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Alcohol consumption reduction using opioid receptor antagonists

A self-monitoring approach to reach stable remission for low-severity alcoholism

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Abstract

When a person has developed alcohol addiction the addictive condition does not vanish even when one has stopped drinking for a long time; instead due to the Alcohol Deprivation Effect, just having one drink later, may drive to relapse.

Alcohol use disorder may turn into a persistent and relapsing disease. Many patients stop drinking easily, even on their own and without treatment when they are overwhelmed by "problems" derived from continued heavy drinking. Once achieved the stable abstinence, they may remain in remission for weeks or months but when they try a drink again, they may be affected by Alcohol Deprivation Effect which is associated to a powerful desire towards a high speed, continuous, unstoppable drinking, ending on the negative consequences of heavy drinking again.

Opioid receptor antagonists (naltrexone and nalmefene) block Alcohol Deprivation Effect, helping alcohol dependent patients to avoid heavy drinking, if they are motivated to do it, furthermore if a patient maintains low-risk alcohol consumption it's possible to consider a clinical remission. Several controlled studies have demonstrated opioid antagonists effectiveness reducing alcohol consumption, especially among people with a low-severity alcohol use disorder. However, high-severity alcohol dependent patients must to start their recovery with a detoxification treatment since they have a better response to abstention than to a reduction oriented treatment program.

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Introduction

First controlled studies related to pharmacotherapy for alcohol dependence disorder efficacy in which we were involved, selected continued abstinence of alcohol as the only acceptable good outcome, considering even an occasional low risk drinking as a relapse and treatment failure (Naranjo, Dongier & Bremmer, 1997; Gual & Lehter, 2001).

Controlled studies with naltrexone started using the concept of heavy drinking as relapse drinking, but we accepted drinking below 5 drinks per occasion for men and 4 drinks for women, as an acceptable limit of non-relapse drinking (Guardia et al., 2002). The COMBINE study showed that patients who had a low-risk drinking behavior, during the 4 months of treatment with naltrexone were successful responders to therapy and showed no negative consequences, same as patients in the control group who adhered to total alcohol abstinence (Falk et al., 2010).

Alcohol dependence disorder is a relapsing disease (Johnson, 2010). Following alcohol addicted patients along some years usually demonstrates a pendulum movement from heavy drinking, or occasional binge drinking, to periods of complete alcohol abstinence, followed by another period of heavy drinking, and so on.

In our culture it is almost impossible to sustain continued alcohol abstinence. Direct and indirect advertisements, holidays, celebrations, and social pressure induce people to have a drink, even when a person is not wishing to do it. In addition, when one has developed an alcohol addiction, alcohol related cues become powerful triggers for alcohol consumption (Schoenmakers et al., 2008).

Months or even years of sobriety do not extinguish the conditioned addictive behavior, but just one single drink has a powerful reinforcing effect on the conditioned drinking behavior leading to an impaired control over drinking, probably the most important alcohol addiction symptom which is completely out of alcohol addiction patient's voluntary control. That's why alcohol addicted people who have been in sustained remission during years, (even taking disulfiram or other medications, even in long term inpatient treatment programs or therapeutic communities) may suffer a relapse after having a first drink again.

Indeed, conditioned addictive behaviors remain active, even after months or years without drinking alcohol, and just one single drink is enough to abolish control over drinking leading to a binge drinking episode and its subsequent negative consequences again, due to the Alcohol Deprivation Effect (Sinclair 1972; 2001).

Despite scientific evidence, people usually believe alcoholism is a temporary and self-limited disorder that may disappear without treatment, just stopping drinking for some weeks or months. Maybe because it is really hard to accept that alcohol addiction is a persistent disease where the addictive conditioning is hard to eliminate but easily reinforced by just a single drink, moreover, it's presumed that while longer the deprivation period, greater the uncontrolled drinking behaviour, after just one drink (Kornet, Goosen and Van Ree, 1990).

The alcohol deprivation effect

When a person has developed an alcohol addiction, after a period of alcohol abstinence, he/she will suffer an increased drinking control impairment just after having a single drink (Sinclair 1972; 2001), dragging alcohol addicted people to a heavy drinking episode, usually associated to negative consequences.

The neurobiological background is that GABAergic neurons maintain a tonic inhibitory action on dopaminergic neurons; at the same time, endogenous opioids have an inhibitory effect on the midbrain ventral tegmental area GABAergic neurons.

