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Symptoms of protracted alcohol withdrawal in patients with alcohol use disorder: A comprehensive systematic review

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Introduction

Alcohol Withdrawal Syndrome (AWS) is a clinical condition which appears after the abrupt cessation or the reduction of alcohol use in a patient affected by alcohol use disorder (AUD) with physical dependence (DSM-5) (1). Major symptoms associated with AWS include anxiety and dysphoria, insomnia and sleep disturbance, tremor, hyperactivity and craving (2-5). It is well known that such symptoms are at maximal levels during the initial time of abstinence. Whereas some of these symptoms, such as tremor, sweating or nausea disappear after a few days, others may persist for several weeks, months or even years (6, 7) characterizing the so-called clinical condition of "protracted alcohol withdrawal" (8).
Given that today the majority of patients undergoing moderate to severe form of AWS can be pharmacologically treated safely and effectively to alleviate major persistent (3) and, consequently, to maintain abstinence from alcohol (2, 9, 10), it is important to investigate which and how such severe symptoms frequently persist in time. To our knowledge, no review investigated the frequency of alcohol withdrawal symptoms after drinking cessation, separately in patients using or not a pharmacological treatment to reduce such symptoms.
We, therefore, conducted a systematic review of the literature aimed at elucidating how selected major alcohol withdrawal symptoms (i.e., craving, sleep disturbance and anhedonia) are protracted in patients with AUD after drinking cessation.

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Methods

The methods of the present systematic review were defined following the Prepared Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol of the present review has been registered in Prospero (registration number: CRD42020211265).

Data sources and search strategy

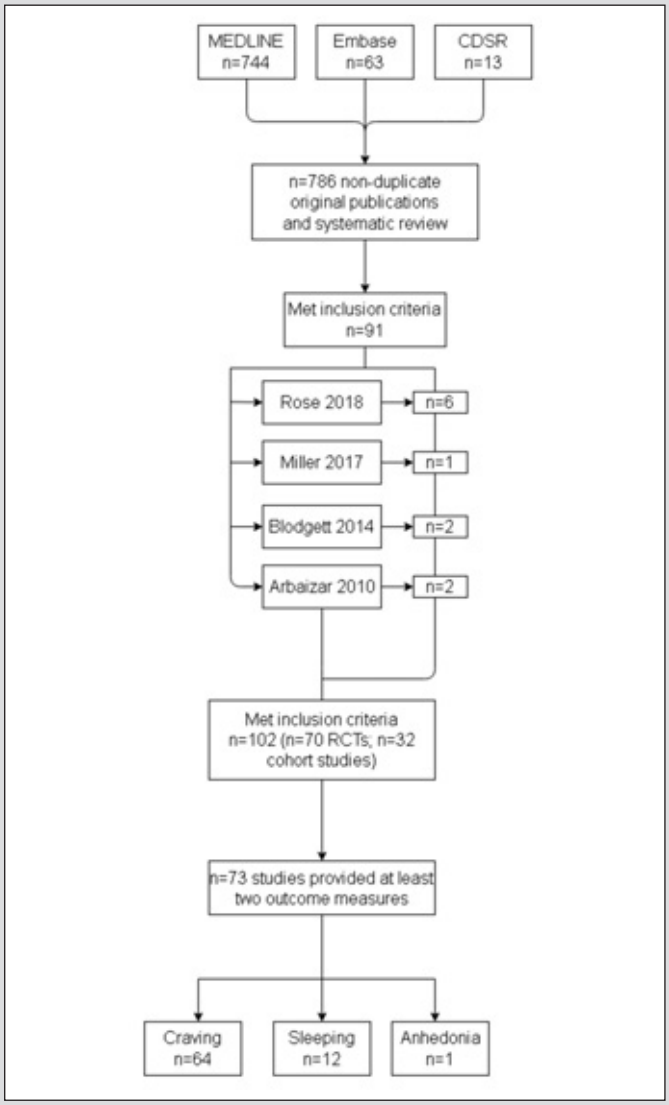
We conducted a systematic review of the literature in Pubmed/MEDLINE, Embase and the Cochrane Database of Systematic Reviews (CDSR). The search string included terms for selected alcohol withdrawal symptoms, including craving, insomnia or sleep disorders and anhedonia, alcohol dependence, including alcoholism and alcohol use disorder, and withdrawal or abstinence (**Supplementary Table 1**). We considered only publications in English language and we limited our research to articles published over the last 15 years (since 1st of January, 2006). Original articles identified in the reference list of eligible meta-analyses and systematic reviews were also screened for inclusion in the present systematic review.

