Capítulo 108

An analysis of the psychiatric treatment efficiency for alcohol use disorder: An integrative review

https://doi.org/10.56238/methofocusinterv1-108

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ABSTRACT
Alcohol addiction has been a problem in Brazil and it tends to get worse even more, the high consumption of alcohol can lead to many diseases, some are acute diseases and chronic disorders. There are many methods to treat these people and reduce the consumption of alcohol, one of the methods is the use of drugs which inhibits the desire for alcohol. For this reason, this integrative review has the objective of reviewing the efficacy of the psychiatric treatment of alcohol dependency with the drugs naltrexone, disulfiram and acamprosate. This integrative review was made with data from: US National Library of Medicine (PubMed); Scientific Electronic Library Online (SciElo). The final sample was 18 articles; The results show that the psychiatric treatment of the alcohol dependency with the studied drugs (naltrexone, disulfiram and acamprosate) have been shown to be effective.

Keywords: alcohol dependency, psychiatric treatment of the alcohol dependency, alcohol dependency epidemiology.

1 INTRODUCTION

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a drink is defined as 14g of alcohol, the quantity present in a can of beer, a long neck bottle, a small glass of wine, a bottle of "ice" and a shot of some distilled spirit13 . The NIAAA also defines binge drinking as the consumption of 5 or more drinks on a single occasion in the last 30 days for men, and 4 or more for women. Such binge drinking causes intoxication, and is associated with violence, accidents, risky sexual behavior, chronic disease and alcohol dependence, and other problems .12

The First National Survey on Alcohol Consumption Patterns in the Brazilian Population, conducted in 2007, interviewed a total of 3007 people over 13 years old and of both sexes from 143 different municipalities, with the result that approximately 16% of the individuals consumed alcohol on a binge 10.

Through the Third National Survey on Drug Use by the Brazilian Population, a survey conducted with the population of the entire national territory in the fourth quarter of 2015, in several urban and rural municipalities, with people of both sexes, age between 12 and 65 years, totaling 153,095,000 people, with 1640 people interviewed, it was possible to observe that 16.5% of the population was binge drinking, approximately 25 million people1 .

In addition, individuals with alcohol dependence were considered those who scored three or more of the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and the criteria used were, spending much of their time to get; use or recover from the effect of the substance; use the substance more often or in larger quantities than intended; needed larger amounts (increased dosage) to get the same effect; could not decrease or stopped using substances; continued to use the substance even after knowing it was causing or aggravating physical or mental health problems; stopped doing or decreased time devoted to social, work, or leisure activities due to substance use; Positive response to withdrawal symptoms. Having resulted in 1.5% of the population, approximately 2.3 million people between 12 and 65 years of age presented dependence, in the last 12 months .1

Compared to the binge drinking of the two surveys in Brazil, it had an increase of 0.5%, representing a possible increase in alcohol dependence, since binge drinking can progress to possible dependence.

For this reason, this integrative review aims to identify the effectiveness of psychiatric treatment with the drugs naltrexone, disulfiram, and acamprosate in people suffering from alcohol dependence disorder, from the literature.

2 METHOD

The method used was the integrative systematic review, which originates from the integration of opinions, concepts or ideas coming from the researches that were used in the method5 . It is the elaboration of a synthesis organized into different topics with the intent of broadening the understanding of the subject. The integrative review must follow 6 steps, which are: identification of the theme and selection of the research question, establishment of inclusion and exclusion criteria, identification of pre-selected and selected studies, categorization of the selected studies, analysis and interpretation of the results, presentation of the review/synthesis of the knowledge3 .

The research question used was formulated in the PICO strategy (P-population; I-interest; C-comparison; O-outcome/outcomes). The correspondents of the PICO question were: P = persons suffering from alcohol dependence disorder ; I = psychiatric treatment with the use of alcohol reduction medication; C = no psychiatric treatment ; O = analyze effectiveness of psychiatric treatment for reducing alcohol consumption compared to no treatment. The final formulation of the base question of this integrative systematic review was, "In people suffering from alcohol dependence disorder, is psychiatric drug treatment effective in reducing alcohol consumption?"

The choice for the integrative review was due to the integration of opinions, concepts or ideas coming from the researches that were used in the method5 . In order to elaborate a synthesis organized into different topics with the intent of broadening the understanding of the subject .3

The scientific studies were searched in the PubMed and SciElo databases. Inclusion criteria were: scientific studies indexed in journals published in Portuguese and English, with full text from 1990 to 2022. This time frame is justified by the date of discovery and the beginning of drug trials for the treatment of alcohol dependence disorder, which are still in use. The keywords used were: alcohol dependence disorder, psychiatric treatment for alcohol dependence, and alcohol dependence epidemiology. As exclusion criteria, published articles that were not full-text and those that did not follow the proposed theme were excluded.

