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Ondansetron in alcohol use disorder: a systematic review

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# Abstract

**Context** Alcohol use disorder (AUD) is a frequent disorder. Few treatments have shown a great efficacy in clinical studies. It is hypothetized that this is due to the fact that AUD suffering people constitute a heterogeneous group composed of various endophenotypes. Ondansetron, a selective 5-HT3 receptor antagonist, has been evaluated in AUD and partciularly in certain subgroups of patients. This review presents clinical studies evaluating its impact.

**Methods** A systematic review was conducted on Pubmed and Wiley Online Library. All 19 clinical trials involving the use of ondansetron in AUD where included.

**Results** Ondansetron was found to be effective mostly in certain subgroups of AUD-suffering patients. The identified subgroups were based on clinical evaluation (age of onset, personality type) and genotype. A number of limitations remains and further studies are needed.

**Keywords** *alcohol use disorder, alcohol dependence, ondansetron, 5-HT*3 *receptors, serotonin, craving, pharmacogenetics,*

*personnalized medicine*

# Introduction

Alcohol use disorder (AUD) is a heterogeneous and chronic relapsing disorder resulting in a complex interaction between neurobiological, genetic and environmental factors. Despite the demonstrated efficacy of some approved medications (acamprosate, naltrexone, disulfiram), a key barrier is the fact that these medications are not effective in every patient pointing out the need for more personalized therapy approaches to overcome this heterogeneity. In this perspective, major advances in pharmacogenetics identified distinct clinical subgroups of AUD according to genetic profiles, that could be associated with differential treatment responses. Thus, the identification of patient subgroups that are most likely to respond favorably to different medications is crucial with a need for a better targeting of medication to specific patients.

Among the additional potential medications, Ondansetron (IUPAC name: (RS)-9-Methyl-3-

[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1Hcarbazol-4(9H)-one), a selective antagonist of the 5-HT3 receptor, has shown some promising results for the treatment of AUD. Ondansetron is approved by ANSM in France and FDA in the USA as an antiemetic for cancer treatment-induced and anesthesia-related nausea and vomiting.

In the late 1980s, Hagan et al. [1] showed that the injection of ondansetron in the ventral tegmental area of the rat brain lessened induced hyperactivation in the nucleus accumbens, pointing out the tight relationship between serotonin function and the mesolimbic dopaminergic reward system. Based on these findings and the role of dopaminergic activity on the rewarding effects of alcohol, researchers have hypothesized that ondansetron could attenuate the pleasurable subjective effects of alcohol and reduce alcohol consumption in AUD suffering patients. Some phase 1 clinical studies [2], [3] found promising results in healthy male volunteers, showing the ability of ondansetron to attenuate the reinforcing properties of alcohol and the desire to use by 5-HT3 receptor blockade. Later phase 2 clinical studies (([4], [5]) suggested differential effects among alcohol-use disorder suffering patients depending on the age of onset (Early-onset alcoholism/Late-onset alcoholism (EOA/LOA), Varma et al. 1994 [9]) ]). Johnson et al (ref) conducted a large RCT study in 271 alcohol dependent patients randomized based on age onset of AUD. Results indicated efficacy of ondansetron compared to placebo in reducing alcohol use, among patients who developed AUD before age 25 only (EOA), which is hypothesized to be linked to individual genetic variations.

As the functional state of the serotonin transporter protein (5-HTT) is an important factor of the serotonergic function control, more recent pharmacogenetic studies have investigated the potential role of 5-HTT genotype on drinking behaviors and alcohol craving ([10]). 5-HTT gene polymorphisms, involving two variants, a short form (S) and a long form (L), have been shown to be associated with differential 5-HT neurotransmission, which could moderate the rewarding effects and the craving for alcohol, and thereby ondansetron treatment response among AUD suffering patients.

Direct inhibition of 5-HT3 receptor is thus hypothesized to alleviate alcohol craving, that is currently considered as a key determinant of relapse vulnerability as well as a major treatment target. A better knowledge of the potential impact of 5-HT antagonist medication on alcohol consumption and craving in AUD, as well as individual caracteristics and genotype associated with treatment response is therefore a critical issue to improve treatment approaches and develop personalized medicine in the pharmacotherapy of alcohol use disorder.

We conducted a systematic review of the literature in order to summarize scientific evidence of the efficacy of ondansetron on alcohol consumption and craving as well as clinical or genetic predictors of treatment response.

# Methods

This systematic review was registered in PROSPERO (Registration Number:).

**Databases and search strategy** A PubMed search was conducted in the MEDLINE database and the Wiley Online

Library.

For Medline search, the relevant articles were identified by combining the terms: ("ondansetron"[MeSH Terms] OR "ondansetron"[All Fields]) AND ("alcoholism"[MeSH Terms] OR "alcoholism"[All Fields] OR "alcohol use disorder"[All Fields] OR "alcohol abuse"[All Fields] OR "AUD"[All Fields])

For the Wiley Online Library search we used the keywords "ondansetron" AND "alcoholism".

