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 5HT3 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.

Key words alcohol use disorder, ondansetron, 5-HT3 receptors, serotonin, craving, pharmacogenetics, personnalized medicine*

Contents

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 have highlighted distinct clinical subgroups of AUD according to genetic variation, that could be associated with differential treatment responses. Thus, the identification of patient subtypes that are most likely to respond favorably to different medications is crucial with a need for a better targeting of medication to specific patients.

Amongst the emerging pharmacotherapies for AUD, Ondansetron (IUPAC name: (RS)-9-Methyl-3- [(2-methyl-1H-imidazol1-yl)methyl]-2,3-dihydro-1Hcarbazol-4(9H)-one), a selective antagonist of the 5-HT3 receptor, has shown some promising results. 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.* (Hagan et al. 1987) showed that the injection of ondansetron in the ventral tegmental area of the rat brain lessened induced hyperactivity 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, ondansetron was thought to attenuate the pleasurable subjective effects of alcohol and thereby to reduce alcohol

consumption in AUD suffering patients. Some phase 1 clinical studies ((Grant and Barrett 1991), (B. A. Johnson et al. 1993)) found promising results in healthy male volunteers, and provided preliminary evidence on the role of ondansetron in reducing the reinforcing properties of alcohol and the desire to use by 5-HT3 receptor blockade. Later phase 2 clinical studies ((Bankole A. Johnson, Roache, et al. 2000) , (Kranzler et al. 2003)) suggested differential effects among AUD patients depending on the age of onset (Early-onset alcoholism EOA/Late-onset alcoholism LOA) (Varma et al. 1994), which is hypothesized to be linked to individual genetic variations. Interestingly, compared to placebo, ondansetron was associated with reduced drinking and significant reduction in overall craving in randomized placebo-controlled studies ((Bankole A. Johnson, Roache, et al. 2000) + Johnson 2002), but only among patients who developed AUD before age 25 only (EOA), and not among late-onset patients (LOA), presumably by ameliorating serotonergic abnormality

Furthermore, 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 ((Ait-Daoud et al. 2009)). 5-HTT gene polymorphisms, involving two variants, a short form (S) and a long form (L), have been shown to be associated with differential serotonin neurotransmission, which could moderate the rewarding effects and the craving for alcohol, and thereby ondansetron treatment response among AUD suffering patients. In line with this hypothesis, ondansetron was administered in a large study among AUD patients according to the 5-HTT polymorphism [ref Johnson 2011]. Participants with the LL genotype significantly reduced their drinking compared to the LS or SS genotype, suggesting that ondansetron could represent an interesting approach for the personalized treatment of AUD according to specific polymorphism of the 5-HTT gene.

Direct inhibition of the 5HT3 receptor is thus hypothesized to reduce alcohol use and 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 clinical subtypes 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. The aim of this systematic review is to address this issue by assessing scientific evidence of the efficacy of ondansetron on alcohol consumption and craving as well as clinical or genetic predictors of treatment response.

Methods

2.1 Research design

The study involved a systematic review of the literature based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [35]).

2.2. Databases and search strategy

This review was based on the following databases: PUBMED/MEDLINE, Psychinfo, Cochrane, Wiley Online Library. The search was performed for all years up to November, 2024.

The following search terms were used:

For Medline search, the relevant articles were identified by combining the terms:

`("ondansetron"[MeSH Terms] OR "ondansetron"[All Fields]) AND ("alcoholism"[MeSH Terms]`

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"`.

Finally, the Cochrane Library was used by searching `("alcohol use disorder" OR "alcohol dependance") AND "ondansetron" in "Title Abstract Keyword"`.

2.3. Eligibility criteria

Studies were included if they met the following inclusion criteria : + Reported as a peer reviewed journal + 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 treatment response + Papers published in English

Studies were excluded if they were : - Preclinical studies, reviews, opinion papers, protocols, case reports, - Animal studies - Studies in healthy volunteers - Not published in English

2.4. Study selection

Two authors independently examined all titles and abstracts. Relevant articles were obtained in full-text and assessed for inclusion criteria separately by the two reviewers based on the inclusion and exclusion criteria previously mentioned. Disagreements were resolved via discussion of each article for which conformity to inclusion and exclusion

criteria were uncertain and a consensus was reached. The reference lists of major papers were also manually screened in order to ensure comprehensiveness of the review. All selected studies were read in full to confirm inclusion criteria, study type and study population.

