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A clinical remission study of low-severity alcohol use disorder, treated with nalmefene

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Abstract

Background:

When someone develops an alcohol use disorder (AUD), their addiction conditioning does not go away simply by refraining from drinking for some weeks or months. On the contrary, due to the deprivation effect, if one day they try to have just one alcoholic drink they will feel a strong and imperative biological necessity to keep drinking very fast, not being able to stop, which will lead to immediate negative consequences.

The good news is that opioid receptor antagonists, such as naltrexone and nalmefene, have shown efficacy for reducing the deprivation effect, and for reducing alcohol consumption, in people who suffer from low-severity alcohol use disorders.

Alcohol use disorders may turn into a persistent and relapsing disease. Many patients stop drinking easily, even without treatment, when they are overwhelmed by their “problems” associated with heavy drinking. Afterwards they may remain in remission for weeks or months. However, relapses may be devastating either for patients or for their families.

The hypothesis of this study is that the self-monitoring treatment program with nalmefene may obtain a *fast, significant, and continued reduction* in alcohol consumption, without negative consequences in low-severity AUD patients.

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Methods:

We included AUD patients meeting DSM-5 criteria. Those who showed an alcohol *withdrawal* syndrome or an *unstable* medical, psychiatric or addictive comorbidity disorder (except tobacco use disorder), were considered high severity AUD, and they were excluded.

Low-severity AUD patients followed a self-monitoring outpatient treatment program, assisted with nalmefene, with a goal to reduce alcohol consumption for 12 weeks. They came to 4 visits (baseline, 4th week, 8th week and 12th week). After the baseline assessment visit, they began to take one 18 milligram tablet of nalmefene each day, and from the second week of treatment they chose to take it daily or “as needed”.

Outcome variables are (1) total monthly alcohol consumption, (2) daily average alcohol consumption, (3) the score of DrinC Inventory (assessing negative consequences of heavy drinking) and (4) biological markers of heavy drinking, such as gamma-glutamyl transpeptidase (GGT), mean corpuscular volume (MCV) and carbohydrate deficient transferrin (CDT). Variables (1), (2) and (3), were assessed baseline and monthly, and GGT, MVC and CDT, baseline and at the end of the study treatment.

Results:

Thirty AUD patients have been included in the study, 18 men and 12 women. Ages between 31 and 72 years old, mean 50.73 ($\pm$ 11.41) years old. Half of them, 15 patients, completed the 12 week study and the other half dropped out before study completion. Total alcohol consumption, average daily alcohol consumption, and DrinC score differed statistically significantly between baseline and the other time points. Post-hoc tests revealed a statistically significant decrease in these three variables from pre-treatment to 4th week, 8th week, and 12th week of treatment. However, post-hoc comparisons between successive time points (i.e., 4th week vs. 8th week, and 8th week vs. 12th week of treatment) did not reach statistical significance.

Mean total (monthly) alcohol consumption decreased from 1887 (baseline) to 813.8 grams of pure alcohol at the 4th week, and to 695 grams at 12th week. Mean average daily alcohol consumption decreased from 69.65 to 29 grams per day at the 4th week, and to 24.57 grams per day at the 12th week. And mean DrinC score decreased from 15.7 (baseline) to 3.43 at the 4th week, and to 3.13 at the 12th week. And these differences are statistically significant.

The three biological markers of heavy drinking showed a decrease from baseline to the 12th week, which reached statistical significance for MCV, but not for GGT or CDT.

Conclusion:

The results of this study confirm that low-severity AUD patients, who followed the self-monitoring treatment program with a reduction oriented goal, assisted with nalmefene, obtained a *fast, significant and sustained reduction* of alcohol consumption, and at the same time, of negative consequences of heavy drinking, during the whole three months of treatment with nalmefene.

Furthermore, if low-severity AUD patients treated with nalmefene reach and maintain a low-level of risk alcohol consumption pattern, and if their negative consequences associated to heavy drinking disappear, they may be considered in clinical remission.

1. Introduction:

Alcoholism (including alcohol abuse and alcohol dependence disorder) is the single psychiatric disorder that has a higher prevalence in the United States of America (Regier et al., 1990). From the *NESARC study*, the most prevalent psychiatric disorders during the last 12 months, were the whole anxiety disorders (11.08%), the whole mood disorders (9.21%), and alcoholism (8.46%) (Including alcohol abuse and alcohol dependence) (Grant et al., 2004).