The study was developed from March to June 2022, through data collection that began through a preliminary exploratory reading, where 35 articles were identified from a careful and selective reading and the fulfillment of exclusion criteria 18 articles were selected

After selecting the studies, all the material was recorded, and the main information was compiled into categories. Subsequently, a descriptive analysis of each category was performed in order to establish an understanding and broaden the knowledge about the researched theme.

This research took into consideration the ethical aspects according to the norms of the Brazilian Association of Technical Norms (ABNT, 2002) and the Copyright Law (Brazil, 1998)

3 RESULTS AND DISCUSSION

Eighteen articles were selected for the systematic integrative review, and the following chart shows the 11 articles on the pharmacological treatment of alcohol dependence disorder according to title and author, year, journal, objective, and conclusion.

Title and Author	Year	Magazine	Goal	Conclusion
Effectiveness of acamprosate in treatment outpatient of alcohol addicts - Danilo Antonio Baltieria and Arthur Andradeb War 2	2003	Rev Bras Psychiatr 2003;25(3):156-9	Evaluate the effectiveness and safety of the acamprosate in treatment outpatient of seventy-five sex patients male, with age between 18 and 59 years old, with diagnosis of reliance on alcohol by ICD-10.	Acamprosate has been shown to be safe and effective in treatment of alcohol-dependent patients and in the maintenance of abstinence for 24 weeks.
Treatment pharmacological of alcohol dependency - Luís André Castro and Danilo Antonio Baltieri 4	2004	Brazilian Journal of Psychiatry	review pharmacotherapy for dependency of alcohol with emphasis on naltrexone, disulfiram acamprosate.	
TREATMENT PHARMACOLÓGICO USED NA DEPENDENCE ON ALCOHOL: ONE REVIEW - Adriano da Costa Tavares Mazurek Fabio Bahls Machado 3 6	017	The opioidantagonist naltrexone decreases relapse, reduce days of consumption and prolongs periods of abstinence. Acamprosate restores the normal activity of the glutamate and GABA systems. Disulfiram has demonstrated be more effective for patients who believe in its effectiveness and remain adherent to the reatment mento. Ondansetron has shown promising in the onset alcohol dependence early, but needs study more extensive. Topiramate (up to 300 mg/day) was more effective than placebo in the treatment of alcohol dependence.	search information about dependency to alcohol as well as its treatment.	alcoholism is a condition of dependency, characterized by a compulsion to consume alcohol in an uncontrollable way, making with which its treatment and prevention is a constant concern. The main problems related to are concerning the confrontation of addiction and treatment pharmacological. Being the drugs disulfiran, naltrexone, acamprosate available for dependence and the coadjuvant treatment to avoid possible relapses with the drugstopiramate, gabapentin, carbamazepine. still have few drugs to be used in the treatment of alcohol dependence. The absence of the