Study selection and eligibility criteria

Eligible articles were those providing information on at least one outcome of interest (i.e., craving, insomnia or sleep disorder and anhedonia) after alcohol detoxification. For the aims of the present review, only publications providing data from longitudinal studies (i.e., randomized clinical trials, RCT, or prospective cohort studies, including case-cohort studies) were considered as eligible articles. Unpublished studies, conference abstracts and proceedings, dissertations, theses and, more in general, non-peer reviewed papers were not considered.

Using our comprehensive search strategy, the 25th of February 2020, we found 744 articles in Pubmed/MEDLINE, 63 in Embase (excluding those common to MEDLINE), and 13 in CDSR. After the exclusion of 34 duplicates, we obtained a total of 786 articles. Once retrieved the full text for all these publications, two independent researchers (EB and AL) evaluated each publication on the basis of pre-defined eligibility criteria. Overall, 102 articles met the inclusion criteria (**Figure 1**).

Figure 1 - Flowchart of the systematic review on the symptoms of protracted alcohol withdrawal in patients with alcohol use disorder



Data extraction

Information on first author, year of publication, study type, country, study period, type of population, method of diagnosis assessment, possible treatment for alcohol cessation, number of subjects and outcomes provided were retrieved and described (**Supplementary Table 2**). Various publications were also described according to methods of outcome assessment, type of measures provided, estimates, other outcomes provided in the study and comments on the outcomes (**Supplementary Table 3**).

Statistical analyses

Each eligible article inherent to craving and insomnia or sleep disorders has been described and summarized. Extracted data included the mean values of various scales used to determine the presence of craving, insomnia or sleep disorders. Pooled mean estimates for craving and insomnia or sleep disorder measures, at baseline and at various follow-up times after withdrawal, were estimated computing inverse-variance weighted means of various studies. For the most frequently used scales of craving (i.e., OCDS) and sleep (i.e., ESS), we also fit linear splines with study as random intercept to take into account the correlation between repeated measures within the same subjects. We estimated the Akaike's Information Criterion (AIC) of linear splines with 0 knots (linear regression) or 1 knot set in each time point. To select the optimal model fitting our data, we chose the model minimizing AIC. With reference to OCDS, the same procedure has been used for stratified analyses by treatment. In order to investigate differences across treatments, interaction between time after withdrawal and treatment was tested using linear regression models. In a post-hoc analysis, linear splines were also fit for measures of anxiety and depression. All statistical analyses were performed using Stata 15 (StataCorp. 2017, College Station, TX, USA).

Results

Of the 102 publications having met the eligibility criteria, including 70 RCTs and 32 cohort studies, 88 provided data on craving (**Supplementary Table 4**), 21 on sleep disorders (**Supplementary Table 5**) and 1 on anhedonia. Of the 102 publications, 73 provided at least two estimates of the scales used to measure selected symptoms at baseline (alcohol withdrawal) and after at least one time at follow-up. In particular, 64 studies provided information on craving, 12 on sleep disorders and 1 on anhedonia.

Of the 64 studies focusing on craving, 39 were RCTs and 25 were observational cohort studies. Overall, 37 (57.8%) studies assessed craving using OCDS, 16 (25.0%) using PACS, 14 (21.9%) using VAS, 3 (4.7%) using ACS and 2 (3.1%) using ACQ.

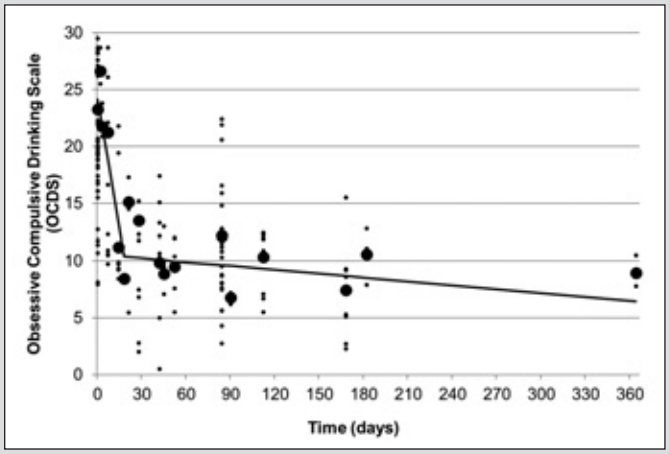
Linear spline for alcohol craving measured by OCDS over time is plotted in **Figure 2** (n=34 studies). The optimal model for OCDS had one knot at 18 days. OCDS decreased from 24.2 at baseline to 18.8 at 1 week, 13.5 at 2 weeks, 10.3 at 1