Alcohol consumption induces a release of beta-endorphin able to inhibit GABAergic neurons, producing a network effect that elicits a phasic surge of dopamine in the nucleus accumbens and other limbic structures involved in craving and drinking behavior control (Johnson & North, 1992; Clapp et al., 2008). Therefore it's not only a psychological effect but also a critical neurobiological phenomenon for people who have developed an alcohol addiction.

Alcohol addicted brain shows a hypodopaminergic state (Volkow et al., 1996), as well a more sensitized endogenous opioid system (Heinz et al., 2005). Under this alcohol neuro-adaptation state just one drink may have a big impact on neurotransmission systems associated with a powerful reinforcing effect leading to a clear alcohol drinking control impairment.

Good news are that opioid antagonists such as naltrexone or nalmefene block alcohol-induced dopamine release in the nucleus accumbens (Benjamin et al., 1993) and also block alcohol deprivation effect, avoiding endogenous opioids specific receptors activation and consequently decreasing nucleus accumbens phasic dopamine surge (Sinclair 1972; 2001; O'Brien, Volpicelli, & Volpicelli, 1996).

Opioid Receptor Antagonists Pharmacology

Alcohol consumption may be modified by manipulating endogenous opioid system. Acute administration of alcohol triggers, release of opioid peptides, which induce positive reinforcing effects, and loss of control (Reid, 1990).

Midbrain ventral tegmental area opioid receptors activation produces GABA interneurons hyperpolarization as well dopaminergic neurons disinhibition and subsequent dopamine release increasing in the nucleus accumbens (Johnson & North, 1992), favouring alcohol craving, self-administration, and loss of control over drinking.

In laboratory studies conducted experimental rats, naltrexone and nalmefene achieved an alcohol positive reinforcing effect reduction diminishing drink compulsion, number of consumed units as well alcohol speed consumption (Davidson, Palfai, Bird, & Swift, 1999; Drobos, Anton, Thomas, & Voronin, 2004).

Naltrexone and nalmefene, both opioids receptors blockers, prevent opioid system increased activity after alcohol consumption, reducing relapse risk which could drive towards an excessive alcohol consumption (Guardia-Serecigni, 2011).

A study by Karhuvaara et al. (2007) led to a new procedure called targeted nalmefene, in which people with excessive alcohol consumption were instructed to take the drug when they had a risky drinking situation.

Naltrexone 50 miligrams tablets are rapidly absorbed in one hour; 21% circulates bounded to plasma proteins and has a 3.9 hours half life (reaching 9.7 hours after chronic administration), showing a decline on plasmatic levels in 24 hours. Naltrexone undergoes intense first-pass hepatic metabolism through the cytosol system, mediated by the 3 hydrodiol-dehydrogenase being converted to the longer half life (12.9 hours) metabolite in 6-beta-naltrexo which acts as a mu, delta and kappa opioid receptors competitive antagonist. Even when it's not selective, this metabolite shows greater affinity for the mu receptor, blocking opioid receptors for 24 hours. Naltrexone associated side effects may be nausea, headache, dizziness, vomiting, abdominal discomfort, anorexia, asthenia, insomnia or anxiety. These can appear in the initial days of treatment, are usually of low intensity and tend to disappear (Ortiz Camúñez, 1996).

Nalmefene 18 milligrams tablets are rapidly absorbed, reaching a peak plasmatic concentration 2-3 hours after administration. Compared with naltrexone, nalmefene has greater bioavailability (40-50%) and a longer half life.

Nalmefene acts as a mu, delta and kappa opioid receptors competitive antagonist showing greater affinity for delta and kappa ones, with partial agonist effect over the kappa opioid receptors. It is primarily metabolized by glucuronide conjugation and does not display dose dependent hepatotoxicity which improves its safety profile on hepatic impaired patients. Nalmefene possible side effects are dizziness, nausea, sleep disorder, dry mouth, headache, tachycardia, sweating, muscle spasms, anorexia, weight loss or asthenia. Exceptional symptoms of confusion, hallucination and dissociative have also been reported (Niciu & Arias, 2013).

Alcohol Addiction Severity

Drinking control impairment is the most important alcohol addiction symptom. Probably most of alcohol addicted patients show it as an isolated low-severity symptom, at the beginning of their addiction disease, and at this point it is easy to treat it, because opioid receptor antagonists, such as naltrexone or nalmefene, may be enough to overcome the early low-severity addiction.