				pharmacist in the social care center (CAPS) and the insertion of the family as well as a psychological and pharmacotherapeutic follow-up can help to insert the individual back into society.
The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder Charlotte H. Jørgensen, Bolette Pedersen, and Hanne Tønnesen [8]	2011	Alcoholism: Clinical and Experimental Research	The aim of this study was to review the effect of disulfiram in the treatment of patients with AUD. The effect of disulfiramwas evaluated according to the primary outcome of an intake of alcohol below 30 and 20 g／d for menand women, respectively, as wellas secondaryoutcomes such as days until relapse, alcohol intake, and numbers of drinking days.	Supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. However, there is a need for more homogeneous and high-quality studies in the future regarding the efficacy of disulfiram.
Efficacy of Naltrexone and Acamprosate for Alcoholism Treatment: A Meta-Analysis Henry R. Kranzler and Jeffrey Van Kirk [9]	2001	Alcoholism: Clinical and Experimental Research	In the absence of studies that compare the effects of these medications, we used meta-analyticapproach to the literature to compare the efficacy of naltrexoneand acamprosatein alcoholism treatment	Both naltrexone and acamprosate are efficacious in reducing alcohol consumption in alcoholics. However, their specific role in alcoholism treatment remains to be more clearly defined. New approaches to the use of these medications and development of new medications are needed if pharma- cotherapy is to play a substantial role in the treatment of alcoholism.
Mechanism of Action of Acamprosate. Part I. Characterization of Spermidine-SensitiveAcamprosate Binding Site in Rat Brain Mickael Naassila, SalouaHammoumi, Elisabeth Legrand, Philippe Durbin, and Martine Daoust 11	1998	Alcoholism: Clinical and Experimental Research	The aim of this study was to characterize acamprosate binding and establish whether this showed any relation to sites on the NMDA receptor complex	in, at least one binding site of acamprosate on brain membranes is spermidine- sensitive, and probably di- rectly modulates the NMDA receptor complex. This bind- ing site is probably not a "spermidine receptor" on the NMDA receptor complex, but it modulates this site allos- terically and can in turn be modulated by spermidine bind- ing. The consequences for NMDA receptor function are likely to be complex, with acamprosate being best described as a "partial co-agonist" for the NMDA receptor. This action may be relevant to its interactions with ethanol and the NMDA receptor, and with its clinical use in relapse prevention.
Comparison of disulfiram and placebo in treatment of alcohol dependenceof adolescents HELMUT NIEDERHOFER& WOLFGANG STAFFEN 14	2003	Drug and Alcohol Review	The aim of our study was to assess the efficacy and safety of long-term disulfiram treatment in adolescent alcohol dependence. In this double-blind, placebo-controlled study we recruited 26 adolescents, aged 16 19 years, withchronic or episodic alcohol dependence. Patientswere allocatedtreatment randomlywith disulfiram (200 mg daily) or placebo for 90 days. Patients were assessed on the day treatment started and on days 30 and 90 by interview, self report, questionnaire and laboratoryscreening. Patientswere classified asabstinent, relapsingor non-attending. Time to first treatment failure (relapse or non-attendance) was the primary outcome measure. Thedisulfiram (n = 13) and placebo (n = 13) groups were wellmatched in terms of baseline demographicand alcohol-related variables To determine theeffectiveness ofopioid antagonists in attenuatingor preventingthe relapses in alcohol	Twenty-six (of 49) patients completed the 90-day double- blind treatment. The proportion of patients who remained abstinent (i.e. had not had treatment failure) was higher in the disulfiram group than in the placebo group throughout the 90 days of treatment (Mantel - Cox test). On day 90 two of theplacebo-treated patients,compared with seven disulfiram-treated patients, had been abstinent continuously (p = 0.0063). Mean cumulative abstinence duration was signifi- cantly greater in the disulfiram group than in the placebo group [68.5 (SD 37.5) vs. 29.7 (19.0) days; p = 0.012]. The most common reason for withdrawal was relapse in both groups. More than 50% of withdrawals occurred within the first 30 days of treatment; thereafter the rate diminished progressively. There were no significant differences between the disulfiram and placebo groups for the 44 checked side effects.

			dependentsin comparisontoplacebo, other medicationsand sychosocial treatments.	
ROESNER, Susanne et al. Opioid antagonists for alcohol dependence [15]	2010	Cochrane databaseof systematic reviews		The review included 29 RCTs. Except two of nalmefene, all others investigated NTX. In comparison to placebo, a short- term treatment of NTX significantly decreased the relapse [RR (95% CI) = 0.64 (0.51 to 0.82)] and decrease the return to drinking [RR (95% CI) = 0.87 (0.76 to 1.00)]. In the respect of acceptability, NTXsignificantly diminishedwithdrawal [RR (95% CI) = 0.82 (0.70 to 0.97). While a medium-term treatment of NTX gave no benefit for relapse prevention, it was found to be beneficial on increasing time to first drink and diminishing craving. A medium-term treatment of NTX was superior to acamprosate in reducing relapses, standard drinks and craving. NTX plus an intensive psychosocial treatment (PST) was not superior to NTX plus a simple PST on any short-term outcomes. For a medium-term treatment, NTX plus an intensive PST was superior to NTX plus a simple PST in increasing time to first drink and decreasing craving.
SRISURAPANONT, Manit; JARUSURAISIN, Ngamwong. Naltrexone for thetreatment alcoholism: a meta-analysis of randomized controlled trials. [16]	2005	International Journalof Neuropsychopha rmacology	Many trials of naltrexone have been carried out in alcohol-dependent patients. This paper is aimed to systematically review its benefits, adverseeffects, and discontinuation of treatment.	A total of 2861 subjects in 24 RCTs presented in 32 papers were included. For short-termtreatment, significantly decreased relapses [relative risk (RR) 0.64, 95 % confidence interval (CI) 0.51- 0.82], but not return to drinking (RR 0.91, 95 % CI 0.81-1.02). Short-term treatment of naltrexonesignificantly increased nausea, dizziness, and fatigue in comparison to placebo [RRs (95% CIs) 2.14 (1.61-2.83), 2.09 (1.28-3.39), and 1.35 (1.04-1.75)]. Naltrexone administration did not significantly diminish short-term discontinuation of treatment (RR 0.85, 95% CI 0.70-1.01). Naltrexone should be accepted as a short-term treatment for alcoholism.
TEIXEIRA, Joana. Pharmacological Treatment Alcohol Abstinence Syndrome. 17	2022	ActaMedica Portuguesa	Review of guidelines available in the literature about Treatment from alcohol withdrawal syndrome in order todetermine which pharmacological treatment is recommended.	It is essential to maintain a high level of suspicion for the possible onset of alcohol abstinence syndrome in all clinical settings. In such cases, it is important to know how to intervene early.