Table 1 - Mean estimates at baseline and at various follow-up times for craving and sleep disorders measures, obtained using a linear spline model with random intercept

Outcomes	*Number of studies*	*Time (days) of the possible knot#*	*Mean estimates of various scales at different time points*						
			Baseline	*1 week*	*2 weeks*	*3 weeks*	*1 month*	*2 months*	*3 months*
Craving									
OCDS	34	18	24·2	18·8	13·5	10·4	10·3	9·9	9·7
OCDS (treated)	29	21	23·9	18·8	13·7	8·7	8·7	8·7	8·8
OCDS (GABA)	21	20	24·7	19·2	13·6	8·8	8·8	8·6	8·3
OCDS (non-GABA)	14	39	22·7	18·7	15·8	12·3	8·8	4·6	6·6
OCDS (non-treated)	16	4	25·3	13·9	13·7	13·4	13·2	12·3	11·4
PACS	11	4	16·1	8·6	8·6	8·7	8·8	9·1	9·3
VAS	11	28	4·4	3·5	2·7	1·9	1·1	1·3	1·5
Sleep disorders									
ESS	3	NA	7·3	7·3	7·3	7·3	7·2	7·2	7·1

ESS: Epworth Sleeping Scale; NA: not available; OCDS: Obsessive Compulsive Drinking Scale; PACS: Penn Alcohol Craving Scale; VAS: Visual Analogue Scale
The knot is the time point where the optimal linear spline model changes slope. NA means that no knot has been identified

Figure 2 - Linear spline for craving measured by Obsessive Compulsive Drinking Scale (OCDS) over time, until one year of follow-up



Knot observed 18 days after withdrawal; β1 (x<18): -0.76 (p-value<0·001); β1+β2 (x?18): -0·01 (p-value=0·163)

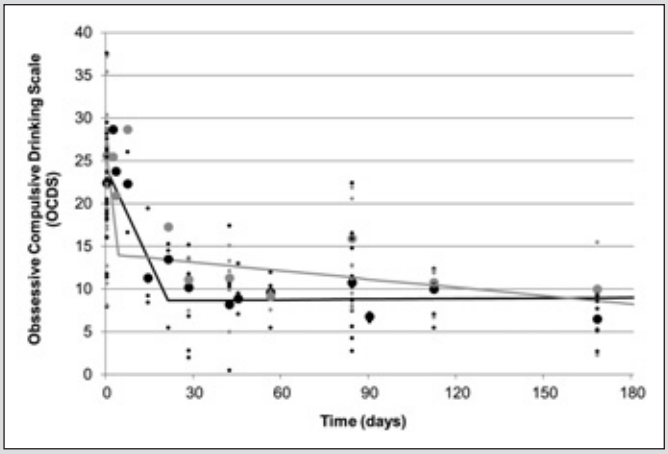
month and 9.7 at 3 months (**Table 1**). The corresponding estimates considering 29 studies providing data on OCDS among subjects treated were: 23.9, 18.8, 13.7, 8.7, and 8.8, whereas considering 16 studies on non-treated subjects, estimates were: 25.3, 13.9, 13.7, 13.2, and 11.4. No statistically significant difference has been observed between treated and non-treated groups (p=0.837; **Figure 3**); however, even if linear splines showed knots at different time, the OCDS declined below 10 more rapidly among treated subjects rather than non-treated subjects.

Among the 12 studies on sleep disorders, 11 were RCTs and 1 was a cohort study. Of these 12 studies, 4 (33.3%) assessed sleep disorder using ESS, 4 (33.3%) using TST, 3 (25.0%) SOL, and 3 (25.0%) PSQI. The optimal model for sleep disorders measured by had no knot, and ESS remained stable being 7.3 at baseline, 7.3 at 1 week, 7.3 at 2 weeks, 7.2 at 1 month, and 7.1 at 3 months.

Only one study (11) provided information on anhedonia using a VAS scale and a SHAPS. This study, based on 44 patients treated with two different doses of Acetyl-L-Carnitine and 20 patients in the placebo group, showed that the VAS scale for anhedonia among patients treated with Acetyl-L-Carnitine decreased from 5.2 at baseline to 3.1 after 10 days and 2.4 after 80 days. The corresponding estimates in the placebo group were 6.2 at baseline, 5.6 after 10 days and 3.7 after 80 days from alcohol cessation. Similar decreases have been observed using the SHAPS scale.

