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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.

Ondansetron (IUPAC name: (RS)-9-Methyl-3-

[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1Hcarbazol-4(9H)-one), is a selective antagonist of the 5-HT3 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-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 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".

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.

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

**Records iden**

**tified from:**

Pubmed (k =

90)

Wiley Online

Library (k = 8)

**Removed before screening:**

Duplicate records (k = 6)

**Records**

**screened**

(k = 92)

**Excluded:**

(k = 73)

Reviews (k = 57)

Unrelated (k = 8)

Animal (k = 5)

Guidelines (k = 2)

Case study (k = 1)

**Included**

**records**

Clinical tri

als (k = 19)

Figure 1:

Flow chart

# 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, 19 were finally retained meeting the inclusion criteria,published between 1994 and 2015.

**Study characteristics** Of the 19 clinical trials, 17 were randomized controled trials (RCT) or analysis of previous RCT, and 2 were prospective open-label studies [5] [18]. The study duration ranged from 2 to 12 weeks.

The 19 clinical trials, published between 1994 and 2015, analysed 10 distinct study populations described in Table 1.

In total, 1053 subjects where enrolled, of which 1036 met criteria for alcohol use disorde. Patients were mostly males (75.7 %), and had a mean age of 40.7.

Patients enrolled were diagnosed as alcohol dependent according to the DSM-III-TR ([11], [4]), DSM-IV ([19], [12], [13], [5], [18], [21]), DSM-IV-TR ([20], [26]) or ICD10 ([25]). Some studies required additional criteria, such as more than 35 standard drinks per week for men or 28 for women ([20], [26]), more than 30 drinks per week for men or 21 forwomen ([23]), morethan 3standard drinks per day and a Michigan Alcohol Screening Test greater than 5 ([12], [4], [13])or anAUDITscoregreater than 8([21]). Whereas most trials ([11], [12], [4], [13], [5], [18]) concerned treatmentseeking patients, some ([19], [20], [26]) did not. Most of the studies excluded patients using any other drug than alcohol.

In most studies, using drugs was considered as an exclusion criteria either directly ([5], [19], [20], [21], [26]) and/or afterpositivedrugscreening([11], [12], [4], [13], [19], [25]). 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 ([18], [19]).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1: Population description  Original publication; Sample Proportion Mean Dropout Treatment Psychiatric Other  Location subsequent analysis size of male age rate seeking diagnosis SUD‡   |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | A Sellers 1994 [11] North America 71 | | | 100 % | 43.55 21 % | | **yes** | **yes**∗ | no | | B Johnson 2000a [12]; [13][14] San Antonio, USA 20 | | | 75 % | 38.0 | 30 % | **yes** | no | no | | C Johnson 2000b [4]; [15][16][17] Houston, USA 321 | | | 70 % | 40.6 | 41 % | **yes** | no | no | | D Kranzler 2003 [5] | North America 40 | | 67.5 % | 43.7 | 30 % | **yes** | no | no | | E Dawes 2005 [18] | San Antonio, USA 12 | | 58.3 % | 18 | 25 % | **yes** | **yes**∗ | **yes**† | | F Myrick 2008 [19] | Northridge, USA | 107 | 72.9 % | 25.69 | N.A. | no | no | **yes**† | | G Kenna 2009 [20] | Providence, USA | 20 | 80 % | 44.1 | 25 % | no | no | no | | H Johnson 2011 [21]; [22][23][24] North America | | 283 | 73.1 % | 44.7 | 33 % | **yes** | no | no | | I Corrêa Filho 2013 [25] | São Paulo, Brazil | 102 | 100 % | 42.91 50 % | | Un. | **yes**∗ | no | | J Kenna 2014 [26]; [27] | Providence, USA | 77 | 65 % | 43.4 29 % | | no | no | no | | Total |  | 1053 | 75.7 % | 40.7 35.4 % | | 78.5 % | 17.6 % | 11.3 % |   Description of the 10 distinct study population used by the 19 clinical trials. Letters A to J 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; SD: standard deviation; SUD: substance-use disorder; Un.: unknown* |

Psychiatric disorders were exclusion criteria in most studies([4], [12], [13][5], [20], [21], [27]). Twostudiesspecified that only major diagnosis ([19]) or clinically significant disorders ([25] [18]) were exclusion criteria major. In the study of Edward et al. ([11]) a Montgomery/asberg Depression scale score below 15 and a Spielberger State-Trait anxiety inventory score below 55 were required.