The *alcohol use disorder (AUD)*, as assessed by DSM-5 classification (A.P.A., 2013), is an addictive disease that responds to a specialized treatment, whose efficacy increases when patient and doctor share the same therapeutic goals, either reduction or abstinence (Guardia-Serecigni, 2015a). However, in comparison with the other psychiatric patients, AUD patients are the least likely to get specialized treatment (Kohn et al., 2004); may be due to illiteracy, absence of diagnostic screening, or the wrong believe that alcoholism treatment is not very effective (Hasin et al., 2007).

Alcohol use disorder (AUD) may turn into a relapsing and persistent disease, with very wide differences in severity, from very low to a very high severity. In fact, it may reach a high severity like intravenous heroin, cocaine or methamphetamine addiction, but it may be of low-severity, similar to just heavy drinking. It may be a sustained, intermittent or episodic disorder but its remission is not usually a definitive one, because it remains a high vulnerability to relapse that may decrease progressively after years of continued alcohol abstinence (Maisto, Hallgren, Roos, Witkiewitz, 2018).

Probably the most important symptom of AUD, and one of those which appears since the beginning of the addictive disease, is *the impaired control over drinking*, that may be of higher or lower intensity, depending on the severity of alcohol addiction (Guardia-Serecigni, 2015a).

When a person has developed an alcohol use disorder (AUD), his/her addictive conditioning does not extinguish just by stopping drinking for some weeks or months. On the contrary, due to the *deprivation effect*, the day when they try to have just one alcoholic drink they feel a strong and

imperative biological necessity to keep drinking very fast, not being able to stop drinking, and ending up with heavy drinking that is associated to immediate negative consequences (Guardia-Serecigni, 2019).

However, these scientific evidences are very different from the general believes of population, who may (1) have difficult to identify an alcohol use disorder, (2) trust mostly in the patient willpower than in the efficacy of specialized alcoholism treatment (including pharmacotherapy), and (3) believe that, after some weeks or months without drinking alcohol will cure the alcohol addiction (Guardia-Serecigni, 2011).

AUD patients usually believe that their difficulties with alcohol are only temporary and that, after some weeks or months without drinking alcohol, they will be able to have just one drink, without negative consequences. At the same time, it is really difficult that they accept a specialized treatment. Most of them refuse the diagnosis of AUD and they are not interested in an abstention oriented treatment program. It is possible that they accept to stop drinking for a while, but usually followed with a relapse in a few weeks or months. They use to think that the problem has to be solved by themselves, by their own willpower, and they are not ready to maintain a complete and continued abstention, at least at the first stages of their recovery. Probably, sooner or later they will have one drink again, they will suffer the *deprivation effect*, they will be dragged to a heavy *binge drinking episode*, and *negative consequences* will reappear (Guardia-Serecigni, 2019).

The *deprivation effect* is not just a psychological event, but also neurobiological phenomenon related to the functioning of opioid system. The good news is that opioid receptor antagonists, such as naltrexone or nalmefene, may blunt or even block it (Kornet et al., 1990; Sinclair, 2001).

Negative consequences of heavy drinking and acute alcohol intoxication may be (1) the dis-inhibition of violent instinctive impulses that favor the development of conflicts, arguments, fights, aggressions and injuries. (2) Sexual dis-inhibition, favoring non planned or not desired sexual contacts (Hughes et al., 2009). (3) Motor coordination impairment, which may produce accidents and injuries (Taylor & Rehm, 2012). (4) Deadly poisoning by alcohol alone or associated to other substances (opioids, and/or benzodiazepines) (Wang et al., 2018; Guardia-Serecigni, 2018). And (5) harm to others (Karriker-Jaffe et al., 2018).

AUD patients, threatened by family and partner conflicts or admonished by a low job performance or driving while intoxicated, ask for help to reduce their alcohol consumption and to reach a low-risk alcohol consumption. However most of them prefer *drinking reduction goals* because they do not want to give up drinking completely (Guardia-Serecigni, 2019).