For the PsycInfo search, the keywords were "ondansetron or zofran" AND "alcoholism or alcohol dependence or alcohol abuse or alcoholic or alcohol addiction".

Two authors independently examined titles and abstracts. Relevant articles were obtained in full-text and assessed for inclusion criteria blindly by the two reviewers. Disagreement was resolved via discussion to reach consensus. Data from the eligible articles were independently extracted by two reviewers using a standardized data extraction form. Extracted data included participant characteristics, study design, treatment outcomes and results, how confounders were controlled for, and limitations.

**Eligibility criteria**

Studies were included if they met the following inclusion criteria :

- Reported as a peer reviewed journal

- Studies concerning individuals suffering from AUD, with no restrictive criteria regarding age, sex, ethnic origin, or place of living.

- assessing the impact of ondansetron on AUD and/or predictors of ondansetron reatment response

- Papers published in English

Studies were excluded if:

* preclinical studies, reviews, opinion papers, protocols, case reports,
* animal studies
* studies in healthy volunteers
* studies not published in english

**Records identified fr**

**om:**

Pubmed (k = 90)

Wiley Online (k = 8)

PsycInfo (k = 68)

Additional (k = 1)

**Removed before screening:**

Duplicate records (k = 52)

**Records**

**screened**

(k = 115)

**Excluded (k = 94):**

Reviews (k = 59)

Clinical trials (k = 19)

Animal (k = 10)

Guidelines (k = 3)

Book chapters (k = 2)

Case study (k = 1)

**Included records**

(k = 21)

Figure 1:

Flow chart

**Assessment of risk of bias in included studies** Two review authors independently assessed the risk of bias of each included study using thethe revised Cochrane tool for assessing risk of bias in randomised trials (RoB 2 [11]), in accordance with methods recommended by Cochrane collaboration. The risk-of-bias plot in Figure 2 was generated using the Robvis online tool [12]. The following judgements were used : high risk, low risk or unclear (either lack of information or uncertainty over the potential for bias). Authors resolved disagreements by consensus, and a third author was consulted to resolve disagreements if necessary.

The Newcastle Ottawa Scale (NOS) was used for assessing single-arm nonrandomized studies, without evaluating the “comparability” item. ?

# Results

**Searchresults** ThePrismaflowchartpresentingthestudies selection is shown in Figure 1. A total of 90 results were found in the MEDLINE database and 8 additional studies were found on Wiley Online Library.

In total, 92 unique records were screened. Of the screened studies, 20 were finally retained meeting the inclusion criteria,published between 1994 and 2015.

**Study selection** Of the 21 clinical trials, 17 were randomized controled trials (RCT) or analysis of previous RCT, and 3 were prospective open-label studies ([5], [20], [21]). The study duration ranged from 2 to 12 weeks.

**Quality assessment and risk of bias**

**Sample characteristics**

The 21 clinical trials, published between 1994 and 2015, analysed 11 distinct study populations described in Table 1.

In total, 1088 subjects where enrolled, of which 1071 met criteria for alcohol use disorder. Patients were mostly males (75.3 %), and had a mean age of 41.0.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Table 1: Population description  Original publication; Sample Males Mean Dropout Treatment Excluded Other  Location subsequent analysis size (%) age rate seeking PD SUD‡   |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | A Sellers 1994 [13] Toronto, Canada | | 86 | 100 % | 43.6 | 17.4 % | **yes** | **no**∗ | no | | B Johnson 2000a [14]; [15][16] San Antonio, USA | | 20 | 75 % | 38.0 | 30 % | **yes** | yes | no | | C Johnson 2000b [4]; [17][18][19] Houston, USA | | 271 | 70 % | 40.6 | 42 % | **yes** | yes | no | | D Kranzler 2003 [5] | Farmington, USA | 40 | 67.5 % 43.7 | | 30 % | **yes** | yes | no | | E Dawes 2005a [20]; [21] | San Antonio, USA | 12 | 58.3 % 18 | | 25 % | **yes** | **no**∗ | **yes**† | | F Myrick 2008 [22] | Northridge, USA | 107 | 72.9 % 25.7 | | N.A. | no | yes | **yes**† | | G Kenna 2009 [23] | Providence, USA | 20 | 80 % 44.1 | | 25 % | no | yes | no | | H Johnson 2011 [24]; [25][26][27] Charlottesville, USA 283 | | | 73.1 % 44.7 | | 33 % | **yes** | yes | no | | I Corrêa Filho 2013 [28] São Paulo, Brazil | | 102 | 100 % 42.91 50 % | | | Un. | **no**∗ | no | | J Kenna 2014 [29]; [30] Providence, USA | | 77 | 65 % 43.4 29 % | | | no | yes | no | | K Sherwood Brown 2021 [31] Dallas, USA | | 70 | 60 % 44.9 34 % | | | Un. | **no** | Un. | | Total | | 1088 | 75.3 % 41.0 35.4 % | | | 79.9 % | 75.2% | 10.9 % |   Description of the 11 distinct study population used by the 19 clinical trials. Letters A to K are attributed to each study population in chronological order of first publication for later referral.  ‡*: except nicotine;* †*: cannabis use allowed;* ∗*: except clinically significant disorders; c: except cannabis-use disorder; n: except nicotine-use disorder; N.A.: non applicable; PD: psychiatric diagnosis; SD: standard deviation; SUD: substance-use disorder;* |

