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α-2 Adrenergic Recipients, Valproic and Carbamazepine Acids as an Adjuvant Treatment in Moderate-Grave Alcoholic Abstinence: Systematic Review

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Abstract

Alcohol dependence is among the main risk factors for health in most developed and developing countries. Therapeutic success in moderate-grave abstinence could be increased with adjuvant treatment to benzodiazepines. In our environment, agonists α-2 (clonidine and dexmedetomidine), valproic acid and carbamazepine are the most used. The objective of this work was to carry out the thorough search, critical analysis and summary of the evidence to provide an overview of the effectiveness of these drugs when used without a certain time of treatment compared to each other, against any intervention, placebo or other interventions. A bibliographic search was carried out in databases (PubMed/Medline, Lilacs, and Embase). Two reviewers selected, extracted the data and evaluated the bias risk of independently included studies using the covidence software. The disagreements were resolved by consensus. We perform meta-analysis using revman 5.3 and subgroup analysis by study design. 22 studies were included where none of them presented a risk of bias in all domains, and most studies presented at least one domain with high bias risk. Studies with statistically low results showed that dexmedetomidine and valproic acid decrease the requirements of benzodiazepines in patients receiving placebo. In addition, when valproic acid is combined with benzodiazepines achieve a stable and continuous decrease in abstinence measured in CIWA-AR scale. Clonidine was the only one described that presented a decrease in heart rate against placebo with high significance, clinical situation to be in mind in front of the sympathomimetic syndrome that characterizes alcohol withdrawal syndrome.

Keywords: Alcohol, Abstinence, Carbamazepine, Valproic acid, Dexmedetomidine, Clonidine, Substance consumption

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Introduction

Alcohol consumption disorders are among the most prevalent mental disorders worldwide, being highly disabling and are associated with many physical and psychiatric comorbidities. This causes them to contribute substantially to increase morbidity and mortality worldwide. Argentina is one of the countries with the greatest alcohol consumed in the region. In our country there are consumption data of 9.8 L of pure alcohol per capita, for an 8 L regional average and with increasing projections for the year 2025 [1].

The consumption of this substance in moderate condition in most people considered healthy may not be detrimental, however, in some people, due to different genetic and/or environmental issues they lose control capacity developing dependence. Chronic alcohol exposure produces in the central nervous system (CNS) adaptive changes in various neurotransmitter systems, including GABA, glutamate and norepinephrine roads to compensate for alcohol-induced destabilization and restore a neurochemical balance. This adaptive phenomenon results in long-term reductions in the effects of alcohol in the CNS, that is, it generates tolerance. The abrupt reduction or cessation of alcohol intake produces an acute imbalance due to both the acute reduction of GABA's activity and the increase in glutamergic action, with the consequent hyperexcitability and development of abstinence symptoms that can begin in a few hours after the last alcohol intake. The positive regulation of dopaminergic and noradrenergic pathways could be responsible for the development of hallucinations and autonomous hyperactivity during alcoholic withdrawal syndrome [2-6].

When patients with a history of long-standing alcohol intake decrease or cease their consumption can present alcoholic abstinence syndrome (AAS) where the patient's cognitive functioning worsens, increases morbidity and hospital mortality, prolongs hospitalization days, adds costs elevated and increase the load of health personnel. The beginning can be abrupt, it is often preceded by signs that are not complicated or sometimes complicated by seizures. It may appear after 48 - 72 h after the last alcoholic intake [7].

In the natural evolution of severe abstinence where we can witness delirium tremens, the patient may die due to the serious hydro electrolytic imbalance or a crisis of hyperpyrexia and multiorgan failure. The repetition of the delirium tremens presents a risk of serious sequelae with the appearance of chronic deficit or dementia disorders [8].

The treatment par excellence in alcohol withdrawal syndrome is represented by benzodiazepines. However, treatment can offer difficulties both in the proper implementation of prophylaxis and the treatment being necessary to implement other drugs to control the symptoms of withdrawal and improve the survival of the patient.