In a post-hoc analysis, among our selected studies, we found 30 studies providing information on one measure of depression at baseline and at least one time point at follow-

Figure 3 - Linear spline for craving measured by Obsessive Compulsive Drinking Scale (OCDS) over time, until six months of follow-up, in strata of pharmacological treatment (in black: treated with a pharmacological drug, in grey: treated with placebo)



Treated (black): Knot observed 21 days after withdrawal; β1 (x<21): -0·75 (p-value<0·001); β1+β2 (x≥21): 0·00 (p-value=0·710)
Placebo (grey): Knot observed 4 days after withdrawal; β1 (x<4): -2·83 (p-value<0.001); β1+β2 (x≥4): -0·03 (p-value=0·007)
Interaction treatment*time: β=-0·00, p-value=0·837

up, and 24 studies on anxiety. The most frequent scales were BDI (10 studies) for depression and STAI (7 studies) for anxiety. The optimal models for depression (BDI) had one knot at 9 days, BDI decreasing from 17.8 at baseline to 12.7 at 1 week, 8.4 at 2 weeks, 8.4 at 1 month, and 8.2 at 3 months. The corresponding model for anxiety (STAI) had no knots, STAI decreasing from 52.1 at baseline, 51.5 at 1 week, 51.0 at 2 weeks, 49.9 at 1 month, and 45.5 at 3 months.

Discussion

This is the first systematic review showing the persistence of selected symptoms of PAW, (including craving, sleep disorder, and anhedonia) after the resolution of the acute alcohol withdrawal phase. In fact, despite these symptoms progressively reduce their intensity, they do not completely disappear for several months. In addition, patients treated with GABA-ergic compounds present a more rapid and drastic improvement of craving.

Craving, defined as an intense, urgent, or abnormal desire to use an addicted substance or to follow a compulsive behavior, is considered one of the most important symptoms which characterized addicted subjects. For this reason it has been introduced as one of the 11 items to perform a diagnosis of substance use disorder in the last version of the Diagnostic and Statistical Manual of Mental Disorder-5 version (1). Craving has become a crucial symptom of compulsive and obsessive desire for an addictive substance (in this case for alcohol) indirectly used to monitor the variations towards the appetite for substance after the detoxification period in order to accomplish the more adapted counselling and pharmacological approach to maintain abstinence and/or to avoid relapses. Several scales such as OCDS, ACS, and PACS exist to monitor the intensity of craving and the efficacy of specific drugs in reducing craving according to time since drinking cessation both in RCTs and observational cohort studies. It is worth noting that OCDS, VAS, and PACS are the most utilized scales to monitor craving for alcohol in patients with AUD (12). While OCDS is used to investigate the presence of craving characterized by a minimum of 0 and a maximum of 40 points identifying also two types of craving (obsessive and compulsive) (13), VAS is a visual scale mainly used to investigate intensity of this symptom with a range from 0 to 10 (14), and PACS is composed of five items (each item on a scale of 0-6) that capture craving over the previous week (score >20 identifies people having the craving symptom; score 15-20 defines people with 'moderate' and 'sometimes' symptom, and score <15 indicates no symptom) (15, 16). In addition, it is well known that craving may be one of the most frequent symptoms accountable of relapses in heavy drinking (17, 18). Moreover, several years ago craving was considered a symptom of AWS (19,20), and only during the last couple of decades it acquired a different form of consideration becoming an independent "condition of mind" apart AWS (15, 21) and with specific characteristics (22, 23). In our systematic review, as evidenced by the innovative application of linear splines able to summarize the evidence, the OCDS and PACS scores show a drastic reduction of their scores particularly during the first 4 weeks of treatment, while VAS score has a more linear evolution. This might be explained by the fact that craving intensity is drastically reduced during the first weeks of treatment but without being completely suppressed during the subsequent weeks and months. In addition, when we stratified studies in two subgroups by treatment (pharmacological vs. non-pharmacological), craving intensity appeared to be reduced more markedly in patients following a pharmacological treatment compared to patients treated with placebo; in this latter subgroup, indeed, the reduction was linear and not pronounced such as for the other group. Given that differences between treatment and non-treatment group are not significant, likely due to the fact that analyzed studies were not designed with this endpoint, some considerations are dutiful, since this is the first review that analyzes efficacy of treatment for protracted withdrawal syndrome. Interestingly, the treatment group shows a pronounced reduction of craving after three weeks and maintains similar values until the end of the sixth month, while the non-treatment group shows a less deep reduction of craving after 1 month, continuing to decrease and reaching the level of the treated group only after almost six months. A possible interpretation of these data is that craving follows physiological curve of reduction during the first six months after interrupting alcohol abuse and that introducing a specific pharmacological treatment can substantially anticipate the reduction that normally would be obtained only after six months. According to this hypothesis, that must be confirmed with future studies, specific pharmacological treatment would be indicated in the first six months after the resolution of AWS, in order to reduce craving and therefore to prevent alcohol relapse.