2.5. Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each included study using the revised Cochrane tool for assessing risk of bias in randomized trials (RoB 2 (Sterne et al. 2019)), in accordance with methods recommended by Cochrane collaboration. The risk-of-bias plot in Figure 2 was generated using the Robvis online tool (McGuinness and Higgins 2020). The following judgments 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, (Peterson et al. 2011)) was used for assessing single-arm non-randomized studies. However, it had to be adapted by removing the Comparability item for two of the studies that lacked a control group.

2.6. Collecting data

Results

3.1. Study selection

A total of 90 results were found in the MEDLINE database, 68 on PsycInfo, 35 on Cochrane Library and 8 additional studies were found on Wiley Online Library. A total of 134 articles were identified through the search of the databases. After reading the full text, 21 met inclusion criteria for this review. This process is described in the PRISMA flowchart **(Figure 1).** Among the 21 included studies, 18 were randomized controlled trials (RCT) or analysis of previous RCT, and 3 were prospective open-label studies ((Kranzler et al. 2003), (Dawes, Johnson, Ait-Daoud, et al. 2005), (Dawes, Johnson, Ma, et al. 2005)). The study duration ranged from 2 to 12 weeks. The selected articles were published between 1994 and 2015.

3.2. Quality and risk of bias assessment

Randomized controlled trials where analyzed using the Cochrane Rob2 tool (see Figure 2 for the traffic-light plot). Two studies had a low concern of bias ((Sellers et al. 1994), (Myrick et al. 2008)), most of the studies showed some concern of bias and one had a high concern ((Corrêa Filho and Baltieri 2013)). The high dropout rate of the studies was the most concerning factor and affected the Domain 3 of the Risk of Bias tool

which represent bias due to missing outcome result. For the 3 prospective study, the Newcastle-Ottawa scale was used (see Figure 6). The risk of bias was evaluated as acceptable as one study scored 7 out of 9 possible points and the two others scored 6 out of 7 (adapted score).

3.3. Study results

Results are presented according to their primary outcomes. Among the 21 included studies, x assessed odansetron efficacy through alcohol use (n=11), craving (n=) and mood effect (n=). X studies examined moderators of treatment outcomes. The first set of studies **(Tables 2, 3 and 4)** investigated alcohol use, craving and mood disturbances as clinical outcomes for odansetron efficacy, while the second set (**Table 5**) examined the moderators of treatment outcomes.

3.3.1 Sample characteristics

The included studies involved 11 distinct study populations whom characteristics are described in **Table 1.**

In total, !1088 subjects were enrolled, of which !1071 !(%) met criteria for alcohol use disorder. Patients were mostly males !n= ;!75.3 % with a mean age of !41.0 years.

Patients enrolled were diagnosed as alcohol dependent according to the DSM-III-TR ((Sellers et al. 1994), (Bankole A. Johnson, Roache, et al. 2000)), DSM-IV ((Myrick et al. 2008), (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Ait-Daoud et al. 2001), (Kranzler et al. 2003), (Dawes, Johnson, Ait-Daoud, et al. 2005), (Bankole A. Johnson et al. 2011)), DSM-IV-TR ((Kenna et al. 2009), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)), DSM-5 ((Brown et al. 2021)) or ICD-10 ((Corrêa Filho and Baltieri 2013)). Some studies required additional criteria, such as more than 35 standard drinks per week for men or 28 for women ((Kenna et al. 2009), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)), more than 30 drinks per week for men or 21 for women ((Seneviratne and Johnson 2012)), at least 15 standard drinks in the week before enrollement ((Brown et al. 2021)), more than 3 standard drinks per day and a Michigan Alcohol Screening Test greater than 5 ((Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Bankole A. Johnson, Roache, et al. 2000), (Ait-Daoud et al. 2001)), an AUDIT score greater than 8 ((Bankole A. Johnson et al. 2011)) or a diagnosis before the age of 25 ((Brown et al. 2021)). Whereas most trials ((Sellers et al. 1994), (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Bankole A. Johnson, Roache, et al. 2000), (Ait-Daoud et al. 2001), (Kranzler et al. 2003), (Dawes, Johnson, Ait-Daoud, et al. 2005)) concerned treatment-seeking patients, some ((Myrick et al. 2008), (Kenna et al. 2009), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)) did not. Drug use and disorder was considered as an exclusion criteria in most included studies. Thus, participants who reported drug use ((Kranzler et al. 2003), (Myrick et al. 2008), (Kenna et al. 2009), (Bankole A.