The problem is that severity of alcohol addiction increases progressively if impaired drinking control is not treated from the addiction process beginning. While disease progresses, some other comorbidities associated with alcoholism severity increasing, appear such as psychiatric disorders, cognitive deficits, family-job adjustment difficulties, financial-legal problems. Even alcohol withdrawal syndrome may be superimposed.

High severity alcohol addicted patients should be engaged in an abstention oriented treatment program, starting by an alcohol detoxification treatment, followed by medications with proven efficacy on relapse prevention such as naltrexone, acamprosate or disulfiram associated with psycho-social treatment (Kranzler & Soyka, 2018). However, clinical evidence indicates that these patients usually reject to stop drinking, (at least on the beginning of the treatment), and even

when motivational intervention may help, usually it is not enough for long term patient stabilization if proper medication is not administered.

The belief that control over drinking is voluntary and depends on the patient's willpower is widespread. Even when patients stop drinking, usually they hope to have a drink in the future and don't accept the goal of complete and continued abstinence. Besides that, some alcohol addicted patients don't achieve abstinence but are able to reduce alcohol consumption significantly receiving an opioid antagonist at the treatment beginning, and later it's also possible they might even change the original objective of reduction for another of abstinence. In any case, what is really important is to get alcoholic patients into treatment (Rehm et al., 2013).

Reduction treatment programs may be better accepted for most of patients, especially at the beginning of the alcoholism-treatment, favoring adherence and retention into the treatment program. Therefore, when continued abstinence is not possible after a detoxification treatment, opioid receptor antagonists may induce a reduction in total and daily alcohol consumption, and when the prior daily alcohol consumption level was very high, even a small reduction in consumption may yield a substantial decrease in diseases and injuries secondary to very heavy drinking (Rehm et al., 2012; Laramée et al., 2015).

Alcohol consumption reduction for low-severity alcohol-dependent patients

Alcohol total and continued abstinence is the ideal goal when one wishes to recover from alcohol addiction, then stop drinking can be easy if patients are ready to do it, especially if they receive help with specific medication for alcohol detoxification. However it is very difficult not having a drink again later and the problem is that just one drink may drive the patient to relapse, due to the Deprivation Effect (Sinclair & Alho, 2002; Guardia-Serecigni, 2015a).

That's why reduction programs are effective for the low-severity alcoholic patients. Naltrexone and nalmefene have shown an alcohol consumption reduction from the first day of treatment, reaching a significant difference from placebo from the second month of treatment onwards (Guardia et al., 2002; Anton et al., 2006; Van den Brink et al., 2014).

Just one opioid antagonist tablet (50 mg of naltrexone or 18 mg of nalmefene), taken at least one hour before the first drink, may reduce the one drink impact of the addicted brain decreasing Alcohol Deprivation Effect intensity, allowing this way to a low-severity alcohol-dependent patient to stop drinking, and avoid relapse to heavy drinking; however high severity alcoholism, high alcohol impact on the brain, or not taking medication properly may interfere with this treatment success (Guardia-Serecigni, 2015b).

Opioid antagonists treatment using naltrexone or nalmefene is safe, well-tolerated, simple, and does not require psychotherapy, but just motivationally oriented medical management and psycho-social support for helping with other "problems" that may increase relapse risk. However, a poor outcome may be expected when the patient shows high severity alcoholism characterized by a full morning withdrawal syndrome or any psychiatric, addictive or medical active comorbidity that have not been stabilized before reduction treatment start.

In addition, opioid antagonists may not be indicated when the patient have an active opioid dependence disorder or needs to take opioid medication for pain, caught, diarrhea, or is pregnant nursing, or suffers a severe liver or kidney disease.

Stable Remission

If the patient takes the opioid antagonist every time he/she will have a drink, an extinction pharmacologic process develops because such medication decreases or even removes the alcohol reinforcing effect. The repetition of the experience of drinking alcohol, not paired with its expected reinforcing effect, induces an effective extinction process (Sinclair, 2001) allowing the patient to recover his/her freedom to choose between either not drinking alcohol or maintaining a low-risk dinking, that means below 40 grams of alcohol per day in men, and below 20 grams in women. (Witkiewitz et al., 2018).

Most alcohol addicted patients prefer drinking reduction goals because they do not want to give up drinking completely. In fact, if they learn to maintain low-risk drinking it's possible to avoid heavy drinking negative consequences successfully and obtain the same benefits of those who remain in continued alcohol abstinence (Falk et al, 2010). Therefore, they are just behaving as alcohol addiction free people. At this point it may be considered that the patient reached alcoholism clinical remission and when this occurs there is a clear improvement in his/her self-efficacy, self-esteem, mood, anxiety, sleep disorder, and other psychiatric symptoms commonly secondary to hopelessness, despair and desperation because of out of control drinking. At the same time, their families recover confidence on the patient and they get out of patient's uncertainty, frequent relapsing behavior; the above produces on the recovered patient a big improvement in family relationships and work capacity.