Patients enrolled were diagnosed as alcohol dependent according to the DSM-III-TR ([13], [4]), DSM-IV ([22], [14], [15], [5], [20], [24]), DSM-IV-TR ([23], [29]), DSM-5 ([31]) or ICD-10 ([28]). Some studies required additional criteria, such as more than 35 standard drinks per week for men or 28 for women ([23], [29]), more than 30 drinks per week for men or 21 for women ([26]), at least 15 standard drinks in the week before enrollement ([31]), more than 3 standard drinks *Un.: unknown*

per day and a Michigan Alcohol Screening Test greater than 5 ([14], [4], [15]), an AUDIT score greater than 8 ([24]) or a diagnose before the age of 25 ([31]). Whereas most trials ([13], [14], [4], [15], [5], [20]) concerned treatment-seeking patients, some ([22], [23], [29]) did not.

In most studies, using drugs was considered as an exclusion criteria either directly ([5], [22], [23], [24], [29]) and/or afterpositivedrugscreening([13], [14], [4], [15], [22], [28]). Nicotine use and nicotine use disorder were often not considered as an exclusion criteria ([4], [5]) and cannabis use was tolerated in a few trials ([20], [22]).

Current or previous treatment for substance use disorder or other disorders was an exclusion criteria for some studies, one study ([13]) excluded patients having benefited from a treatment program or a formal self-help group in the past year, some others ([32], [15], [20]) excluded patients having benefited from such treatment in the past 30 days.

Pharmacological treatment were sometimes exclusion criteria, as a few studies excluded patients being prescribed stimulants, sedatives, hypnotics or treatment that could have an effect on alcohol consumption or mood ([28], [4], [14], [15], [20]), and another study ([31]) excluded people having been treated with naltrexone, acamprosate,disulfiram or topiramate 2 weeks prior inclusion or current treatment with phenytoin, carbamazepine, rifampicine, apomorphine or tramodol (due to potential interactions with ondansetron). Psychiatric disorders were exclusion criteria in most studies([4], [14], [15][5], [23], [24], [30]). Twostudiesspecified that only major diagnosis ([22]) or clinically significant disorders ([28] [20]) were exclusion criteria major. In the study of Sellers *et al.* ([13]) a Montgomery/asberg Depression scale score below 15 and a Spielberger State-Trait anxiety inventory score below 55 were required. Notably, one study ([31]) enrolled only people with a concurrent psychiatric diagnosis, which had to be either bipolar I, II or NOS disorder, schizoaffective disorder (bipolar type), cyclothymic disorder ormajordepressivedisorder(MDD)withmixedfeatures(but excluded those with a Hamilton Rating Scale for Depression (HRSD) or Young Mania Rating Scale (YMRS) greater or equal to 35 and people who had attempted suicide in the 12 months prior to enrollment).

Many studies also required good health at enrollment and notably excluded frequent AUD comorbidities such as elevated bilirubin ([4], [23]), liver enzymes ([20], [23]), [31]), livercirrhosis([28], [31])orseverealcoholwithdrawal([14], [4], [20]) sometimes defined as a Clinical Institute Withdrawal Assessment for Alhocol revised (CIWA-Ar) greater than 10 ([31]).

Different subgroups were identified. Early onset alcoholics (EOA) and late onset alcoholics (LOA) were defined by the age of onset of their substance use disorder, respectively before or after the age of 25. This paradigm was used in 9 studies ([4], [14], [15], [16], [17], [18], [5], [19]), [31]. Six studies ([24], [26], [25], [30], [29], [27]) delin-

