appears to be more complete.[25] The Alcohol Timeline Followback (TLFB) combines the number of heavy drinking days (easily related to PHDD), the number of drinking days (similarly related to PDD), the total alcohol intake (which is most probably quite difficult to be reliably filled in by patients), the percentage of participants who relapsed and the time to relapse. Importantly, relapse is here defined by at least one heavy drinking day. This is questionable, as abstinence corresponds to no drinking at all. Therefore, it is possible that a patient is no longer abstinent but has not experienced relapse.

In the particular trial of Luquiens et al. [25], there seems to exist an increase in the number of abstinent patients treated with psilocybin as well as a decrease in the number of drinking days of these same patients. However, as opposed to Bogenschutz et al.[5], no significant evolution of heavy drinking days was detected. All those measurement scales do often differ and should always be put in comparison one to another.

2. Psilocybin and craving

One could argue that alcohol consumption depends not only on the patient's AUD, but also on external factors, such as the availability of alcohol at home or an eventual familial influence. Therefore, the effect of psilocybin should be more evident on the patient's strong desire to drink, also known as craving.

Yet again, craving can be assessed by using different methods, such as Penn Alcohol Craving Scale (PACS). It is also possible to use the Short Index of Problems. Incidentally, the latter is also designed for drugs. In both cases, the patient answers questions regarding his desire to drink and the consequences of it. More recently, new questionnaires specifically designed to assess craving for alcohol have been developed.[26] Although they have not yet been used in clinical trials with psilocybin, it would be interesting to determine if they yield novel results.

For instance, the Craving Experience Questionnaire (CEQ) takes into account both intensity and frequency of craving. It is also designed for other addictive substances. Nevertheless, this questionnaire fails to report for AUD consequences on everyday life. This important aspect of the disease is dealt with through the Alcohol Quality of Life Scale (AQoLS). The seven dimensions assessed are : social relationships, activities, living conditions, self-care, negative emotions, sleep and loss of control. Thus a wide vision of the patient's illness is described.[25]

From this angle, results appear more favourable to psilocybin. With the exception of Pagni et al.,[22] psilocybin has been shown to reduce craving.[2,5,25] It is thus possible that the lack of significance when assessing PHDD is due to external factors, that do not impact craving.

If psilocybin were indeed able to reduce craving, it could be used against AUD in adjunction to another treatment, since it appears unable to reduce alcohol consumption in itself. A radical lifestyle change would be necessary to recover from AUD, but psilocybin could definitely help patients to control their craving.[27]

Nevertheless, the strong biases inherent to patients' self-report make this aspect of the study somewhat unreliable. Obviously, some patients tend to minimize their alcohol consumption, whereas others could behave the opposite way, by exaggerating the amount of alcohol they drink. More objective methods of assessing the effects of psilocybin in AUD are missing and are of strong interest.

3. Other targets of psilocybin

Alternatively, it is possible to measure outcomes other than alcohol consumption or craving. As AUD remains the disease of interest, these additional factors will ultimately need to be compared with alcohol consumption. Nonetheless, they can bring valuable information about the psychiatric mechanisms of AUD.

Personality has been assessed by common standard surveys to determine if psilocybin might be associated with particular personality changes. Some changes in personality traits have been detected, such as decreased neuroticism or increased extraversion in the psilocybin group. However, due to the heterogeneity of the tests used, the results of clinical trials are difficult to compare.[28,29]

Moreover, a link between personality change and alcohol consumption has only been established by Pagni et al.[28] Gold et al. also tested for such a correlation but were not in fact able to reproduce these results. [29] This suggests that AUD cannot be described only from a personality perspective.

Finally, functional MRI (fMRI) was used once by Pagni et al. in order to visualise the effects of psilocybin on the brain responses to alcohol-related stimuli. This was made possible by blood-oxygen-level (BOLD) contrast, a method based on the fact that the most stimulated brain regions consume more oxygen than others. Concretely Pagni et al. presented patients with positive, negative and alcohol-related stimuli. Next, they tested whether there was any change after psilocybin adjunction. Although not strictly related to AUD, results performed on alcohol-related stimuli indicated that psilocybin seems to have an impact on the oxygen consumption of some brain regions (for instance the left superior medial prefrontal cortex[22] Nonetheless, fMRI has also been applied in the study of other diseases so it could be a good way of proceeding forward in the physio pathological study of AUD.[30]

If we could understand exactly which brain regions are the most importantly altered in AUD, we could search for a more specific treatment. A molecule that could target a particular psychiatric mechanism would be administered at higher dose without fear of adverse effects on other brain functions.[31]