Given the complexity of alcohol actions in the brain, the combination

of medicines could work better than individual agents alone by inducing additive effects through actions on multiple neurochemical objectives. To that end, several recent studies have evaluated this approach. Some available data suggest that agents that are not benzodiazepines can offer a safe and effective alternative for prophylaxis and treatment in AAS. On the other hand, some of the current protocols with benzodiazepines may be accompanied by different eventualities and, in some cases, significant side effects [9].

In severe abstinence, other non-benzodiazepine drugs are used, being in our environment α-2 (clonidine and dexmedetomidine), valproic acid and carbamazepine those of greater use. On the other hand, the use of neuroleptics can help control hallucinations [10].

In this review, a thorough search, critical analysis and summary of evidence has been carried out to provide an overview of the effectiveness of agonists α-2 (clonidine and dexmedetomidine), valproic acid and carbamazepine. That is, evidence from primary studies was included prioritizing randomized controlled studies or randomized quasi.

The construction of tables that synthesize the evidence they provide for each of the outcomes included, the quality of the evidence in a quick, accessible format and has been assessed on the quality of the evidence has also been carried out.

Material and Methods

We carry out a systematic review and a meta-analysis following the methods of cochrane [10] and the prism statements for reports [11, 12].

Eligiility criteria

Types of studies

Randomized clinical trials and non-random clinical trials. Systematic reviews were considered as a source of studies and other study designs were used only to describe the intervention.

Types of participants

Adult participants (≥ 18 years) of male and female sex with a diagnosis of alcohol consumption disorder in the period of moderate-shave withdrawal. The studies will be limited to written in Spanish and English.

Type of intervention

Studies with an intervention of agonists of adrenergic receptors α-2, valproic acid and/or carbamazepine without certain time of treatment compared to each other, against any intervention, placebo or other interventions.

Type of results measures

The primary outcome was the evaluation in the improvement of clinical parameters through validated scales, particularly the revised version (CIWA-AR). Other recognized and accepted scales for the evaluation of the symptoms will be shot alcohol withdrawal scale (SAWS), alcohol communicate. We also set out to characterize the adverse effects of the treatment, mortality and duration of hospital stay.

Search strategy

A bibliographic search was carried out in databases (PubMed/Medline, Lilacs, and Embase) without specifying dates period. In addition to the databases, a search for cross-references was made manually and literature in specialized magazines. The search strategy included headers of the database and key words where they were limited to random controlled tests (ECA) and non-randomized controlled tests (ECNA) using search filters. The search terms were grouped by concept using boolean operators (OR) and will combine using (and). The terms mesh, decs and emree of search were alcohol consumption disorder (alcohol use disorder), severe and severe alcohol withdrawal (moderate alcohol withdrawal syndrome/severe alcohol withdrawal syndrome) α-2-adrenergic agonist, dexmedetomidine, clonidine, valproic acid (Acid valproic/sodium valproate), carbamazepine, random controlled test (randomized controlled trial) and non-random controlled test.

Looking for other resources

Additional articles were found when reviewing the document references lists identified by electronic searches.

Data collection and analysis

After the elimination of duplicates, the remaining studies imported to a systematic review software called covidence (Covidence, N.D.), which was used to perform the selection, extraction and evaluation of the quality of the review components through title/abstract (TIAB) and the full text exam was done independently by two reviewers. The full text of all the studies considered potentially relevant was recovered. The discrepancies were resolved by consensus between them. In case of disagreements, it was resolved by a third party.

Big risk assessment in studies included

For this work, potential bias risks for all ECA and ECNA included through the cochrane tool were evaluated to assess the risk of bias [13]. This tool evaluates bias in six different domains. Random sequence generation (selection bias), allocation concealment (selection bias), participating and personnel blindness (realization bias), blindness of the outcome evaluators (detection bias), incomplete result data (dropout), selective results report (report bias). Each domain received a high or unclear bias risk score according to the author's criteria described.