Table 2: Treatment efficacy on alcohol use reduction

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sample Design Study Treatment  characteristics Timeframe protocol | | | | | Primary outcome measures | | Results |
|  | Size (†) |  | *(weeks)* | Dosage | Duration | |  |
| Sellers 1994  [13] | 74 (A) | RCT | 9 | OND:  0.25 mg  2mg | 6 w | DDD  (standard drink  13g) | Principal analysis: trend but N.S.;  *Post hoc* analysis: effective when heavy drinkers (>10DD) excluded \* |
| Johnson 2000a  [14] | 20 (B) | RCT | 8 | OND  4 µg/kg bid  +NAL  25 mg bid | 8 w | DD, DDD and  PDA | Reduced DD\*, DDD\* and PDA  (N.S) compared to placebo |
| Johnson 2000b  [4] | 321 (C) | RCT | 12 | OND:  1 µg/kg bid  4 µg/kg bid  16 µg/kg bid | 11 w | DD, DDD, PDA and plasma CDT  (standard drink  12 g) | In EOA, OND was superior\* to placebo on DD, DDD for all dosage and on CDT for 1 and 4 µg/kg bid. OND at 4µg/kg bid was superior to placebo on PDA and DAW |
| Ait-Daoud 2001b  [16] | 20 (B) | RCT | 8 | OND  4 µg/kg bid  +NAL  50 mg | 8 w | log serum CDT | EOA treated with OND+NAL had lower CDT levels compared to placebo\* |
| Kranzler 2003  [5] | 40 (D) | PT | 8 | OND:  4 µg/kg bid | 8 w | DD, DDD,  DrInC score, log CDT ratio | EOA had greater\* decrease in DD, DDD and alcohol related problems than LOA |
| Kenna 2009  [23] | 20 (G) | RCT | 8 | SER  200 mg  OND  0.5 mg | 2/3 w | ASAE volume  (mL), DDD | In L/L, OND reduced\* ASAE alcohol volume and DDD compared to SER |
| Johnson 2011  [24] | 283 (H) | RCT | 13 | OND:  4 µg/kg bid | 11 w | DDD, PDA | In L/L, less DDD and higher PDA in OND vs. placebo\*; In OND, less DDD and higher  PDA in L/L vs L-S/S |
| Corrêa Filho 2013 102 (I)  [28] | | RCT | 12 | OND:  16 mg | 12 w | PDA, PHDD  (standard drink  14g) | OND was superior than placebo to reduce %HDD \* |
| Kenna 2014a 77 (J)  [29] | | RCT | 9 | SER 200 mg or OND  0.5 mg | 3 w | ASAE volume  (mL), DDD | OND resulted in reduction in  DDD compared to SER\* |
| Kenna 2014b 77 (J)  [30] | | RCT | 9 | SER 200 mg or OND  0.5 mg | 3 w | ASAE volume  (mL), DDD | Among women only, L/L + OND and L-S/S + SER had fewer DDD\* and reduced ASAE\* L/L + SER and L-S/L  + OND |
| Sherwood 2021 70 (K)  [31] | | RCT | 12 | OND  0.5/1/2 or 4 mg  (3.23 ± 2.64 mg) | 12 w | Trend in lower self-reported al-  TLFB, GGT,  cohol use in ondansetron group  CDT  vs placebo (N.S.) | |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1* ***A-OCDS****: Adolescent Obsessive–Compulsive Drinking Scale;* ***ASAE****: alcohol self-administration experiment;* ***bid****: twice a day;* ***CDT****: carbohydrate deficient transferrin;* ***d****: day;* ***DD****: drinks per day;* ***DDD****: drinks per drinking day;* ***GGT****:* 𝛾*-glutamyltransferase;* ***HRSD****: Hamilton Rating Scale for Depression;* ***IDSSR****: Inventory of Depressive Symptomatology–Self-report;* ***L/L****: L/L genotype;* ***L-S/S****: L/S or S/S genotype;* ***NAL****: naltrexone;* ***N.S.****: non significant;* ***OND****: ondansetron;* ***PACS****: Penn Alcohol Craving Scale;* ***PDA****: proportion of days abstinent;* ***PHDD****: percentage of heavy drinking days;* ***SD****: standard drinks;* ***SER****: sertaline;* ***TLFB****: Timeline Follow Back* ***w****: week;* ***YMRS****: Young*

*Mania Rating Scale;*

Table 3: Treatment efficacy on craving and cue-induced craving

Primary

Sample Design Study Treatment Results

outcome

characteristics Timeframe protocol

measures

Size (†) *(weeks)* Dosage Duration

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ait-Daoud 2001a 20 (B)  [15] | | RCT | 8 | OND  4 µg/kg bid  + NAL 50 mg | 8 w | OND+NAL was effective at reCraving ducing craving\*; reduction in (measured with craving was correlated by re-  OCDS) duction of drinking in medica-  tion group |
| Johnson 2002  [17] | 253 (C) | RCT | 12 | OND:  1 µg/kg bid  4 µg/kg bid  16 µg/kg bid | 11 w | OND at 4µg/kg was associated  Craving (Visual in craving reduction in EOA but  Analog Scale not LOA compared to placebo\* |
| Myrick 2008  [22] | 107 (F) | RCT | 2 | OND 0.5 mg + NAL 50 mg  or  OND 0.5 mg or NAL 50 mg | 8 d | Craving for  Alcohol  Diminished craving and cue-  Score, Alcohol induced activation of the stria-  Cue–Induced  tum with NAL\*, NAL+OND\*  Ventral Striaand OND (N.S)  tum Activation  Score |
| Sherwood 2021  [31] | 70 (K) | RCT | 12 | OND  0.5/1/2 or 4 mg  (3.23 ± 2.64 mg) | 12 w | PACS No significant difference |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1* ***A-OCDS****: Adolescent Obsessive–Compulsive Drinking Scale;* ***ASAE****: alcohol self-administration experiment;* ***bid****: twice a day;* ***CDT****: carbohydrate deficient transferrin;* ***d****: day;* ***DD****: drinks per day;* ***DDD****: drinks per drinking day;* ***GGT****:* 𝛾*-glutamyltransferase;* ***HRSD****: Hamilton Rating Scale for Depression;* ***IDSSR****: Inventory of Depressive Symptomatology–Self-report;* ***L/L****: L/L genotype;* ***L-S/S****: L/S or S/S genotype;* ***NAL****: naltrexone;* ***N.S.****: non significant;* ***OND****: ondansetron;* ***PACS****: Penn Alcohol Craving Scale;* ***PDA****: proportion of days abstinent;* ***PHDD****: percentage of heavy drinking days;* ***SD****: standard drinks;* ***SER****: sertaline;* ***TLFB****: Timeline Follow Back* ***w****: week;* ***YMRS****: Young*