Johnson et al. 2011), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)) and/or had a positive drug screening test ((Sellers et al. 1994), (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Bankole A. Johnson, Roache, et al. 2000), (Ait-Daoud et al. 2001), (Myrick et al. 2008), (Corrêa Filho and Baltieri 2013)) were often excluded, except for cannabis use in a few trials ((Dawes, Johnson, Ait-Daoud, et al. 2005), (Myrick et al. 2008)). Receipt of alcohol use disorder treatment prior to enrollment was an exclusion criteria; one study ((Sellers et al. 1994)) considered treatment over the previous 12 months, and 3 ((Bankole A. Johnson, Cloninger, et al. 2000), (Ait-Daoud et al. 2001), (Dawes, Johnson, Ait-Daoud, et al. 2005)) over the previous 30 days.

Some studies excluded participants who had been treated with stimulants, sedatives, hypnotics or with treatment that could have an effect on alcohol consumption or mood ((Corrêa Filho and Baltieri 2013), (Bankole A. Johnson, Roache, et al. 2000), (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Ait-Daoud et al. 2001), (Dawes, Johnson, Ait-Daoud, et al. 2005)). In one study ((Brown et al. 2021)), 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) were exclusion criteria.

Psychiatric disorders were exclusion criteria in most studies ((Bankole A. Johnson, Roache, et al. 2000), (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Ait-Daoud et al. 2001) (Kranzler et al. 2003), (Kenna et al. 2009), (Bankole A. Johnson et al. 2011), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Fricchione, et al. 2014)). Two studies considered only major diagnosis ((Myrick et al. 2008)) or clinically significant disorders ((Corrêa Filho and Baltieri 2013) (Dawes, Johnson, Ait-Daoud, et al. 2005)) as exclusion criteria. In the study of Sellers *et al.* ((Sellers et al. 1994)), a Montgomery/Asberg Depression scale score below 15 and a Spielberg State-Trait anxiety inventory score below 55 were required. In contrast, one study ((Brown et al. 2021)) enrolled only people with a concurrent psychiatric diagnosis.

Many studies also required good health at enrollment and notably excluded frequent AUD comorbidities such as elevated bilirubin ((Bankole A. Johnson, Roache, et al. 2000), (Kenna et al. 2009)), liver enzymes ((Dawes, Johnson, Ait-Daoud, et al. 2005), (Kenna et al. 2009)), (Brown et al. 2021)), liver cirrhosis ((Corrêa Filho and Baltieri 2013), (Brown et al. 2021)) or severe alcohol withdrawal ((Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Bankole A. Johnson, Roache, et al. 2000), (Dawes, Johnson, Ait-Daoud, et al. 2005)) ((Brown et al. 2021)).

Considering participants subtypes, 9 studies ((Bankole A. Johnson, Roache, et al. 2000), (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Ait-Daoud et al. 2001), (Ait-Daoud et al. 2001), (Bankole A. Johnson et al. 2002), (Bankole A. Johnson et al. 2003), (Kranzler et al. 2003), (Roache et al. 2008)), (Brown et al. 2021)) focused on clinical characteristics based on age of onset, before or after the age of 25 (EOA and LOA, while 6 studies examined patient subtypes according to their genotypes ((Bankole

A. Johnson et al. 2011), (Seneviratne and Johnson 2012), (Bankole A. Johnson et al. 2013), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Fricchione, et al. 2014), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014), (Hou et al. 2015)). The most frequent investigated gene was SLC6A4, coding for the serotonin transporter that 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 were 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).

Ondansetron dosage ranged from 1 µg/kg bid (twice a day) to 16 mg per day with the most frequent dosage being 4 µg/kg bid. One study ((Brown et al. 2021)) used a flexible dosage according to treatment response that could range from 0.5 to 4 mg bid (with a mean dose of 3.24 ± 2.64 mg/day).

Four studies ((Bankole A. Johnson, Ait-Daoud, and Prihoda 2000), (Ait-Daoud et al. 2001), (Ait-Daoud et al. 2001), (Myrick et al. 2008)), involving 127 patients, used ondansetron in combination with naltrexone (50 mg/d). Three studies (n=97 patients) compared ondansetron (0.5 mg/d) to sertraline (200 mg/d) ((Kenna et al. 2009), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Fricchione, et al. 2014), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)). Treatment duration ranged from 8 days to 11 weeks. Pill count or riboflavin dosage were used for assessing treatment compliance.