Nalmefene is an opioid receptor antagonist, which blocks the deprivation effect, and produces a reduction in the amount of alcohol drunk per occasion. Therefore, nalmefene may help low-severity AUD patients to reach their reduction goal, when treated as described in the ESENSE studies (Van den Brink et al., 2014; Mann et al., 2013; Gual et al, 2013)

In addition, nalmefene reduces or blocks the reinforcing effect of alcohol, and the repetition of the experience of not perceiving the expected reinforcing effect, when drinking alcohol, may induce an effective extinction process (Sinclair, 2001). Progressively the patient recovers his or her

freedom for choosing between either not drinking alcohol, or maintaining a *low-risk drinking*, below 40 grams of alcohol per occasion (or per day) in men, and below 20 grams in women, which is the WHO low-level of risk associated with a better physical health and quality of life (Witkiewitz et al., 2018). And, if they learn to maintain a low-risk drinking pattern, they may avoid successfully the negative consequences of heavy drinking, and they may obtain the same benefits as AUD patients who remain in continued abstinence from alcohol (Falk et al, 2010).

The hypothesis of this study is that low-severity AUD patients, treated with a self-monitoring approach and nalmefene, will show a fast, significant, and continued reduction (1) of alcohol consumption, (2) of negative consequences of heavy drinking, and (3) of biological markers of excessive alcohol consumption.

2. Methods:

2.1. Study Design

This is an observational, phase IV study on the effectiveness of nalmefene “as needed” for the reduction of alcohol consumption, negative consequences, and biological markers of heavy drinking, in low-severity alcohol use disorder patients, asking for treatment, who prefer a reduction goal.

We have included 30 low-severity alcohol use disordered patients, treated at the Addictive Behaviors Unit of Psychiatry Department of Santa Creu and Sant Pau Hospital, Autonomous University of Barcelona (Spain). And we have compared the evolution of alcohol consumption and of negative consequences at baseline, 4th, 8th, and 12th weeks; and GGT, CDT, and VCM at baseline and 12th week of treatment with nalmefene.

During baseline visit we have collected information about personal and family history; patterns and amount of alcohol consumption during the previous 4 weeks; details on personal alcohol addiction, negative consequences of heavy drinking, and possible medical, psychiatric and/or addictive comorbidities. We have performed also a complete laboratory test, before starting the treatment with nalmefene and also at the end of the 12th week of treatment with nalmefene.

We have assessed (1) *DSM-5 diagnostic criteria* for alcohol use disorder and alcohol withdrawal symptoms (A.P.A., 2013); (2) previous month alcohol consumption, following the *Timeline Follow-back* procedure (Sobell and Sobell, 1992), counting daily and total alcohol in grams of pure alcohol; and (3) possible *negative consequences of heavy drinking*, using the *DrinC Inventory* (Miller, Tonigan and Longabaugh, 1995). And we have repeated the assessment of alcohol consumption and negative consequences of drinking at the 4th, 8th and 12th week of treatment.

2.2. Selection of Patients:

Inclusion criteria have been: meeting DSM-5 alcohol use disorder criteria, and having the intention to reduce alcohol consumption.

Exclusion criteria have been: younger than 18 years old; more than 4 symptoms of alcohol withdrawal in the morning; personal history of severe alcohol withdrawal (such as convulsions or delirium); severe or unbalanced medical, psychiatric or addictive comorbidities; active opioid

dependence, the need to take opioid prescription drugs for cough, diarrhea or pain; alcohol consumption below 60 grams of alcohol per occasion in men (40 grams in women); and score of DrinC Inventory below 5 points.

2.3. The Self-monitoring Approach

Before starting the treatment, patients intending to reduce their alcohol consumption were instructed to *self-monitor* their daily alcohol consumption (or abstention) in the easiest simple way, such as writing down just the number and kind of drinks that they had each day, and to bring their self-monitoring sheet to each monthly visit.

They were instructed also to take a pill of nalmefene (18 milligrams), at least one hour before the first drink, every day that they had an alcoholic drink, and also to write down (in the same self-monitoring alcohol consumption sheet) which days they had a tablet of nalmefene and which ones they had not. It has been important for assessing their compliance with the pharmacological treatment and also for persuading the patient to take nalmefene each day they had the possibility to have a drink.