*Mania Rating Scale;*

Table 4: Treatment efficacy on mood disturbances

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sample Design Study characteristics Timeframe | | | Treatment protocol | Primary  Results  outcome measures |
| Size (†) |  | *(weeks)* | Dosage | Duration |
| Johnson 2003 253 (C)  [18] | RCT | 12 | OND:  1 µg/kg bid  4 µg/kg bid  16 µg/kg bid | OND 16 µg/kg bid was effec-  11 w Mood (Profile tive\* on reducing some mood  of Mood States disturbances in EOA |
| Sherwood 2021 70 (K)  [31] | RCT | 12 | OND  0.5/1/2 or 4 mg  (3.23 ± 2.64 mg) | Reduction in HRSD in on-  12 w HRSD, IDS-  dansetron group vs control\*. SR, YMRS  N.S. for other measures |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1* ***A-OCDS****: Adolescent Obsessive–Compulsive Drinking Scale;* ***ASAE****: alcohol self-administration experiment;* ***bid****: twice a day;* ***CDT****: carbohydrate deficient transferrin;* ***d****: day;* ***DD****: drinks per day;* ***DDD****: drinks per drinking day;* ***GGT****:* 𝛾*-glutamyltransferase;* ***HRSD****: Hamilton Rating Scale for Depression;* ***IDSSR****: Inventory of Depressive Symptomatology–Self-report;* ***L/L****: L/L genotype;* ***L-S/S****: L/S or S/S genotype;* ***NAL****: naltrexone;* ***N.S.****: non significant;* ***OND****: ondansetron;* ***PACS****: Penn Alcohol Craving Scale;* ***PDA****: proportion of days abstinent;* ***PHDD****: percentage of heavy drinking days;* ***SD****: standard drinks;* ***SER****: sertaline;* ***TLFB****: Timeline Follow Back* ***w****: week;* ***YMRS****: Young*

*Mania Rating Scale;*

eated subgroups based on their genotype. The most frequent investigated gene was SLC6A4, coding for the serotonin transporter contains a polymorphism in the promoter region, the 5-HTT-linked polymorphic region, with a "short" (S) and "long" (L). Individuals possessing two long alleles (L/L) have been found to respond differently to serotoninergic treatments than those having either one (L/S) or two (S/S) short alleles. Another allele, rs1042173-TT, also on the serotonine transporter gene predicted a better response to ondansetron on alcohol use. Other genes of interest, HTR3A and HTR3B, which regulate the 5HT3 receptor had polymorphisms which influenced response to ondansetron (rs1150226-AG and rs1176713-GG in HTR3A and rs17614942-AC in HTR3B).

**Treatment protocols** Ondansetron dosage was between 1 µg/kg bid (twice a day) and 16 mg per day with the most frequent dosage being 4 µg/kg bid. One study ([31]) used a flexible dosage which varied in function of treatment response and could range from 0.5 to 4 mg bid (with mean dose at exit being 3.24 ± 2.64 mg/day).

Four studies ([14], [15], [16], [22]) involving 127 patients in total used ondansetron in combination with naltrexone at a dosage of 50 mg per day .

Three studies (97 patients) evaluated ondansetron against sertraline, at a dosage of 200 mg per day ([23], [30], [29]).

The treatment duration varied between 8 days to 11 weeks.

Treatment compliance was evaluated through pill count or riboflavin dosage.

**Treatment outcomes** Efficacy was most often assessed by evaluating the number of standard drinks and derived variables such as defined by the Alcohol Timeline Followback (TLFB) method [33]. Drinking outcomes were drinks per day (DD), drinks per drinking day (DDD), percentage of day abstinent (PDA), heavy drinking days (days with more than 5 drinks per day) percentage of heavy drinking day (PHDD). Standard drink definition varied between different studies, it was defined as 12 g ([4][24]), 13 g ([13] or 14 g[28]) of pure ethanol.