Results

Description of studies

628 studies of all searched electronic databases were identified, 42 were excluded in duplicates. Of the 586 studies that were analyzed by title and summary, 537 were considered irrelevant to qualitative and quantitative synthesis; 49 articles in full text were recovered for a more detailed evaluation, 27 of them were excluded, 11 where participants do not meet inclusion criteria, 8 where the intervention does not meet inclusion criteria, 5 with study of the study that does not meet criteria of criteria Inclusion, 2 errors in comparators and 1 describes a study designed by another author. 22 studies fulfilled all the criteria to be included in the work.

The flow diagram summarizes the identification of the trials included.

Included studies

The details of the studies included below the annex will be listed.

They were included in review 22 essays with a total of 1150 participants: Agricola et al. [14], Balldin and Bokstrom [15], Baumgartner and Rowen [16, 17], Flygenring et al. [18], Hillbom et al. [19], Kalyoncu et al. [20], Lambie et al. [21], Longo et al. [22], Lucht et al. [23], Malcolm et al. [24], Manhem et al. [25], Mueller et al. [26], Myrick et al. [27], Reoux et al. [28], Ritola and Malinen [29], Robinson et al. [30], Rosenthal et al. [31], Schik et al. [32], Seifert et al. [33],

Stuppaeck et al. [34], and Wilkins et al. [35].

11 studies that compared carbamazepine vs another drug was included: Agricola et al. [14], Balldin and Bokstrom [15], Flygenring et al. [18], Hillbom et al. [19], Kalyoncu et al. [20], Lucht et al. [23], Malcolm et al. [24], Ritola and Malinen [29], Schik et al. [32], Seifert et al. [33], Stuppaeck et al [34].

5 studies that compared clonidine vs another drug were included: Balldin and Bokstrom [15], Baumgartner and Rowen [16, 17], Manhem et al. [25], Robinson et al. [30], 1 study Wilkins et al. [35] compare clonidine vs Placebo.

5 studies that compared valproic acid vs another drug was included: Hillbom et al. [19], Lambie et al. [21], Longo et al. [22], Myrick et al. [27], Rosenthal et al. [31], 2 studies compare [19, 28] valproic acid with placebo.

1 study that compares dexmedetomidine vs Placebo: Mueller et al. [26] was included.

The treatment duration varied from 4 days to 14 days. The countries of origin of the studies were Germany, Australia, Denmark, United States, Finland, Italy, New Zealand, United Kingdom, Sweden, and Turkey.

Excluded studies

27 studies were excluded, of which 11, participants did not comply with the inclusion criteria [36-46]. In 8 of the studies their interventions did not comply with the inclusion criteria [47-54]; 5 Studies did not meet the criteria of this work in their design [55-59]; 2 studies presented errors in comparators [60, 61] and 1 study describes a study designed by another author [62].

Risk of bias in studies included

None of the studies included presented under a risk of bias in all domains, and most studies presented at least one domain at high risk of bias.

Effect of interventions

Metanalysis was performed for studies that there were comparable interventions, with the same qualification scales for continuous result measures or had the same binary results. As we could not obtain concrete or homogeneous definitions of the scales to measure reducing withdrawal symptoms, dichotomous results were considered. The results are evaluated from nine main comparisons:

- Carbamazepine compared to other drugs.
- Carbamazepine + another drug, comparison to other drugs.
- Clonidine compared to another drug.
- Clonidine compared to placebo.
- Valproic acid compared to other drugs.
- Valproic acid compared to placebo.
- Valproic acid + another drug, comparison to other drugs.
- Dexmedetomidine compared to placebo.
- Carbamazepine compared to valproic acid and placebo.

Carbamazepine compared to other drugs

Although some clinical heterogeneity (studies designs, control types and the days of total trials) was observed, a global meta-analysis of carbamazepine treatment administered by any route vs other drugs was completed. The objective was to allow a significant meta-analysis of the same kind of drug with the same expected biochemical action.