The *self-monitoring approach* is a step wise procedure that has some milestones that have to be reached progressively, it needs the acceptance and the collaboration of the patient and it helps patients to (1) become aware of their alcohol problem, (2) acknowledge the necessity of external help, (3) understand the therapeutic effects of opioid antagonists, and (4) accept that they have to follow the guidelines of low-risk alcohol consumption (Guardia-Serecigni, 2019).

2.4. Pharmacological treatment

Other prescription drugs for the treatment of alcoholism, such as disulfiram, cianamide, acamprosate or naltrexone, were not allowed in this treatment study. Psychiatric drugs, such as antidepressants or anxiolytics were allowed if the patient was taking them before form starting nalmefene treatment. Allowed prescriptions of psychiatric medication, for patients who showed anxiety or insomnia during the study treatment, have been pregabalin for anxiety, between 25 and 150 milligrams per day, and escitalopram, 10 mg/day for depression.

The treatment has been developed completely as out-patient. We have counted total and average daily amount of drinking in grams of pure alcohol, from the daily self-monitoring sheet that patients have filled up daily, and we have discussed about it in each visit. The first week of treatment, patients have taken a daily tablet of nalmefene, and afterwards they have chosen between daily or “as needed” use, if they preferred to take it just on days of possible alcohol consumption.

2.5. Outcome Variables and procedure

Main outcome variables were (1) alcohol consumption in total grams of pure alcohol and (2) average of daily alcohol consumption, (3) the score of the Drinker Inventory of Consequences (DrinC) (Miller, Tonigan, Longabaugh, 1995) to assess the amount of negative consequences of the heavy drinking, during the prior 4 weeks.

Secondary outcome variables were the reduction in the biological markers of excessive alcohol consumption, such as gamma-glutamyl-transpeptidase (GGT), middle corpuscular volume (MCV), and carbohydrate deficient transferrin (CDT).

Participants were assessed at baseline, 4th, 8th, and 12th week visits.

2.6. Statistical Analysis

Demographic and clinical characteristics of the patients have been reported with descriptive statistics.

Analyses of primary outcomes (i.e., DrInC score, Total alcohol consumption, and Average alcohol consumption) were conducted according to the intention-to-treat (ITT) principle, that is including all enrolled participants regardless of whether they completed the intervention or not. Missing data were treated with the last observation carried forward approach. To examine differences in the aforementioned primary outcomes, repeated-measures analysis of variance (ANOVA) was used with Greenhouse-Geisser correction as needed and post-hoc tests using the Sidak correction.

Analyses of secondary outcome variables (i.e., MCV, GGT, and CDT) has been performed with paired t-test comparing baseline data with 12th week data.

2.7. Ethics

The study has been approved by the Ethical Committee of the Santa Creu and Sant Pau Hospital, of Barcelona, Spain. Written informed consent has been obtained from each AUD patient, before starting baseline visit.

3. Results:

3.1. Sample

Thirty AUD patients have been included in the study, 18 men and 12 women. The range of ages were between 31 and 72 years old, mean 50.73 ($\pm$ 11,41) years old.

Following severity criteria of DSM-5 diagnosis of alcohol use disorder, 10 patients (33.3%) were classified as mild, 8 patients (26.7%) as moderate, and 12 patients (12%) as severe. But these are different severity criteria than the ones we have used for the selection of low-severity AUD patients who entered in the treatment study, such as the presence of an alcohol withdrawal syndrome or unbalanced medical, psychiatric or addictive comorbidities.

Half of them, 15 patients, completed the 12 week study and the other half were drop outs.

3.2. Efficacy

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean scores on the *DrInC* differed statistically significantly between time points [$F(1.369, 39.695) = 74.026$; $p < 0.001$; $\eta^2_p = 0.719$]. Therefore, it shows a strong effect size.

Post-hoc tests using the Sidak correction revealed a statistically significant decrease in mean *DrInC* scores from pre-treatment to 4-weeks of treatment (mean difference = 12.267; $p < 0.001$)., however post-hoc comparisons between successive time points (i.e., 4-weeks vs. 8-weeks of

treatment, and 8-weeks vs. 12-weeks of treatment) did not reach statistical significance (see Table 1).