Some studies ([15], [17][22]) evaluated alcohol craving, either with a visual analogical scale or with the obsessive compulsive drinking scale (OCDS [34]). One study ([21]) used the Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS) and another ([31]) the Penn Alcohol Craving Scale (PACS) to assess craving.

One study ([22]) used functional magnetic resonance imaging to determine ventral striatum activation. Another study used the Profile of Mood States [35] to evaluate attenuation of mood disturbances. Finally, one study ([31]) used Hamilton Rating Scale for Depression (HRSD), Young Mania Rating Scale (YMRS), and Inventory of Depressive Symptomatology–Self-report (IDS-SR).

A few studies measured carbohydrate deficient transferrin (CDT)([4],[16],[5],[31])asanobjectivemeasureofalcohol

Table 5: Moderators of treatment outcomes

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sample Design Study Treatment  characteristics Timeframe protocol | | | | | Primary outcome measures | | Results |
|  | Size (†) |  | *(weeks)* | Dosage | Duration | |  |
| Dawes 2005a  [20] | 12 (E) | PT | 8 | OND:  4 µg/kg bid | 8 w | Safety, tolerability, DD, DDD and PDA | No discontinuation due to adverse effect; within-group decrease in DD\* and DDD\* |
| Dawes 2005b  [21] | 12 (E) | PT | 8 | OND:  4 µg/kg bid | 8 w | A-OCDS, DD,  DDD and PDA | Correlation between drinking scores and A-OCDS scores\* |
| Roache 2008  [19] | 271 (C) | RCT | 11 | OND:  1 µg/kg bid  4 µg/kg bid  16 µg/kg bid | 11 w | DD, DDD,  PDA | Babor type A/B better discriminated subtypes based on baseline severity; EOA/LEO better predicted response to OND |
| Seneviratne 2012 41 (H)  [26] | | RCT | 11 | OND:  4 µg/kg bid | 11 w | DDD | In OND group, DDD was associated positively with 5’-  HTTLPR mRNA levels in L/L |
| Johnson 2013 283 (H)  [25] | | RCT | 11 | OND:  4 µg/kg bid | 11 w | DDD, PHDD,  PDA | 5 different genotypes predicted efficacyofONDonalcoholconsumption\* |
| Hou 2015 251 (H)  [27] | | RCT | 11 | OND:  4 µg/kg bid | 11 w | reduction of  PHDD from  baseline | Data mining approaches (such as interaction trees and virtual twins) successfully identified subgroups benefiting from  OND |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1* ***A-OCDS****: Adolescent Obsessive–Compulsive Drinking Scale;* ***ASAE****: alcohol self-administration experiment;* ***bid****: twice a day;* ***CDT****: carbohydrate deficient transferrin;* ***d****: day;* ***DD****: drinks per day;* ***DDD****: drinks per drinking day;* ***GGT****:* 𝛾*-glutamyltransferase;* ***HRSD****: Hamilton Rating Scale for Depression;* ***IDSSR****: Inventory of Depressive Symptomatology–Self-report;* ***L/L****: L/L genotype;* ***L-S/S****: L/S or S/S genotype;* ***NAL****: naltrexone;* ***N.S.****: non significant;* ***OND****: ondansetron;* ***PACS****: Penn Alcohol Craving Scale;* ***PDA****: proportion of days abstinent;* ***PHDD****: percentage of heavy drinking days;* ***SD****: standard drinks;* ***SER****: sertaline;* ***TLFB****: Timeline Follow Back* ***w****: week;* ***YMRS****: Young*

*Mania Rating Scale;*

use. Three studies ([23], [30], [29]) measured or the volume of alcohol consumed in an alcohol self administration. 𝛾glutamyltransferase levels were used as an outcome in one study ([31]).

**Study results** The 21 clinical trials where subdivided in two main subgroups according to their primary outcomes. The first set of studies (Tables 2, 3 and 4) evaluated the efficacy of ondansetron, by evaluating its impact on alcohol use, craving and mood disturbances. The second set (Table 5) evaluated the moderators of treatment outcomes.

**Alcohol use reduction** Eleven studies, summarized in Table 2 evaluated the impact of ondansetron, alone or in combination with naltrexone on alcohol use. The main outcomes were mostly self-reported changes in alcohol consumption in standarddrinks(usingthepreviouslydefinedTLFBmethod). A few studies used objective measures: plasma CDT ([4], [16], [5], [31]), GGT ([31]) or the volume of alcohol consumed in an alcohol self administration ([23], [30], [29]).

Inasampleof71malessufferingfromalcoholdependence (DSM-III-TR), Sellers *et al.* [13] showed a trend (p = 0,06), and *post hoc* analysis indicated a significative impact on AUD patients drinking less than 10 drinks a day. The effect of ondansetron was shown to be non-linear, as 0,25 mg was more effective than 2 mg.