3.3.2 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 (Sobell and Sobell 1992). 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 across the studies, either 12 g ((Bankole A. Johnson, Roache, et al. 2000)Bankole A. Johnson et al. (2011)), 13 g ((Sellers et al. 1994) or 14 g (Corrêa Filho and Baltieri 2013)) of pure ethanol. Furthermore, objective measures of alcohol use were used in 8 studies with either carbohydrate deficient transferrin (CDT) ((Bankole A. Johnson, Roache, et al. 2000), (Ait-Daoud et al. 2001), (Kranzler et al. 2003),Brown et al. (2021)), or the volume of alcohol consumed during self-administration ((Kenna et al. 2009), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Fricchione, et al. 2014), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)), and γ-glutamyltransferase in one study ((Brown et al. 2021)). X studies examined the effects of ondansetron on alcohol craving. Some studies ((Ait-Daoud et

al. 2001), (Bankole A. Johnson et al. 2002)Myrick et al. (2008)) evaluated alcohol craving, either with a visual analogical scale or with the obsessive compulsive drinking scale (OCDS (Anton, Moak, and Latham 1996)) and the Penn Alcohol Craving Scale (PACS). ((Brown et al. 2021)) One study ((Dawes, Johnson, Ma, et al. 2005)) used the Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS). One study ((Myrick et al. 2008)) used functional magnetic resonance imaging to determine ventral striatum activation during cue-exposure, in addition to cue-induced craving assessment. Finally, two studies examined the effcts of ondasetron on mood. One study ((Bankole A. Johnson et al. 2003)) used the Profile of Mood States (Mcnair, Lorr, and Droppleman 1989) to evaluate attenuation of mood disturbances, and another study ((Brown et al. 2021)) the Hamilton Rating Scale for Depression (HRSD), the Young Mania Rating Scale (YMRS), and the Inventory of Depressive Symptomatology–Self-report (IDS-SR).

3.3.3 Effects of ondansetron on 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 according to the TLFB method, plasma CDT ((Bankole A. Johnson, Roache, et al. 2000), (Ait-Daoud et al. 2001), (Kranzler et al. 2003), (Brown et al. 2021)), GGT ((Brown et al. 2021)) or the volume of alcohol consumed during self-administration ((Kenna et al. 2009), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Fricchione, et al. 2014), (Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)).

In a sample of 71 males suffering from alcohol dependence (DSM-III-TR), Sellers *et al.* (Sellers et al. 1994) showed a significant impact of ondansetron on alcohol reduction, when patients drinking more than 10 drinks per day at baseline were excluded from the analysis, with the lower ondansetron dose (0,25 mg/d) producing the greatest reduction from baseline.

One randomized control trial (Bankole A. Johnson, Ait-Daoud, and Prihoda 2000) (n = 20) examined the impact of a combination of ondansetron and naltrexone only among EOA participants. Results found significant effect on reduction of drinks per day, drinks per drinking day, 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 (Ait-Daoud et al. 2001).

In the only trial taking place outside of North America, Corrêa Filho *et al.* (Corrêa Filho and Baltieri 2013) showed a significant reduction of heavy drinking days (7,8 % vs 11,7%, p=0.02) but not of other alcohol-related clinical outcomes.

3.3.4. Effects of ondansetron on alcohol use reduction according patient subtypes

EOA vs LOA

In a later trial (Johnson *et al.* 2000b (Bankole A. Johnson, Roache, et al. 2000)), Johnson et al. examined ondansetron efficacy according to patient subtypes (EOA vs LOA) among a sub-sample of 271 patients. Ondansetron was found to be significantly more effective than placebo in reducing alcohol consumption among EOAs but not LOAs. Ondansetron at 4 μg/kg *b.i.d.* 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 EOAs, all other dosages were superior to placebo on the two first criteria. These results were subsequently replicated by Kranzler *et al.* in 2003 (Kranzler et al. 2003), who showed a significant reduction (compared to baseline) in most alcohol-related measures (drinks per day, drinks per drinking days, DrinC total score) among EOAs and LOAs who received ondansetron (4 μg/kg *b.i.d.*). A significant difference was also found according to patient subtypes, with significant greater decrease of drinks per day, drinks per drinking day and DrinC total score among EOAs. Changes in the level of carbohydrate-deficient transferrin were consistent with changes in self-reported drinking behavior.

Patient genotypes

In a randomized controlled trial, Johnson *et al.* (Bankole A. Johnson et al. 2011) randomized 283 patients by genotype in the 5'-regulatory region of the 5-HTT gene (LL/LS/SS). Individuals with the L/L genotype 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).

Two other studies examined treatment response according to the L/L genotype using a self-administration experiment. The study of Kenna *et al.* (Kenna et al. 2009), among 15 non-treatment seeking individuals, found that participants with the L/L genotype who were administered ondansetron (4 μg/kg *b.i.d.*) during 3 weeks drank significantly less alcohol during an alcohol self-administration procedure, than their counterparts being treated with sertaline (200 mg per day). In another clinical trial involving 77 participants, the same authors provided limited support that ondansetron may reduce drinking in non treatment-seeking individuals with the LL genotype ((Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Vuittonet, et al. 2014)). Further analysis ((Kenna, Zywiak, Swift, McGeary, Clifford, Shoaff, Fricchione, et al. 2014)) 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 during alcohol self-administration experiment.