Many studies also required good health at enrollment and notably excluded frequent AUD comorbidities such as elevated bilirubin ([4], [20]), liver enzymes ([18], [20]), liver cirrhosis([25])or severe alcohol withdrawal ([12], [4], [18]).

Different subgroups were identified. Early onset alcoholics (EOA) and late onset alcoholics (LOA) were define by the age of onset of their substance use disorder, respectively before or after the age of 25. This paradigm was used in 8 studies ([4], [12], [13], [14], [15], [16], [5], [17]). Six studies ([21], [23], [22], [27], [26], [24]) delineated subgroups based on their genotype. SLC6A4, the gene 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.

**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. Four studies (127 patients) used ondansetron in combination with naltrexone at a dosage of 50 mg per day ([12], [13], [14], [19]). Three studies (97 patients) evaluated ondansetron against sertraline, at a dosage of 200 mg per day ([20], [27], [26]).

The treatment duration varied between 8 days to 11 weeks.

Treatment compliance was evaluated through pill count or riboflavin dosage.

**Treatment outcomes** Efficacy was mostly assessed by evaluating the number of standard drinks and derived variables such as defined by the Alcohol Timeline Followback (TLFB) method [28]. Drinking outcomes where 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][21]), 13 g ([11] or 14 g[25]) of pure ethanol.

Some studies ([13], [15][19]) evaluated alcohol craving, either with a visual analogical scale or with the obsessive compulsive drinking scale (OCDS [29]).

One study ([19]) used functional magnetic resonance imaging to determine ventral striatum activation. Another study used the Profile of Mood States [30] to evaluate attenuation of mood disturbances.

**Study results** The 19 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

Table 2: Treatment efficacy on alcohol use reduction

Primary

Sample Design Study Treatment Results

outcome

characteristics Timeframe protocol

measures

Size (†) *(weeks)* Dosage Duration

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sellers 1994  [11] | 74 (A) | RCT | 9 | OND:  0.25 mg  2mg | 6 w | Principal analysis: trend but  DDD  N.S.; *Post hoc* analysis: ef-  (standard drink fective when heavy drinkers  13g)  (>10DD) excluded \* | |
| Johnson 2000a  [12] | 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  [14] | 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  [20] | 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  [21] | 283 (H) | RCT | 12 | 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)  [25] | | RCT | 12 | OND:  16 mg | 12 w | PDA, PHDD  OND was superior than placebo  (standard drink  to reduce %HDD \*  14g) | |
| Kenna 2014a 77 (J)  [26] | | RCT | 9 | SER 200 mg or OND  0.5 mg | 3 w | ASAE volume OND resulted in reduction in  (mL), DDD DDD compared to SER\* | |
| Kenna 2014b 77 (J)  [27] | | RCT | 9 | SER 200 mg or OND  0.5 mg | 3 w | Among women only, L/L  + OND and L-S/S + SER  ASAE volume  had fewer DDD\* and reduced (mL), DDD  ASAE\* L/L + SER and L-S/L +  OND | |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1 ASAE: alcohol self-administration experiment; bid: twice a day; CDT: carbohydrate deficient transferrin; d: day; DD: drinks per day; DDD: drinks per drinking day; L/L: L/L genotype; L-S/S: L/S or S/S genotype; NAL: naltrexone; N.S.: non significant; OND: ondansetron; PDA: proportion of days abstinent;*

*PHDD: percentage of heavy drinking days; SD: standard drinks; SER: sertaline; w: week;*

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)  [13] | | 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  [15] | 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  [19] | 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 |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1 ASAE: alcohol self-administration experiment; bid: twice a day; CDT: carbohydrate deficient transferrin; d: day; DD: drinks per day; DDD: drinks per drinking day; L/L: L/L genotype; L-S/S: L/S or S/S genotype; NAL: naltrexone; N.S.: non significant; OND: ondansetron; PDA: proportion of days abstinent; PHDD: percentage of heavy drinking days; SD: standard drinks; SER: sertaline; w: week;*