In a small scale randomized control trial [14] (n = 20, exclusively EOA), a combination of ondansetron and naltrexone showed significant effect on reduction of drinks per day (0.99 ± 0.60 vs 3.68 ± 0.63, effect size = 1.42) and drinks per drinking day (3.14 ± 0.87 vs 6.76 ± 0.71, effect size = 1.71), as well as a trend in reducing the percentage of abstinent days, compared to placebo.

A subsequent analysis of the sample by Ait-Daoud *et al.* showed that the combination of ondansetron and naltrexone was associated with significantly lower CDT levels [16].

In a later trial (Johnson *et al.* 2000b [4]), 271 patients of the 321 enrolled were given ondansetron at various dosages (1, 4 and 16 µg/kg of body weight, twice a day). In this study, ondansetron was found to be significantly more effective than placebo in reducing alcohol consumption among EOA but not LOA. Ondansetron at 4 µg/kg *b.i.d.*, which was (non significantly) superior to the other dosages, was more effective than placebo on drinks per day (1.56 vs 3.30, p = 0.01), drinks per drinking day (4.28 vs 6.90, p = 0.004), percentage of day abstinent (70.10 vs 50.20, p = 0.02) and mean log CDT ratio (-0.19 vs 0.12, p = 0.01). Among EOA, all other dosages were superior to placebo on the two first criteria.

These results were subsequently replicated by Kranzler *et al.* in 2003 [5], who showed a significant reduction (compared to baseline) in most alcohol-related measures (drinks per day, drinks per drinking days, DrinC total score) among EOA and LOA who received ondansetron (4 µg/kg *b.i.d.*. A significant difference was also found between EOA and LOA receiving ondansetron, benefiting the former on drinks per day, drinks per drinking day and DrinC total score.

A larger-scale clinical trial, conducted by Johnson *et al.* [24], enrolling 283 patients showed that L/L-subjects receiving ondansetron significantly reduced their alcohol consumption, measured by drinks per drinking day and percentage of days abstinent as compared to placebo (respectively -1.62, p = 0.007 and 11.27%, p = 0.023).

In a small-scale study with 15 non-treatment seeking individuals, Kenna *et al.* [23] showed that patient with L/L genotype on the 5-HTTPLPR promoter region of SLC6A4 (further referred as L/L-subjects) that were administered ondansetron (4 µg/kg *b.i.d.*) for 3 weeks drank significantly less alcohol at an alcohol self-administration, compared to similar patients administered sertaline (200 mg per day).

Another clinical trial involving 77 patients, showed limited support that ondansetron may reduce drinking in nontreatment seeking L/L-subjects and was inconclusive in evaluated the effectivness of sertraline in S/L or S/S-subjects ([29]). Further analysis ([30]) pinpointed gender differences as L/L women treated with ondansetron and S/L or S/S women treated with sertraline had significantly less drinks per drinking days and drank less at alcohol selfadministration evaluations.

In the only trial taking place outside of North America, Corrêa Filho *et al.* [28] showed a significative reduction of heavy drinking days (7,8 % vs 11,7%, p=0.02) but not of other measured outcomes.

Recently, Sherwood *et al.* [31] evaluated the efficacy of ondansetron in 70 patients suffering from both amcohol use disorder and bipolar disorder. Results showed a trend in greater reduction of drinking as measured by the TLFB method that failed to reach significance.

**Craving and cue-induced craving** Four studies (Table 3) evaluated the impact of ondansetron on craving.

AnanalysisofthestudypopulationofJohnson*etal.* 2000a ([14])foundthatthecombinationofondansetronandnaltrexone was significantly better than placebo at reducing craving among EOA [15].

Johnson *et al.* 2002 [17] showed that ondansetron at 4 µg/kg *b.i.d.* was associated with a significant reduction in craving (measured by visual analog scale) compared to the placebo group, but only in EOA. In contrast, craving was significantly increased by ondansetron at 1 µg/kg *b.i.d.* among LOA.

In a BOLD-MRI laboratory study, Myrick *et al.* [22] evaluated ventral striatum activation of AUD suffering people, treated for 7 days by either naltrexone, ondansetron, a combination of both or placebo, and "social-drinkers" (control group), when shown alcohol cues or neutral beverage cues. Ventral striatum activation was significantly reduced in the naltrexone, combination and social-drinkers groups. This was correlated with reduced craving scores in these groups. Ondansetron alone wasn’t significantly effective in the reduction of ventral striatum activation nor craving. There was however a trend in the reduction of both.

Sherwood *et al.* [31] evaluated craving with the PACS but found no differences between ondansetron and placebo groups, among patients with bot bipolar disorder and AUD.

**Mood disturbances** One study, presented in Table 4, showed that among EAO only, ondansetron significantly reduced mood disturbances as measured by the POMS scale

([35]).

Sherwood *et al.* [31] showed that ondansetron was significantly more efficacious than placebo in the reduction of HRSD scores, but not of YMRS or IDS-SR scores, among patients suffering from both bipolar disorder and AUD.

**Predictors of treatment outcomes** Finally, six studies, presented in Table 5 didn’t directly evaluate the efficacy of ondansetron but provided useful information on predicton factors or safety and tolerability. ?