Figure 1. Main outcome variable. Monthly total alcohol consumption

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean scores on the *total alcohol consumption* differed statistically significantly between time points [$F(1.143, 33.148) = 33.180$; $p < 0.001$; $\eta^2_p = 0.534$]. Therefore, it shows a moderate-to-strong effect size.

Post-hoc tests using the Sidak correction revealed a statistically significant decrease in mean total alcohol consumption from pre-treatment to 4-weeks of treatment (mean difference = 1073.23; $p < 0.001$). However, post-hoc comparisons between successive time points (i.e., 4-weeks vs. 8-weeks of treatment, and 8-weeks vs. 12-weeks of treatment) did not reach statistical significance (see Table 1).

Figure 2. Other outcome variables

Daily OH = Mean average daily alcohol consumption

DrinC = Drinc score

MCV = Mean Corpuscular Volume

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean scores on the *average daily alcohol consumption* differed statistically significantly between time points [$F(1.146, 33.233) = 34.107$; $p < 0.001$; $\eta^2_p = 0.540$]. Therefore, it shows a moderate-to-strong effect size.

Post-hoc tests using the Sidak correction revealed a statistically significant decrease in mean DrInC scores from pre-treatment to 4-weeks of treatment (mean difference = 40.644; $p < 0.001$). However, post-hoc comparisons between successive time points (i.e., 4-weeks vs. 8-weeks of treatment, and 8-weeks vs. 12-weeks of treatment) did not reach statistical significance (see Table 1).

Table 1. Means and SDs for main outcome variables, and repeated measures ANOVAs with post-hoc tests ($n = 30$)

Variable	Time 1 Baseline		Time 2 4 th week		Time 3 8 th week		Time 4 12 th week		F	p	η^2_p	Sidak post-hoc tests
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
DrInC	15.70	6.67	3.43	4.71	2.67	4.66	3.13	4.75	$F(1.369, 39.695) = 74.026$	< 0.001	0.719	1 > 2, 3, 4*
Total Alcohol Consum.	1887.1	1067.7	813.8	1033.5	685.1	975.3	695.0	971.7	$F(1.143, 33.148) = 33.180$	< 0.001	0.534	1 > 2, 3, 4*
Average Daily Alcohol Consum.	69.65	39.15	29.01	36.73	24.26	34.54	24.57	34.39	$F(1.146, 33.233) = 34.107$	< 0.001	0.540	1 > 2, 3, 4*

* $p < 0.001$; consum.=consumption; MCV=mean corpuscular volume; GGT= gamma-glutamyltranspeptidase; CDT= carbohydrate deficient transferrin.

DrinC score, total alcohol consumption, and average daily alcohol consumption, showed already a significant decrease at the 4th week, which has been maintained or even improved at the 8th and 12th week assessments, in comparison to baseline.

Mean total monthly alcohol consumption decreased from baseline 1887 to 813 grams the 4th week, and to 695 grams of pure alcohol at the end of the study, with a moderate-to-strong effect size. Mean average daily alcohol consumption decreased from baseline 69.65 grams per day to 29 grams the 4th week, and to 24.57 grams per day at the end of the study, with a moderate-to-strong effect size. Mean DrinC score decreased from baseline 15.7 to 3.43 at the 4th week, and to 3.13 at the end of the study, with a strong effect size.

Paired t-test comparing baseline data with 12th week data showed a reduction for biological markers of heavy drinking that reached statistical significance for middle corpuscular volume (MCV), but not for GGT or CDT.

Table 2. Mean and SDs for secondary outcome variables, and paired t-tests results.

Variable	Time 1 Baseline		Time 4 12 th week		t	Degrees of freedom	Significance
	Mean	SD	Mean	SD			
MCV	93.37	4.99	91.94	4.92	2.89	12	0.014
GGT	63.90	81.40	47.60	75.28	1.577	14	0.137
CDT	1.59	2.41	1.49	2.39	.548	9	0.597

3.3. Safety

Adverse events most frequently referred by patients were dizziness, perspiration, fatigue, constipation, dry mouth, restlessness, anxiety, headache, anorexia, insomnia, or irritability. Most of them have been of low intensity, tending to decrease or disappear in some days or weeks of daily treatment. Exceptionally a few patients have shown cognitive disturbances, trouble concentrating, and a high level of anxiety, that have drove them to stop the treatment with nalmefene.