Adverse Effects of Psilocybin

As people were consuming high doses of so-called magic mushrooms, meaning psilocybin, they were losing every sense of reality. They were starting to believe that they were gifted with superpowers, for example the ability to fly. Next they died of defenestration as a consequence of these psychedelic effects. The main danger of using psilocybin is also indirect but of great significance. Fortunately, it appears at higher dose than the ones used in clinical trials.[32]

Aside from two cases of dizziness,[25] adverse effects significantly associated with psilocybin comparatively to placebo have not been reported in the aforementioned trials.[2,5,22,28,29] This means that either there was none or they were as frequent in the psilocybin group as in the placebo group. So far, it is reasonable to conclude that psilocybin does not induce psychedelic effects at clinically tested doses (25mg/70kg). Indeed, this conclusion is of great importance since it is precisely those adverse effects that prevented for years the therapeutical use of psilocybin.

Discussion

Although new trials would benefit from larger sample sizes, other aspects of study design should be improved such as :

- Sample reliability

Patients should be recruited with particular attention granted to their AUD condition. For instance, the average PHDD of included patients should not differ from that typically observed in AUD populations.[2] Indeed it is possible that it exists a correlation between the PHDD prior to treatment and the efficient psilocybin dose. Although this hypothesis has not been clinically tested, it certainly deserves to be considered, as its reliability has been shown in rats.[33]

It is true that due to psilocybin's peculiar history (its prohibition for years), it seems tempting to proceed particularly fast in order to compensate for all those years. Perhaps this is why we see so many clinical trials at the moment. This is no bad thing *per se*, however preclinical trials should definitely be taken into account.

Firstly, psychedelic experimentation on animals has not been slowed down by legislation. Unsurprisingly, it was known since 2018 that psychedelics reduced alcohol consumption.[34] Interestingly, the aforementioned study had used LSD, which may be the most known psychedelic. A comparison between this molecule and psilocybin could very well bring valuable information about the strengths and weaknesses of these two potential therapies.

Secondly, limitation of psychedelic treatment of AUD can also be inferred from preclinical studies. As clinical studies on the long term are quite expensive, psilocybin's effects after a substantial amount of time were only assessed in animals. Notably, psilocybin did not have any long-lasting effects in rat models of alcohol relapse (neither did LSD, for that matter).[35] Thus, it is to be expected that future clinical long-term studies on psilocybin produce mitigated results.

- Efficient control

It is essential that patients receive either psilocybin or an active control, such as diphenhydramine. Nonetheless, this compound has failed to ensure adequate blinding. As patients have been able to guess which treatment they were given, study results have been biased by patients' expectations. Therefore, another agent should be considered as a control.[5] In the context of a feasibility study, Luquiens et al. have used a 1 mg psilocybin dose as a control.[25] At such a low amount, it is doubtful whether this control can be considered as something else as a placebo. It does bring valuable information on psilocybin's potential adverse effects, though.

Interestingly, a 1 mg psilocybin dose had already be tested as a control by Griffiths et al. against depression and anxiety in the context of cancer.[36] Apparently, the conclusion was reached that such a dose could still ignite pharmacological effects. It was therefore proposed that an even smaller dose of 0,01 mg of psilocybin should be administrated. Although this piece of advice has not been followed by Luquiens et al., it could be tested in future trials.

Another possibility for control is methylphenidate. Although its mechanism is different from psilocybin's, it does cause similar effects, such as excitability or increased positive mood. Additionally, in another clinical trial by Griffiths et al., the primary monitor was not able to guess that this definite molecule had been administered. Thus, despite its differences with psilocybin, methylphenidate can also be a decent control drug.[37]

Aside from the three last proposals (1 mg psilocybin, 0,01 mg psilocybin and methylphenidate), it must be said that we are still far from the perfect control molecule. Whether it is diphenhydramine

or niacin,[38] the limited binding remains a severely weak point of clinical trial design. Solving such a problem is capital if one wishes to proceed with trials on bigger scales.

- Normalised tests

The large variety of measurement scales currently in use makes it difficult to compare results across trials. Even alcohol consumption is not consistently measured, let alone craving. Notably, in a trial about current treatment of AUD, up to six alcohol consumption scales were used. They were abstinence, absence of heavy drinking days, abstinence days, PHDD, DPD and drinks per drinking day.[39] This makes the interpretation of results far more difficult, as a treatment can often lead to a significative difference on one scale and not on another one. Overall, DPD is the most precise scale and should be favoured whenever possible,[28] although PHDD should also be checked in every trial.

Even if all these parameters were corrected, clinical trials would still need to enroll a lot more patients than in the previous ones. Those trials were indeed pilot studies, which included up to 100 patients from a single country each time. For psilocybin to obtain a marketing authorisation, phase I clinical trials are needed, with many patients from various countries.