As ondansetron had previously been found useful in early onset alcoholism, Dawes *et al.* [20] evaluated ondansetron among adolescent in a prospective, open-label trial, which showed that ondansetron was safe and well tolerated in adolescents with alcohol dependence. In a subsequent study [21], they found that reduction of drinking (as assest by TLFB) was correlated with reduction in craving, as measured by POCS.

Roache *et al.* 2008 [19] compared the prediction capabilities of the EOA/LOA typology to the type A/type B typology precedently described by Babor *et al.* 1992 [7][8](derived from Type I/II description by Cloninger *et al.* [6]). The A/B typology better described baseline severity of alcohol dependence but treatment response to ondansetron was significantly better predicted by the EOA/LOA typology.

Seneviratne *et al.* [26] produced some evidence that 5’HTTPLR mRNA levels could be used as biomarker to evaluate treatment effectiveness in L/L-subjects treated with ondansetron.

TwostudiesanalysedthepopulationofJohnson*etal.* 2011 [24] and identified genotypes predicting treatment success. Johnson *et al.* 2013 [25] found 5 genotypes which presence predicted efficacy of ondansetron and which where present in a third of the population. Finally, Hou *et al.* [27] further worked on identifying ways of predicting effectivness of ondansetron and found that data mining approaches, such as interaction trees and virtual twins could simplify subgroup identification while limiting statistical errors.

Risk of bias domains

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Study | |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | |  | D1 | D2 | D3 | D4 | D5 | Overall | | Sellers 1994 | ++ | ++ | ++ | ++ | ++ | ++ | | Johnson 2000a | ++ | ++ | −− | ++ | ++ | −− | | Johnson 2000b | ++ | ++ | −− | ++ | ++ | −− | | Ait−Daoud 2001a | ++ | ++ | −− | ++ | ++ | −− | | Ait−Daoud 2001b | ++ | ++ | −− | ++ | ++ | −− | | Johnson 2002 | ++ | ++ | −− | ++ | ++ | −− | | Johnson 2003 | ++ | ++ | −− | ++ | −− | −− | | Myrick 2008 | ++ | ++ | ++ | ++ | ++ | ++ | | Roache 2008 | ++ | ++ | −− | ++ | ++ | −− | | Kenna 2009 | ++ | ++ | −− | ++ | ++ | −− | | Johnson 2011 | ++ | ++ | −− | ++ | ++ | −− | | Seneviratne 2012 | ++ | ++ | −− | ++ | ++ | −− | | Corrêa Filho 2013 | ++ | ++ | xx | ++ | −− | xx | | Johnson 2013 | ++ | ++ | −− | ++ | ++ | −− | | Kenna 2014a | ++ | ++ | −− | ++ | −− | −− | | Kenna 2014b | ++ | ++ | −− | ++ | ++ | −− | | Hou 2015 | ++ | ++ | −− | ++ | −− | −− | |  |  | | | | | | |

Domains: Judgement

D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. x High

D3: Bias due to missing outcome data. − Some concerns

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result. + Low

Figure 2: Risk of bias traffic-light plot (Cochrane Rob2) for the 19 RCT.

# Discussion

To our knowledge, this paper is the only systematic review includingeveryclinicaltrialinvolvingtheuseofondansetron for the treatment of alcohol use disorder. A subsequent research identified 5 systematic reviews in the last 10 years that included the keywords ’ondansetron’ and ’alcohol use disorder’ or ’alcoholism’. Bauer *et al.* 2015 [36] focused on the influence of serotonergic gene variation in substance use pharmacotherapy and included four out of the 21 studies presented here. Naglich *et al.* 2018 [37] focused on combined pharmacotherapy for the treament of alcohol use and thus included 2 studies involving ondansetron and naltrexone. Cservenka *et al.* 2017 [38] focused on pharmacogenetics and the implication of ethnic diversity in the treatment of AUD and included 2 papers. Castrén *et al.* 2019 [39] focused on the recent findings in AUD pharmacoterapy and mentioned ondansetron without including any of the clinical trials. Finally, Bharadwaj *et al.* 2018 [40] focused on the pharmacotherapy for relapse prevention in AUD in the Indian setting and also mentioned ondansetron but didn’t include any trial on this topic.

One review [41] focuses on the role of the serotonin transporter gene in AUD and thus cites 6 of the latest pharmacogenetics studies.

Most of the clinical trials described in this systematic review have stringent inclusion criteria which greatly limits their external validity. Particularly, patients suffering from

dual diagnosis or addicted to several substance (with the exception of nicotine) were often excluded.

**Conclusion** Whereas growing evidence tends to suggest efficacy of ondansetron as a treatment of alcohol use disorder in particular genetic subgroups, nsew studies will be needed to fully conclude. In particular, there is a need for bigger studies evaluating long term changes in alcohol consumption. These studies should also have less exclusion criteria to maximize their external validity.

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