WRIGHT, Curtis; MOORE, Richard D. Disulfiram treatment of alcoholism. [18]	1990	The American journalof medicine	For 40 years, disulfiram has been the most frequentlyused alcohol-aversive drug byAmerican physicians in the treatment of alcohol dependency disorders .We reviewed the clinical literature regarding the risks, benefits, indications, and efficacy of this controversial drug and summarized current knowledge of this therapy.	Disulfiram will produce an aversive reaction with ethanol, usually at a dose between 250 mg/day and 500 mg/day, although some patients may not have an aversive reaction at this level. Cardiac, hepatic, and neurologic toxicity can also occur within this dosage range. If disulfiram is to be used, the patient must clearly understand the risks of drinking while taking the drug, and the physician and patient must agree about the need for continued clinical supervision and monitoring for efficacy and side effects. The physician must also recognize that disulfiram is only an adjunctive therapy and that continued support, supervision, and other therapeutic measures are required. Disulfiram is probably effective in reducing the frequency of alcohol consumption in the compliant patient over the short term (e.g., 6 months). Certain subgroups of patients, such as those who are older, those who are more socially stable, and those who are well-motivated, may experience a beneficial effect for longer periods. The drug may be most effective in reducing short-term alcohol consumption when the compliance of the patient issupervised, although

Alcohol acts as a central nervous system (CNS) depressant, but its abuse causes social problems.Ethanol disrupts the delicate balance between excitatory and inhibitory influences in the brain as well as causing disinhibition, ataxia, and sedation. Chronic use of ethanol causes tolerance, and physical dependence is evidenced by alcohol withdrawal syndrome .7

After oral administration, Ethanol is rapidly absorbed from the stomach and small intestine, being delayed by the presence of food, which increases the gastric emptying time, since it is more rapidly absorbed from the small intestine. After its absorption, the alcohol enters the bloodstream distributing to the entire body .7

Alcohol metabolism begins by the gastric and hepatic Alcohol Dehydrogenases (ADH), resulting in lower Blood Alcohol Levels (BLE) than those ingested. Alcohol is metabolized primarily by hepatic oxidation of alcohol to acetaldehyde by ADH and then to acetic acid by aldehyde dehydrogenase (ALDH). Small amounts of ethanol are excreted in urine, sweat, and breath, but metabolism to acetate transforms 90 to 98% of ingested ethanol .7

Once this ethanol reaches the nervous system, it will alter the balance between excitatory and inhibitory influences in the brain, causing anxiolytic effects, ataxia, and sedation. Several proteins are involved in this process of neuronal excitability, but it is still not known for sure which of them are influenced by ethanol, but among them the most studied are the y-aminobutyric acid receptors which are controlled by ligands (GABAa), having their function accentuated by some classes of sedatives, hypnotics and anesthetic agents; another receptor is the excitatory ionotropic glutamate receptor, such as the N-methyl-D-aspartate (NMDA) class7 .

The symptoms caused by alcohol withdrawal begin within three to 12 hours after discontinuation. Among them are tremors, vomiting, sweating, nausea, insomnia, tachycardia, anxiety, blood pressure elevation, and mood changes. The psychiatric pharmacological treatment of alcohol dependence disorder aims to start the rehabilitation process of the patient, alleviating the withdrawal symptoms and preventing the complications that can happen due to abstinence .17

There are drugs approved by the Food and Drug Administration (FDA) that work in a complementary way to alcohol detoxification, such as Disulfiram, Naltrexone and Acamprosate6 .