4. Discussion:

From the results of this study, nalmefene has showed a significant reduction of total alcohol consumption, average daily alcohol consumption, with a moderate-to-strong effect size. And of DrinC score, with a strong effect size; in just 4 weeks of treatment. And this reduction has been maintained throughout the 12 weeks of treatment.

Total alcohol drinking has been reduced from baseline 1887 ($\pm$ 1067) grams of pure alcohol, to 813.8 ($\pm$ 1033.5) grams in 4 weeks, and to 695 ($\pm$ 971.7) grams at the 12th week of treatment. Average daily drinking has been reduced from baseline 69.65 ($\pm$ 39.15) grams of pure alcohol, to 29.01 ($\pm$ 36.73) grams at the 4th week, and 24.57 ($\pm$ 34.39) grams at the 12th week of treatment. These significant reductions from baseline drinking confirm the hypothesis that low-severity AUD patients treated with a self-monitoring approach, and helped with nalmefene, show a significant reduction of their alcohol consumption.

Furthermore, the significant reduction of DrinC scores from baseline 15.70 ($\pm$ 6.67) to 3.43 ($\pm$ 4.71) with just 4 weeks of treatment, which is sustained until the end of the study 3.13 ($\pm$ 4.75) at the 12th week, which confirms the other hypothesis that *low-severity AUD patients*, treated with *nalmefene* showed a very significant *reduction of negative consequences* of heavy drinking, which

have almost already disappeared at the 4th week of treatment, and they remain almost absent until the end of the study.

In fact, the *DrinC* Inventory is sensible and specific enough to assess the outcome of alcoholism treatment, and it has convergence validity with measures that assess alcohol consumption and quality of life. Therefore, it is considered a useful instrument for assessing the good or bad outcome of an alcoholism treatment program (Kirouac and Witkiewitz, 2018).

In sum, low-severity AUD patients showed a significant reduction of alcohol consumption, and at the same time, of negative consequences from heavy drinking, in only four weeks of treatment. Therefore, they could already be considered in remission, and this clinical remission state remained along the 12 weeks of the study treatment.

Therefore, the results of this study suggests that the self-monitoring approach, helped with nalmefene, may help low-severity AUD patients, interested in reducing either their total alcohol consumption or their occasional heavy drinking, to reach this treatment goal in just 4 weeks, and then maintain their improvement during the next months of treatment. In addition, they may be almost free of negative consequences of heavy drinking also in just 4 weeks of treatment, and maintain this almost absence of negative consequences throughout the 12 weeks of treatment. And this would be in accordance with a secondary analysis of the COMBINE study showing stability of no heavy drinking (Witkiewitz et al., 2017).

If an AUD patient reaches and maintains low-risk alcohol consumption, and negative consequences of drinking disappear, it may be accepted that he or she has reached the clinical remission (Kline-Simon et al., 2017; Witkiewitz et al., 2018).

On the other side, according to Drobes et al. (2003) study, side effects such as dizziness, perspiration, fatigue, constipation, dry mouth, restlessness, anxiety, headache, anorexia, insomnia, and irritability, occurred mostly the first days that nalmefene was taken. Exceptionally, a few patients have shown cognitive disturbances, trouble concentrating, and a high level of anxiety that have drove them to drop out of the study treatment.

It was already known that reduction of alcohol consumption, helped with nalmefene “as needed” use, is a new treatment goal that may be effective for low-severity alcohol-dependent patients (Van den Brink et al., 2014). This study shows, in addition, that (1) a substantial reduction of negative consequences occurs in parallel with the reduction of alcohol drinking and it seems to be as a consequence of this reduction of drinking. (2) Just this substantial reduction of dinking is enough to reach clinical remission, if it is sustained and there are no more heavy drinking episodes.

Due to the persistence of deprivation effect, AUD patients are prone to suffer a heavy drinking episode, the day when they have an alcoholic drink again, if they are not protected with an opioid antagonist, such as naltrexone or nalmefene. Therefore, if they have been trained to take this medication in due time, throughout the self-monitoring alcohol-reduction treatment, the day when they will have a drink again, they will be able to avoid relapse to heavy drinking. Therefore, they will probably reach an even more stable kind of remission than with continued abstention. (Guardia-Serecigni, 2015b).