The situation was more or less the same some 25 years ago, when the efficacy of β -blockers in the treatment of chronic heart failure (CHF) was evaluated. After a first Cardiac Insufficiency Bisoprolol Study (CIBIS) trial, a CIBIS-2 trial was conducted.[40] It included 2647 patients from 18 European countries.[41,42]

This led to another study, CIBIS-3, with decreased dimensions but increased diversity among patients : 1010 people from 18 European countries, Australia and Tunisia. Again, bisoprolol proved to be a viable treatment for CHF. Nowadays, it has obtained marketing authorisation in the context of this disease and has become a reliable medication.[43,44]

Nevertheless, in such large studies, a particular attention should be given to disparities arising between the different groups. For instance, in the context of psilocybin in the treatment of AUD, Pagni et al. conducted a clinical trial which included two different hospitals, but both in the US.[28] Even though they had only 84 patients, they had to take into account some rural-urban differences in personality traits.[45] Therefore, many more precautions will have to be taken as the number and diversity of included patients increase.

Such phase I clinical trials are thus the next step on psilocybin's path to marketing authorisation. If results are shown to be consistent and if no new adverse effect is observed, psilocybin could become a first-line medication. The currently unsatisfactory situation of AUD treatment is another argument to accelerate this process, which is known to take many years.

Perspectives

Ongoing trials are currently being conducted, and the scientific community looks forward to the upcoming new results. PHDD is often used as the primary outcome measure but fMRI is becoming more and more employed.

New clinical trials are also introducing novel approaches, particularly regarding the dosage of psilocybin administered. To observe more striking effects, psilocybin doses have been increased to 30 mg, or even 50 mg (i.e. 2x25 mg).

Finally, psilocybin is also being compared with another drug known for its adverse effects, ketamine. This comparison is particularly relevant since ketamine, although effective, is associated with dissociative and cardiovascular adverse effects. Therefore, while efficacy remains the primary outcome measure, a special attention is devoted to adverse effects.

Conclusions

In conclusion, evidence to date remains insufficient to establish psilocybin as a viable treatment for AUD. Among all studies conducted on this subject, we were only able to cite 6 controlled

randomised trials. Studies which would include more patients should be able to demonstrate psilocybin’s clinical benefits.

On the other hand, psilocybin does not appear to cause significant adverse effects, including hallucinations at the tested dosages, which alleviates concerns regarding its clinical development.

Consequently, ongoing and future clinical trials should provide valuable insights into the efficacy and mechanisms of psilocybin. It must also be emphasized that AUD remains inadequately treated, despite its considerable impact on public health and the urgent need for more effective interventions.

Appendix A. PHDD

PHDD measurements only requires for the patients to write down the days where they have drunk more than 5 SU (4 for women). On the one hand, this method is easy to use as patients only have to recall when they have drunk so much. On the other hand, it is not very precise : to drink 6 SU is not the same as to drink 12 SU. Besides, it fails to point out mild chronic alcohol use disorders, i.e. a patient who would drink 4 SU every day.

Appendix B. Completed Clinical Trials

Table 1. Overview of the completed clinical trials.

Study	Year	n	Substance	Dose	Gender (% women)	Age (mean; SD)	Main Outcome	Adverse Events
Bogenschutz et al.	2022	93	psilocybin	25 mg / 70 kg 25-40 mg / 70 kg	44,2%	46 [12]	Psilocybin administered in combination with psychotherapy produced robust decreases in percentage of heavy drinking days over and above those produced by active placebo and psychotherapy.	None.
Rieser et al.	2022	37	psilocybin	25 mg	38%	37 [12]	A single dose of psilocybin combined with five psychotherapy sessions may not be sufficient to reduce relapse rates and alcohol use in severely affected AUD patients following withdrawal treatment.	13 in the psilocybin and 7 in the placebo group
Pagni et al.	2024	11	psilocybin	25 mg	36%	46	Across both alcohol and emotional cues, psilocybin increased activity in the medial and lateral prefrontal cortex and left caudate, and decreased activity in the insular, motor, temporal, parietal, and occipital cortices, and cerebellum.	
Pagni et al.	2025	84	psilocybin	25 mg 30-40 mg / 70 kg	42%	46	Relative to the placebo group, the psilocybin group showed significant reductions in neuroticism and increases in extraversion and openness.	
Gold et al.	2025	93	psilocybin	unknown	16%	29	Significant reduction in clinical opioid withdrawal symptoms and drug use following treatment	No clinically significant cardiovascular or other medical events occurred in this study
Luquiens et al.	2025	30	psilocybin	25 mg	43%	50	The psilocybin group showed significantly greater abstinence rate, reductions in percentage of drinking days and craving frequency.	10 in the psilocybin and 6 in the control group

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