Finally, alcoholic patients may forget about the alcohol problem that has been interfering in their lives, but that now is over. They have recovered the ability to control their drinking, and now they may have a "normal" live. Drinking is not a problem anymore, and the person stops worrying about drinking control and may focus on other individual, vocational, and family projects.

Alcoholism Recovery

From our clinical practice and research studies, we have assessed the efficacy of opioid antagonists in different alcohol dependence severity levels as well in accordance with diverse subjective outcome expectations of each patient (Guardia et al., 2002; Guardia et al, 2011, Gual et al, 2013).

Although patients say they prefer to stop drinking they don't reject the possibility of having a drink in the future, and very few patients are engaged, (at least at the treatment beginning), with a strict continued alcohol abstinence. Patients and their families don't know about Deprivation Effect, and they even reject to accept this issue, because it's easier to keep thinking that some weeks or months without drinking will heal their alcoholism, and afterwards, they will easily recover the ability to control their drinking behavior. The truth is that sooner or later most of patients try to have a drink and, if they are not protected by an opioid antagonist there's a big chance to relapse. An effective treatment program depends firstly on the patient's preferences (reduction vs. abstention), but also on alcoholism severity. If the patient has the expectation to have a drink in the future, an opioid antagonist is mandatory to provide protection against relapse. But if it's a

case of a severe alcohol addiction, other factors may override opioids antagonist protective thus alcohol continued abstention is the most effective recovery option (Guardia-Serecigni, 2011; Guardia-Serecigni, 2015a).

The Self-Monitoring Approach

Ancient approach of alcoholism was characterized by a more active role of the therapist while the patient was more passive. Motivational intervention style gives back patients the most prominent role (Volpicelli et al., 2001; Miller & Rollnick, 2015).

In the clinical practice, we can see frequently that patients have their own treatment plan and recovery expectations. They are convinced their plan is better than any other designed by a therapist and usually don't accept another plan if they don't believe that it will work in accordance with their beliefs, wishes, needs or preferences.

The first step, before starting treatment is that the patient decides if he/she prefers an abstention or a reduction oriented treatment program; at this point it's important that the patient have been previously informed about the details of each one, and that he/she has a free decision.

It is very important that patients start self-monitoring their alcohol consumption in the easiest simple way, such as writing down just the number of daily drinks they have had. Then, if they bring their self-monitoring to each medical visit, they become confronted by their own records, engaged in an honest disclosure therapeutic relationship, and at the same time begin to recognize and take on responsibility about their own heavy drinking.

Alcohol addiction treatment has several obstacles, mostly at the beginning, but that may reappear after a relapse. People who suffer of alcohol addiction usually show guilt and shame feelings, because most people don't understand that alcoholic drinks are potentially addictive substances, and once the addiction has developed there's a biological "necessity" to drink alcohol rendering more difficult to control the own drinking behaviour. In fact, for the addicted person it's no easy to avoid drinking alcohol neither to avoid heavy drinking after a first drink.

On the other hand, the addiction Stages of Change determine some patient's subjective understanding, attitudes, and decision-making. Motivational readiness for changing patient's drinking patterns may be variable. When negative consequences are important or the patient has been threatened with divorce or other penalties, they are usually ready to stop drinking, but only temporarily. At the beginning of the treatment every patient thinks that after some weeks of sobriety addiction will be over, and they will be able to control their drinking again. But they are not planning a complete and continued abstention.

Facing the fear to be judged or not to be understood, patients tend to deny, minimize, or justify, their heavy drinking. In the usual approach the therapist has to find out how much alcohol the patient drank using some measures that may be persecutory, such as getting collateral information from the family as well ethanol (or of its metabolites) urine or breathe testing. This situation may drive the patient to deny alcohol consumption even more and will preclude his or her acknowledgement of alcohol addiction or problem drinking.

The self-monitoring approach is based in the own information given by the patients, through their daily alcohol consumption records. The advantage of this procedure is that the therapist openly accepts patient's consumptions and it also favours patient's acceptance that their alcohol consumption is something already expected and unavoidable. If patients acknowledge their excessive alcohol consumption in spite of their purpose to reduce drinking, then they may acknowledge also their difficult to control drinking and also the necessity of external help.