Alcohol-dependent patients have their own beliefs, wishes, plans and decisions. *The self-monitoring approach* allows that patients have progressive insights, from experiential learning, that changes their previous misbeliefs and wrong decisions. And, properly assisted by the therapist, who favors the evolutionary change, they may develop more appropriate attitudes and make better decisions (Guardia-Serecigni, 2019).

Low-severity AUD patients may benefit from alcohol *reduction programs*, assisted with naltrexone or nalmefene. This medications obtain some reduction already from the first day of alcohol consumption, but in addition, they reach a significant difference vs. placebo from the 4th week of treatment onwards (Guardia et al., 2002; Anton et al., 2006; Van den Brink, et al., 2014).

An effective AUD treatment program depends firstly on the preferences of the patient (reduction vs. abstention), but also on the *severity* of his/her AUD. If the patient has the expectation to have a drink in the future, an opioid antagonist is a necessary protection for relapse. But, if he or she suffers a *severe* alcohol addiction, other factors may override the protective effect of the opioid antagonist, and *continued abstention* of alcohol is the most effective option for recovery (Guardia-Serecigni, 2011; Guardia-Serecigni, 2015a).

Therefore, high-severity AUD patients should be engaged in *abstention oriented* treatment programs, starting by a detoxification treatment and following with relapse prevention treatment afterwards, with effective medications such as naltrexone, acamprosate or disulfiram, in addition to psycho-social treatment (Kranzler & Soyka, 2018).

The limitations of this study are: (1) this is not a controlled but an observational study, (2) results are valid only for low-severity but not for any AUD patient, and (3) it is a 30 patient's sample. Therefore the same study should be replicate with a bigger sample of AUD patients, from different treatment centers, and also maybe with different levels of AUD severity.

The strengths of this study are (1) the selection of a homogeneous sample of low-severity AUD patients, (2) the prove that the reduction of drinking is an acceptable goal for this subgroup of patients, (3) the relevance of the self-monitoring approach, helped with nalmefene.

New relevant findings of this study treatment are that (1) the reduction of negative consequences (of drinking) go in parallel with the reduction of drinking, (2) this treatment program may obtain a fast and significant reduction of both, drinking and negative consequences, with a moderate-to-strong effect size, and in just 4 weeks of treatment, (3) this treatment program helps to maintain a low-level of drinking and also of negative consequences, throughout the 12 weeks of study treatment, and (4) that this substantial reduction of dinking is enough to reach clinical remission, if it is sustained and no more heavy drinking episodes occur.

5. Conclusions:

1. After a period of sobriety, just one drink may drive AUD patients to a heavy drinking episode, due to deprivation effect.

2. A heavy drinking episode is frequently associated to negative consequences, either for the drinker or for people around him or her.
3. Alcohol addictive conditioning does not extinguish just by some weeks or months of alcohol abstinence.
4. Relapses, due to deprivation effect, in AUD patients, may be devastating either for them or for their families.
5. Nalmefene blunts the deprivation effect, and it may help low-severity AUD patients to reduce their alcohol consumption, below risk-drinking levels.
6. In this study low-severity AUD patients obtain a significant and sustained reduction of alcohol consumption, following the self-monitoring approach, assisted with nalmefene.
7. In addition, in parallel with the reduction of alcohol consumption, they obtain the almost disappearance of negative consequences of heavy drinking.
8. If an AUD patient reaches a sustained low-risk drinking and a disappearance of negative consequences, he or she may be considered in clinical remission.
9. Most AUD patients prefer drinking reduction goals, but the decision about reduction vs. abstinence depends also on the severity of their alcohol use disorder.
10. The self-monitoring treatment program, assisted with nalmefene, may obtain a fast, significant, and continued reduction of alcohol consumption, of negative consequences, and of biological markers of heavy drinking, in low-severity AUD patients.
11. With this treatment program, a significant reduction of negative consequences of heavy drinking may be obtained in 4 weeks of treatment, and continued until the end of the 12th week of treatment.
12. High severity alcohol-dependent patients should be geared towards abstinence treatment program.

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