In addition, when the subgroup of studies was further divided in those following GABA-ergic agents, a more pronounced reduction in OCDS (and craving) has been shown compared with non-GABA-ergic compounds. Despite this difference is not significant and more studies are warranted to understand what type of drugs can better treat PWS symptoms, the efficacy of GABA-ergic agents is consistent with the pathophysiology of PWS, that involves a down-regulation of GABA-ergic system which needs several month to return to equilibrium (24).

Sleep disorder or insomnia is one of the most frequent symptoms reported by patients after the resolution of acute AWS (25). In particular, a review of seven studies reporting data on sleep, using polysomnograph recordings of the brain while people slept, found evidence that sleep abnormalities can persist for 1 to 3 years after stopping alcohol consumption (24,26-32). These abnormalities include difficulty falling asleep, decreased total sleep time, and sleep apnea. In our systematic review, sleep disorder measured with ESS scale has been documented, and it linearly improves with increasing time since stopping.

Moreover, anhedonia a symptom where a person's ability to experience pleasure is decreased, is frequently found in patients with AUD after the detoxification period and it can last for several months (24). Very few studies have examined this particular symptom. Pozzi and colleagues examined anhedonia in individuals who had been abstinent from alcohol, opioids, and/or other drugs for some time, and who had no identified other psychiatric disorders, concluding that

anhedonia appeared to be a symptom of PAW unrelated to other clinical and psychosocial features (32). Again, Martinotti and colleagues found that signs and symptoms, including anhedonia, lasted the duration of a year-long study of people recovering from AUD (33). In our systematic review, in fact, it was possible to examine only the above mentioned studies. Thus, we were not able to obtain a summary figure related to this particular symptom.

Furthermore anxiety and depression are co-morbidities frequently found in patients suffering from AUD (34, 35). In fact it has been estimated that 30-50% of patients with AUD are affected by co-morbid psychiatric conditions (36, 37). For this reason, studies including patients with psychiatric disorder were excluded in our systematic review. Our systematic review, although not specifically designed to comprehensively investigate anxiety and depression, showed in a post-hoc analysis that these symptoms decreased during the 3-6 months after the cessation of acute phase of AWS, but they did not completely disappear, as a consequence of their persistence.

This study presents some limitations. We have included studies investigating the efficacy of medications for the treatment of the acute phase of AWS; in these studies benzodiazepines are the most frequent drugs employed; however these studies are few, and they used only the CIWA-Ar scale to measure the intensity of AWS (38), but not scales measuring craving. Thus, their influence on regression analyses is null. Moreover, minor symptoms of PAW have not been investigated. Furthermore, the investigation of anxiety and depression as symptoms of PAW have not been initially planned in order to avoid the inclusion of studies based on patients with AUD and co-morbid psychiatric condition which would have confounded the attribution of these symptoms to PAW rather than to a psychiatric disorder. Among the strengths, besides the originality and the comprehensiveness of the systematic review, this study gives the possibility to identify and to treat a specific syndrome occurring during the first months of alcohol abstinence which are considered an highly vulnerable period for drinking relapse.

In conclusion, this study confirms the persistence of PAW - in particular, craving and sleep disorder – after the acute phase of AWS emerged clearly when OCDS scale is considered in the placebo subgroup of patients. In addition, it is worth noting that the pharmacological approach might have a role in reducing these symptoms particularly during the first six months of treatment. Namely, GABA-ergic agents (excluding benzodiazepines for addiction liability) seem to be the most effective drugs to achieve this purpose, and to maintain - if prolonged for at least 90 days – the persistence of their effect in comparison with placebo. This result is consistent to neurobiological evidence showing that the re-adaptation time of altered neuronal pathway due to prolonged alcohol abuse, in particular GABA-ergic circuit, can last several months (39,40). This is of crucial importance not only for experts in addiction treatment, but also for physicians since the investigation of the presence of symptoms of PAW may direct the pharmacological therapy appropriately in order to avoid relapse in heavy drinking. It is important that controlled clinical trials aiming to investigate the presence of mayor and minor symptoms of PAW testing specific scales are conducted, including trials investigating specific targeted interventions with the label and off-label drugs currently employed for the treatment of AUD.

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