The first recorded clinical use of disulfiram was in 1949, and it became popularly used for the treatment of alcohol dependence, due to its aversive effect on alcohol and not due to the combined action of therapy. This aversive effect occurs in both alcohol dependent and non-dependent people, as long as the individuals take sufficient doses in the correct manner18 . Disulfiram inhibits the activity of ALDH and causes an increase in acetaldehyde by 5 to 10 times above the normal level of when ethanol is ingested; thus, the ingestion of alcohol by patients being treated with the drug causes acetaldehyde intoxication7 . This accumulation of acetaldehyde generates an increased disulfiram-ethanol reaction that manifests itself in the form of increased pulse rate, redness of the face, tachycardia, hypotension, nausea, vomiting, and in more severe cases, it can even cause cardiovascular collapse. For this reason, disulfiram is a drug indicated for patients who wish to remain abstinent8 . Patients who adhere to disulfiram treatment should be warned that alcohol intake can cause these side reactions7 . Supervised treatment with disulfiram over a short period is effective in people who have alcohol dependence compared with placebo8 . In a study of 26 people suffering from alcohol dependence disorder where 13 were blindly chosen to receive disulfiram and 13 were given placebo for a period of 90 days, the people treated with disulfiram were more successful in remaining abstinent from alcohol than the placebo group14 .

The drug naltrexone is chemically related to the opioid receptor antagonist (naloxone), and it works best if used in conjunction with some type of psychosocial therapy7 . Naltrexone decreases a person's desire to drink alcohol, and is effective in short-term (less than 12 weeks) treatment for alcoholism, preventing relapse and its recommended dose is 50mg/d16 . This drug attenuates the pleasurable effects of alcohol, which may be an answer to why individuals have less desire to ingest alcoholic beverages, a factor that influences the lower rate of relapse after short-term treatment and the lower chance that, if for some reason the individual starts to ingest alcohol again, he/she will be diagnosed with alcohol dependence again15 . Opioid antagonists have been shown to be effective in the treatment of alcohol dependence, with the use of naltrexone in a short period of time (less than 12 weeks) reducing the chance of a relapse to 36% and also reducing the chance of the person returning to be dependent on this substance to 13%18 . Some effects of naltrexone persist after short-term treatment is discontinued. Once, the effects of abstinence from alcohol use established by the use of the drug persisted, in a diminished form, after 4 months of discontinuation15 .

Acamprosate (calcium acetylhomotaurinate) is a drug that was first marketed in France and European countries in order to decrease the craving for alcoholic beverages via the glutamatergic system, preventing relapse in people suffering from alcohol dependence disorder. Ethanol and acamprosate may have similar targets on the NMDA (N-methyl D-Aspartate) receptor complex which may explain the clinical effects of acamprosate11 . These receptors appear to regulate dopaminergic activity in ways that reduce positive reinforcement related to ethanol consumption4 . It is a GABA analog, undergoing little hepatic metabolism and being excreted mainly by renal filtration, it is eliminated after 18h after oral administration7. Compared with patients receiving placebo, those receiving acamprosate treatment were more successful in remaining alcohol-free over the 24-week treatment period. Acamprosate has shown few side effects when used, and is a well-tolerated and safe drug to use2 . In an analysis on the effectiveness of acamprosate, a sample of between 3077 and 3204 people was used. People treated with acamprosate had a 7% to 13% higher success rate than people treated with placebo .9

4 CONCLUSION

The literature review provided a greater understanding of how alcohol works in the human body, as well as an in-depth analysis of the alcoholism as a disease in Brazil based on epidemiological data, and a better knowledge about the drugs used for its treatment.

Alcohol acts as a central nervous system depressant, generating disinhibition, ataxia, and sedation. However, with a constant consumption, it generates a tolerance to the substance, making it necessary to consume larger quantities, causing several future health problems and disturbances at the time of consumption.

From the researches done, alcohol dependency is a recurrent disorder in Brazil with a tendency to increase as the years go by, thus, the treatment of this disease must be seen as something beneficial in society.

The drugs researched were Acamprosate, Disulfiram, and Naltrexone, and, after reading the materials used, it can be concluded that these drugs have proven to be effective in treating alcohol dependence disorder.

Taking into account the patient's demands, there is a better adequacy of treatment according to the time the patient should be treated and the ideal dose, which varies according to the individual's weight; these factors should influence the health professional when choosing the ideal drug.

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