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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-HT_3 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.

Ondansetron (IUPAC name: (RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4(9H)-one), is a selective antagonist of the 5-HT_3 receptor. It is approved by ANSM in France and FDA in the USA as an antiemetic for cancer treatment-induced and anesthesia-related nausea and vomiting.

Serotonin function is an important determinant of alcohol consumption through its relationship with the mesolimbic dopaminergic reward system. 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.

The rewarding effect of alcohol being mediated by dopaminergic activity in the nucleus accumbens, researchers have hypothesized that ondansetron, by modulating the reinforcing effect of alcohol, could also reduce alcohol consumption in AUD suffering patients.

Some phase 1 clinical studies ([2], [3]) have shown promising results on the ability of ondansetron to attenuate the reinforcing properties of alcohol and of the desire to use by 5-HT3 receptor blockade, in healthy male volunteers.

Later phase 2 clinical studies (([4], [5]) have shown differential effects among alcohol-use disorder suffering patients. Different typologies have been previously proposed, based on personality such as type I/II (Cloninger et al. 1987 [6]) or type A/B personalities (Babor et al. 1992 [7], [8]) or simply defined by the age of onset of alcoholism (Early-onset alcoholism/Late-onset alcoholism (EOA/LOA), Varma et al. 1994 [9])]) caracterized by differential course, prognosis and treatment responses. Results from these studies indicated distinct effect of ondansetron among EOA compared to LOA, which is hypothesized to be linked to genetic variations among individuals.

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

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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-HT_3 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 the genetic moderation 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.

Included studies were all clinical trials involving the use of ondansetron as a treatment of AUD.

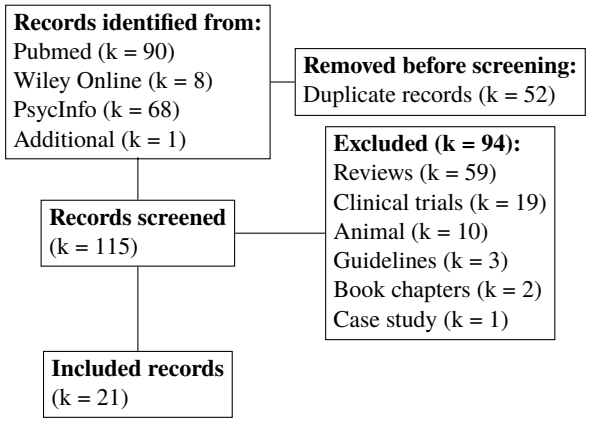

FIGURE 1: Flow chart

Exclusion criteria were studies in healthy volunteers, preclinical studies, reviews, opinion papers, protocols, case reports, and studies not published in English.

Risk of bias Assessment of the risk of bias in the randomised controlled trials was done using the revised Cochrane tool for assessing risk of bias in randomised trials (RoB 2 [11]). The risk-of-bias plot in Figure 2 was generated using the robvis online tool [12].

Results

Search results The Prisma flowchart presenting the studies 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 characteristics 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.

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.

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

TABLE 1: Population description

	Original publication; subsequent analysis	Location	Sample size	Males (%)	Mean age	Dropout rate	Treatment seeking	Excluded PD	Other 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; 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 after positive drug screening ([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]). Two studies specified 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 or major depressive disorder (MDD) with mixed features (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]), liver cirrhosis ([28], [31]) or severe alcohol withdrawal ([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 characteristics	Design	Study Timeframe	Treatment 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 [28]	102 (I)	RCT	12	OND: 16 mg	12 w	PDA, PHDD (standard drink 14g)	OND was superior than placebo to reduce %HDD *
Kenna 2014a [29]	77 (J)	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 [30]	77 (J)	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 [31]	70 (K)	RCT	12	OND 0.5/1/2 or 4 mg (3.23 ± 2.64 mg)	12 w	TLFB, GGT, CDT	Trend in lower self-reported alcohol use in ondansetron group 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;* ***IDS-SR****: 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