With this approach, the patient-therapist relationship becomes a working alliance which promotes a more active role of the patient, whose purpose is an alcohol consumption reduction. At the beginning of the treatment patients usually believe they are able to control drinking by themselves and don't need external help, but just to improve their own willpower.

When patients acknowledge alcohol addiction symptoms such as the need to drink and the difficult to control drinking, they may develop a better understanding of their addictive disease, the necessity of external help and may have a better acceptance of a medication, such as naltrexone or nalmefene.

When patients start to take these medications properly is when their relationship with alcohol drinking begins to change, and not only about their behaviour of drinking but also about their expectations, beliefs, attitudes, and decision-making, about drinking alcohol.

Repeating the experience of drinking, after taking a tablet of an opioid antagonist, patients feel a progressive decrease on the psycho-biological need for a drink and progressively recover their freedom to decide when they wish to stop drinking alcohol because now they are able to choose freely among all different beverages. This decrease in the necessity to drink alcohol is the external demonstration of the addictive conditioning extinction process.

The other important part of the self-monitoring sheet is the daily record of taking (or not taking) the antagonist opioid tablet, because it favours the understanding of the relationship between the pharmacological treatment and its therapeutic effects on the addictive disease.

This is a step wise procedure that has some milestones to reach progressively and needs patient's acceptance and collaboration to reach his or her complete self-management. At first glance it seems easy to get, but usually some drawbacks that interfere with it appear. Therefore it is important to detect possible interferences and work with them in order to reach the proper medication self-administration.

Alcohol-dependent patients have their own beliefs, wishes, plans and decisions. They are not going to do what another person think is better for them, unless something experienced by themselves changes their previous beliefs, wishes or plans. The self-monitoring approach allows patients to sequentially discover evidences against their previous misbeliefs and wrong decisions that, properly assisted by the therapist, may favor the evolutionary change towards more appropriate attitudes and decisions.

Furthermore, during the course of treatment, an analysis can be made about factors increasing drinking risk and patients may learn coping strategies that favor low-risk drinking. If we treat at the same time psychiatric and addictive comorbidities until their stabilization, alcoholism severity and the relapse risk may be reduced substantially, and the outcome may be improved.

Theoretical advices on relapse prevention are usually not incorporated by patients until they have passed through their own risk situations that have induced a craving episode. These are teachable moments that may be important for the patients' education helping them to change misbeliefs, and unproductive attitudes, and behaviors, in order to avoid heavy drinking. This treatment needs a certain degree of motivation, problem-recognition, and the patient's intention to reduce drinking.

Therefore, the self-monitoring approach helps patients to (1) become aware of their alcohol problem, (2) acknowledge the necessity of external help, (3) understand opioid antagonists therapeutic effects, (4) accept they have to follow the low-risk alcohol consumption guidelines, (5) that they will have to take care of their alcohol addictive disease for a long time and (6) they might also have to take this or other medications, mostly on relapse episodes, although they will enjoy very long periods of remission, and even free of medication.

Conclusions

1. Alcohol addiction is a persistent and relapsing disease, because the addictive conditioning is very difficult to extinguish.
2. Most alcohol-addicted patients prefer drinking reduction goals, but the decision about reduction vs. abstention depends also on the severity of the alcohol use disorder.
3. The self-monitoring approach favors a more active and engaged roll of the patients and an easier acceptance of their addictive disease.
4. Having a single drink, after a period of alcohol abstention, may drive the patient to relapse, due o the Alcohol Deprivation Effect.
5. Opioid receptor antagonists (such as naltrexone or nalmefene) block the Alcohol Deprivation Effect and prevent that an occasional alcoholic drink induces a relapse.
6. Opioid antagonists treatment is safe, simple, easy to comply and well accepted by patients.
7. Low-severity alcohol-dependent patients, who choose a reduction goal, may have a good outcome if they take an opioid receptor antagonist.
8. If patients maintain a (continued o occasional) low-risk drinking, and avoid negative consequences of heavy drinking, they reach a clinical remission of alcoholism.

9. Reducing alcohol consumption, below risk-drinking levels, may obtain the same good outcome as continued abstinence.
10. Since reduction-oriented treatment adapts better to the wish of the majority of patients who start alcoholism treatment, they may feel more committed to it, and show a better acceptance, adherence, and retention in the treatment program.
11. However, high severity alcohol-dependent patients should be geared towards abstinence treatment program.

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