Eight studies compared carbamazepine treatment vs other drugs [14, 18, 20, 24, 29, 33, 34].

In 7 studies [14, 18, 20, 24, 29, 33, 34] described abandonment rates for different causes (N = 426 patients), RR 1.08 (0.64, 1.80). The result was statistically not significant.

Delirium: Five studies reported delirium compared one with tiapride [14], one with barbital [18], one with oxacarbamazepine [32], two with benzodiazepines [20, 34] with an incidence of RR 1.30 (0.35, 4.80); 95% IC; 304 participants; I^2 = 15%.

Seizures: Five studies evaluated seizures where one [18] treated with carbamazepine presented the event, one compared to benzodiazepines [34] presented seizures in the control group, with an incidence of RR 0.97 (0.13, 7.11); 95% IC; 304 participants; I^2 = 0%.

Adverse effects: Four studies reported different adverse effects both in the carbamazepine group and in the control group, one with tiapride [14], one with barbital [18], two with benzodiazepines [24, 34] with an incidence of RR 1.38 (0.87, 2.19); 95% IC; 307 participants; I^2 = 0%.

Ciwaar: 2 studies refer to evaluation of this scale [24, 34] with an incidence of RR 2.10 (-4.69, 0.49); 95% IC; 123 participants; I^2 = 0%.

The quality of the evidence is low since all studies had a high risk of dropout bias and the number of events in each group was small, which resulted in broad confidence intervals that includes both the benefit and the appreciable damage.

Carbamazepine plus another drug compared to other drugs

Only one study [23] was found during the search which evaluated the use of carbamazepine plus another groups. Therapeutic efficacy was evaluated through different variables separately during the nine days of the protocol, where no differences (5% significance level) were observed in the total scores of the SAWS.

Together, participants treated with carbamazepine reported the most common adverse events: cutaneous rash, drowsiness, headache and nausea. Occasionally events such as acids elevation of liver enzymes, dizziness and tingling in members were reported. On the other hand, within the criterion of side effects this article [23] is the only one of all those who refer to the use of carbamazepine that demonstrates the incidence of diplopia and alteration in the march in the carbamazepine group which was transitory when suspending the suspending the treatment.

Mortality due to any cause, quality of life or hospital stay none of the studies included that compared carbamazepine reported this result.

Clonidine compared to other drugs

The review using clonidine has certain limitations being that in most studies there is a very small sample size, and in various patient populations. On the other hand, the objectives to investigate from the works differed from one other. Although some clinical heterogeneity was observed (the designs of the studies, the types of control drugs and the days of totals of the trials), in some results an evaluation was applied.

Five studies compared clone treatment vs other drugs [15-17 25, 30] with a total of 209 participants. These works described abandonment rates or suspension of treatment for different causes with RR 0.56 (0.27, 1.14).

Delirium: 2 studies refer to evaluation of this scale [15, 25] with an incidence of RR 0.60 (0.09, 4.23); 95% IC; 58 participants; $I^2 = 0\%$. This result is non-statistically significant.

The analysis scarcely sampled and described in these studies on events have limited detailed evaluation through meta-analysis. Only 1 study [30] with 40 patients described seizures in 2 patients who were receiving clonidine and 2 patients with hallucinations. 2 studies [15, 30] with 78 participants showed results of adverse events with moderate heterogeneity ($tau^2 = 3.78$; $Chi^2 = 2.64$, df = 1 (p = 0.10); $I^2 = 62\%$) and with RR 0.50 (0.02, 15.28). 1 study [25] with 20 patients described delirium for alcoholic abstinence in a patient per group. 1 study [16] showed a decrease in abstinence measured on a scale of different variables during treatment describing a decrease during treatment ($p < 0.001$) significantly lower in the group that received clonidine compared to that which chloriazepoxide received.