	Sample characteristics	Design	Study Timeframe	Treatment protocol		Primary outcome measures	Results
	Size (†)		*(weeks)*	Dosage	Duration		
Ait-Daoud 2001a [15]	20 (B)	RCT	8	OND 4 µg/kg bid + NAL 50 mg	8 w	Craving (measured with OCDS)	OND+NAL was effective at reducing craving*; reduction in craving was correlated by reduction of drinking in medication group
Johnson 2002 [17]	253 (C)	RCT	12	OND: 1 µg/kg bid 4 µg/kg bid 16 µg/kg bid	11 w	Craving (Visual Analog Scale	OND at 4µg/kg was associated in craving reduction in EOA but 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 Score, Alcohol Cue–Induced Ventral Striatum Activation Score	Diminished craving and cue-induced activation of the striatum with NAL*, NAL+OND* and OND (N.S)
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;* ***IDS-SR****: 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 characteristics	Design	Study Timeframe	Treatment protocol		Primary outcome measures	Results
	Size (†)		*(weeks)*	Dosage	Duration		
Johnson 2003 [18]	253 (C)	RCT	12	OND: 1 µg/kg bid 4 µg/kg bid 16 µg/kg bid	11 w	Mood (Profile of Mood States	OND 16 µg/kg bid was effective* on reducing some mood disturbances in EOA
Sherwood 2021 [31]	70 (K)	RCT	12	OND 0.5/1/2 or 4 mg (3.23 ± 2.64 mg)	12 w	HRSD, IDS-SR, YMRS	Reduction in HRSD in ondansetron group vs control*. 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;* ***IDS-SR****: 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]) as an objective measure of alcohol

TABLE 5: Moderators of treatment outcomes

	Sample characteristics	Design	Study Timeframe	Treatment 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 [26]	41 (H)	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 [25]	283 (H)	RCT	11	OND: 4 µg/kg bid	11 w	DDD, PHDD, PDA	5 different genotypes predicted efficacy of OND on alcohol consumption*
Hou 2015 [27]	251 (H)	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;* ***IDS-SR****: 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. γ-glutamyltransferase 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 standard drinks (using the previously defined TLFB method). 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]).

In a sample of 71 males suffering from alcohol dependence (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 non-treatment 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 self-administration 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.

An analysis of the study population of Johnson *et al.* 2000a ([14]) found that the combination of ondansetron and naltrexone 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.

Moderators 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.

Two studies analysed the population of Johnson *et al.* 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.

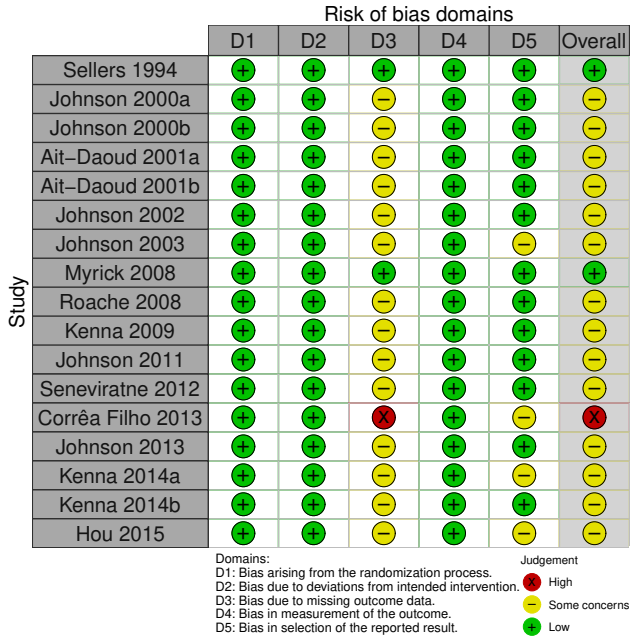

FIGURE 2: Risk of bias traffic-light plot (Cochrane Rob2) for the 19 RCT.

Discussion

To our knowledge, this paper is the only systematic review including every clinical trial involving the use of ondansetron 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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