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) RCT  [16] | 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 |

*\*: significant result;* †*: population (A) to (J) as defined in Table 1 ASAE: alcohol self-administration experiment; bid: twice a day; CDT: carbohydrate deficient transferrin; d: day; DD: drinks per day; DDD: drinks per drinking day; L/L: L/L genotype; L-S/S: L/S or S/S genotype; NAL: naltrexone; N.S.: non significant; OND: ondansetron; PDA: proportion of days abstinent;*

*PHDD: percentage of heavy drinking days; SD: standard drinks; SER: sertaline; w: week;*

Table 5: Moderators of treatment outcomes

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Sample Design Study Treatment  characteristics Timeframe protocol | | | | Primary outcome measures | | Results |
|  | Size (†) |  | *(weeks)* | Dosage | Duration | |  |
| Dawes 2005  [18] | 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\* |
| Roache 2008  [17] | 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  [23] | 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  [22] | 283 (H) | RCT | 11 | OND:  4 µg/kg bid | 11 w | DDD, PHDD,  PDA | 5 different genotypes predicted efficacyofONDonalcoholconsumption\* |
| Hou 2015  [24] | 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 ASAE: alcohol self-administration experiment; bid: twice a day; CDT: carbohydrate deficient transferrin; d: day; DD: drinks per day; DDD: drinks per drinking day; L/L: L/L genotype; L-S/S: L/S or S/S genotype; NAL: naltrexone; N.S.: non significant; OND: ondansetron; PDA: proportion of days abstinent;*

*PHDD: percentage of heavy drinking days; SD: standard drinks; SER: sertaline; w: week;*

use, craving and mood disturbances. The second set (Table 5) evaluated the moderators of treatment outcomes.

**Alcoholusereduction** Tenstudies, summarizedinTable2 evaluatedtheimpactofondansetron, aloneorincombination 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 and the volume of alcohol consumed in an alcohol self administration expremient.

Inasampleof71malessufferingfromalcoholdependence (DSM-III-TR), Sellers et al. [11] 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 [12] (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 [14].

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. [21], 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. [20] 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 ([26]). Further analysis ([27]) 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. [25] showed a significative reduction of heavy drinking days (7,8 % vs 11,7%, p=0.02) but not of other measured outcomes.

**Cravingandcue-inducedcraving** Threestudies(Table3) evaluated the impact of ondansetron on craving.

AnanalysisofthestudypopulationofJohnsonetal. 2000a ([12])foundthatthecombinationofondansetronandnaltrexone was significantly better than placebo at reducing craving among EOA [13].

Johnson et al. 2002 [15] 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. [19] 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.

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

([30]).

**Moderators of treatment outcomes** Finally, five 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. [18] evaluated ondansetron among adolescent in a prospective, open-label trial, which showed that ondansetron was safe and well tolerated in adolescents with alcohol dependence.

Roache et al. 2008 [17] 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 dependance but treatment response to ondansetron was significantly better predicted by the EOA/LOA typology.

Seneviratne et al. [23] produced some evidence that 5’HTTPLR mRNA levels could be used as biomarker to evaluate treatment effectiveness in L/L-subjects treated with ondansetron.

TwostudiesanalysedthepopulationofJohnsonetal. 2011 [21] and identified genotypes predicting treatment success. Johnson et al. 2013 [22] found 5 genotypes which presence predicted efficacy of ondansetron and which where present in a third of the population. Finally, Hou et al. [24] 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.

# Discussion

Overall, these studies show promising result for the use of ondansetron in AUD-suffering people. In particular subgroups, such as early-onset alcoholics, LL-genotypes for the SLA6A4 gene, or AUD-suffering people having one of the five genotypes identified in [22], ondansetron was shown to have a therapeutic effect which might be comparable or better than currently used medication. This paves the way to new discoveries and application in personalized medicine.

However, most of the studies 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 excluded more often than not.

Moreover, ethical issues related to mass genotyping may prevent these type of information to be used for treatment prediction.

**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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