Adverse effects: Two studies [15, 30] reported different adverse effects in 9 of 78 participants such as seizures, hallucinations, orthostatic hypotension, drowsiness and nausea with an incidence of RR 9.78 (1.16, 82.25); 95%IC; $I^2 = 4\%$.

Clonidine compared to placebo

One study [35] describes the comparison of clonidine vs Placebo where the score used to measure the severity of withdrawal shows an increase of 0.95 points and a decrease of 3.9 points after the use of clonidine (previous mean 11.4 ± 1.9). Clonidine was significantly more effective than placebo (p = 0.004). The mean heart rate was 108 ± 4 beats per minute (bpm) in the patients evaluated. With clonidine administration, the mean maximum drop-in heart rate was 13.8 bpm vs 5.6 bpm with placebo. The difference between the effects of placebo and clonidine was highly significant (p = 0.002). This work concluded that, through the variables evaluated, clonidine suppresses alcohol withdrawal symptoms.

Valproic acid compared to other drugs

Two studies compared treatment with valproic acid vs other drugs [22, 31] with a total of 58 participants. Both studies report that valproic acid was well tolerated, with unpleasant effects related to mild nausea being described in two patients. The reduction in alcohol withdrawal symptoms occurred more rapidly and consistently in the valproic acid treatment group than in the benzodiazepine control group with a decrease in CIWA-AR scale values, although the difference between the groups was not statistically significant. Furthermore, they remained completely abstinent after six weeks compared to either of the detoxification groups [22]. When valproic acid was compared to phenobarbital, no differences were found between both groups in the different tests that were used, however, a marked decrease in withdrawal symptoms was evident in the first days in patients with valproic acid. On the other hand, control subjects received drugs to control withdrawal almost twice as many times as the experimental group (39 for phenobarbital, 20 for valproic acid; t = 2.29, p < 0.05) [31].

Valproic acid compared to placebo

Two studies compared the treatment with valproic acid vs Placebo [21, 28] with a total of 84 participants.

The different analyzes carried out by researchers. They showed that a significantly lower total of the subjects treated with valproic acid required minor amounts of benzodiazepines (Oxazepam). Physical symptoms disappear slightly faster in patients in treatment with sodium valproate with an average of 2.0 days until recovery against 2.6 days in the control group [21].

An 18 (6%) subject in the experimental group had an increase in withdrawal symptoms (CIWA-AR-scale measurement) above the baseline. On the contrary, the placebo group had 7 subjects of 18 (40%) with increase in withdrawal symptoms (average increase in points of the scale by 4.6; SD = 1.8; range = 3 - 8; p = 0.05) [28].

As for tolerance, no significant differences were found between the groups where the subjects presented nausea, drowsiness, dyspepsia, confusion, dizziness, vomiting, memory problems, or abdominal pain. Both works said that the subjects treated with valproic acid reported experiencing drowsiness in one or more days than in the placebo group.

Valproic acid plus another drug compared to other drugs

A study [27] complied with the selection criteria in which it compared the treatment with valproic acid to which another drug (Lorazepam) vs Lorazepam was added with a total of 11 patients.

An immediate decrease was evidenced in CIWA-AR scores in the group that received the treatment with valproic acid while the control group showed a comparatively slower and more unstable decrease. On the other hand, the experimental group by presenting major descents in the symptomatology sign of abstinence, minor values of lorazepam were required against the control group, with an average of 3.3 mg compared to 10 mg (DF = 5 9, $p \leq 0.28$).

Drug tolerance in the control group was favorable without describing adverse effects in any group while in the experimental group a decrease in platelet count in the group that received non -statistically significant valproic acid is described.

Dexmedetomidine compared to placebo

A study compared the use of dexmedetomidine with placebo [26] with a total of 24 participants. Rescues with benzodiazepines 24 h after the start of the study were numerically but not statistically minor in the experimental group (22.3 mg; IQR = 9.3 - 53.3) compared to the control group (77.1 mg; IQR = 10.3 - 182; p = 0.33). However, when the lorazepam requirements are evaluated 24 h before the study compared to 24 h later, a lower, statistically significant value is evidenced in the experimental group (-56.4 mg; IQR = -94.5 to -16.8 against -8 mg).