Alcohol and bipolar disorder participants

Recently, Sherwood *et al.* (Brown et al. 2021) evaluated the efficacy of ondansetron in 70 patients suffering from both alcohol 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.

3.3.5. Effects on craving and cue-induced craving

Four studies (**Table 3**) examined the impact of ondansetron on craving.

An analysis of the study population of Johnson *et al.* 2000a ((Bankole A. Johnson, Ait-Daoud, and Prihoda 2000)) found that the combination of ondansetron and naltrexone was significantly better than placebo in reducing craving among EOAs (Ait-Daoud et al. 2001). Johnson *et al.* 2002 (Bankole A. Johnson et al. 2002) 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 EOAs. In contrast, craving was significantly increased by ondansetron at 1 µg/kg *b.i.d.* among LOAs.

In a BOLD-MRI laboratory study, Myrick *et al.* (Myrick et al. 2008) examined ventral striatum activation of AUD patients during cue-exposure, according to treatment group (naltrexone, ondansetron, a combination of both or placebo), and compared to social-drinkers. Ventral striatum activation was significantly reduced in the naltrexone, combination and social-drinker groups, and this reduction was correlated with reduction in craving scores. Ondansetron alone was not significantly effective in the reduction of ventral striatum activation nor craving. There was however a trend in the reduction of both.

The study of Sherwood *et al.* (Brown et al. 2021) found no differences between ondansetron and placebo groups, among patients with both bipolar disorder and AUD.

3.3.6. Effects on mood disturbances

Two studies investigated the impact of ondansetron medication on mood (**Table 4**). One study ((Bankole A. Johnson et al. 2003)) showed that ondansetron significantly reduced mood disturbances as measured by the POMS scale among EAOs only. Sherwood *et al.* (Brown et al. 2021) 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.

3.3.7. Predictors of treatment outcomes

Finally, six studies, presented in **Table 5,** provided data on predictors of treatment outcomes.

As ondansetron had previously been found useful in early onset alcoholism, Dawes *et al.* (Dawes, Johnson, Ait-Daoud, et al. 2005) evaluated ondansetron among adolescents in a prospective, open-label trial, which showed that ondansetron was safe and well tolerated

in adolescents with alcohol dependence. In a subsequent study (Dawes, Johnson, Ma, et al. 2005), they found that reduction of drinking correlated with reduction in craving. Roache *et al.* 2008 (Roache et al. 2008) compared the prediction capabilities of the EOA/LOA typology to the type A/type B typology described by Babor *et al.* 1992 (Babor et al. 1992) (derived from Type I/II description by Cloninger *et al.* (Cloninger 1987)). 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.* (Seneviratne and Johnson 2012) 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 (Bankole A. Johnson et al. 2011) and identified genotypes predicting treatment success. Johnson *et al.* 2013 (Bankole A. Johnson et al. 2013) found 5 genotypes that are highly prevalent in the general population and that predicted efficacy of ondansetron. Finally, Hou *et al.* (Hou et al. 2015) further worked on identifying ways of predicting effectiviness of ondansetron and found that data mining approaches, such as interaction trees and virtual twins could simplify subgroup identification while limiting statistical errors.

Discussion

To our knowledge, the present review is the only systematic review assessing efficacy of including 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 (Bauer et al. 2015) 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 (Naglich et al. 2017) focused on combined pharmacotherapy for the treament of alcohol use and thus included 2 studies involving ondansetron and naltrexone. Cservenka *et al.* 2017 (Cservenka, Yardley, and Ray 2016) focused on pharmacogenetics and the implication of ethnic diversity in the treatment of AUD and included 2 papers. Castrén *et al.* 2019 (Castrén, Mäkelä, and Alho 2019) focused on the recent findings in AUD pharmacotherapy and mentioned ondansetron without including any of the clinical trials. Finally, Bharadwaj *et al.* 2018 (Bharadwaj, Selvakumar, and Kuppili 2018) 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 (Thompson and Kenna 2015) 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. The high dropout rate (mean dropout rate 35.4%) could impact the validity of the findings, but evidence to identify whether or not dropout rate favors medication is lacking.

Finally, out of the seven registered trials that have no published papers yet, three haven't had any updates for more than ten years whereas one reported non significant results. This may pose a publication bias that is to be taken in consideration.

Conclusion

Whereas growing evidence tends to suggest efficacy of ondansetron as a treatment of alcohol use disorder in particular genetic subgroups, further studies are 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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