The measurement values on the CIWA-AR scale in the first 24 h after starting the drug was similar between the experimental group and control.

Four patients presented bradycardia, while three presented hypotension, all in the group with dexmedetomidine. These effects were not evidenced in any patient with placebo.

The duration of the stay in the intensive care unit (ICU) and the duration of the hospital stay were similar.

Carbamazepine compared to valproic acid and placebo

A study [19] was found where effectiveness and tolerance were compared in patients receiving carbamazepine, valproic acid and placebo. Two patients of 46 who received valproic acid presented delirium cadres, while 1 of 49 of those who received placebo developed it; They were not described in the group that was treated with carbamazepine.

Tolerance in terms of the adverse effects of patients who received sodium valproate was much better than the carbamazepine group. However, this was dose dependent, since the highest dose often resulted in treatment.

This study refers to the fact that neither carbamazepine nor sodium

valproate gave complete protection against abstinence seizures in doses established by the protocol.

Discussion

In this review, we identify 22 works with a total of 1150 participants who examined a variety of pharmacotherapies for the treatment of moderate and severe AAS. There was no solid evidence that some kind of drug, used as an adjuvant to benzodiazepines, was more effective on each other to prevent or reduce abstinence, reduce the number of drugs used or reduce hospital stay. However, we find a low quality of evidence that carbamazepine and clonidine can improve the clinical picture of the patient that has delirium. With a statistically non-significant result, we find that dexmedetomidine and valproic acid decrease the requirements of benzodiazepines in patients who received placebo, even when combining valproic acid with benzodiazepines achieve a stable and continuous decrease in abstinence measured in CIWA-AR scale. Clonidine was the only one described that presented a decrease in heart rate against placebo with high significance, clinical situation to be in mind in front of the sympathomimetic syndrome that characterizes alcohol withdrawal syndrome.

A motivation for this review was to find treatments and objectives for future research in a condition that has been historically difficult to deal with pharmacotherapy. In fact, during the search, several treatments projects were identified that promise to be good options.

Finally, we found that the topiramate, designed to work through GABAergic roads regulating the release of dopamine, was potentially effective for abstinence and justifies a continuous exploration, but given the pharmaceutical forms in which they are found, its use is difficult to use patients in ICU.

Observations and Limitations

This work has expected limitations and is somehow understandable by the challenges involved in the continuous evaluation of patients with problematic substance consumption.

We had a limited capacity to compare and make a meta-analysis of the results of the studies because many studies did not report the data established in the objectives or used different measures. It is also possible that the lack of important findings was due to insufficient statistical power to detect differences.

Our scope was broad, and we trust existing clinical trials when they are available. We seek to minimize disadvantages; perform updated searches to identify more recent trials; and refer to bibliography used by the different authors of each selected work.

Our search was limited to studies in English and Spanish with the probability that the exclusion of studies in different languages could alter the conclusions.

Conclusion

Although a significant amount of works appeared, in most of them the populations of studies were small and the data for most of the results did not reach statistical significance. It is necessary to build a protocol where the degree of SAA measured in CIWA-AR-scale, incidence of seizures, Delirium tremens, hospital stay, mortality, health resources used by patients who needed to be hospitalized and estimate the economic impact annual from the use of health resources and potential indirect costs by said internships. There are still different variables to study, for example, doses, new combinations, periods of treatment time, loading and maintenance dose.

The evidence collected on the effects and safety of drugs described in this work is insufficient to determine the balance between the benefits and damage that the choice of a certain therapeutic strategy can generate. Therefore, there is a broad spectrum of doubts to be answered through research and to perform a careful evaluation of the therapeutic alternatives we have.

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Conflict of Interest

None.

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