**Alcohol-medication interactions: A systematic review and meta-analysis of placebo-controlled trials**

*Running head*

Alcohol-medication interactions

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**ABSTRACT** *(233 words)*

Alcohol and other xenobiotics may limit the therapeutic effects of medications. We aimed at investigating alcohol-medication interactions (AMI) after the exclusion of confounding effects related to other xenobiotics. We performed a systematic review and meta-analysis of controlled studies comparing the effects induced by alcohol versus placebo on pharmacodynamic and/or pharmacokinetic parameters of approved medications. Certainty in the evidence of AMI was assessed when at least 3 independent studies and at least 200 participants were available.

We included 107 articles (3,097 participants): for diazepam, cannabis, opioids, and methylphenidate, we found significant AMI and enough data to assign the certainty of evidence. Alcohol consumption significantly increases the peak plasma concentration of diazepam (low certainty; almost 290 participants), cannabis (high certainty; almost 650 participants), opioids (low certainty; 560 participants), and methylphenidate (moderate certainty; 290 participants). For most medications, we found some AMI but not enough data to assign them the certainty grades; for some medications, we found no differences between alcohol and placebo in any outcomes evaluated. Our results add further evidence for interactions between alcohol and certain medications after the exclusion of confounding effects related to other xenobiotics. Physicians should advise patients who use these specific medications to avoid alcohol consumption. Further studies with appropriate control groups, enough female participants to investigate sex differences, and elderly population are needed to expand our knowledge in this field.

**Short phrases suitable for indexing terms**

1. Among participants taking diazepam, those who consumed alcohol achieved higher peak plasma concentration (low certainty; almost 290 participants) and area under the curve (very low certainty; 270 participants) of this medication compared to those who consumed placebo
2. Among participants taking cannabis, those who consumed alcohol achieved higher peak plasma concentration (high certainty; almost 650 participants), in a shorter time (very low certainty; more than 300 participants), and have a longer elimination half-life (moderate certainty; almost 250 participants) of Delta (9)-tetrahydrocannabinol (THC) compared to those who consumed placebo
3. Among participants taking opioids, those who consumed alcohol achieved higher peak plasma concentration (low certainty; 560 participants) and in a shorter time (moderate certainty; 554 participants) of opioids compared to those who received placebo
4. Among participants taking methylphenidate, those who consumed alcohol achieved higher peak plasma concentration (moderate certainty; 290 participants) and area under the curve of this medication compared to those who consumed placebo

**Key words:** Alcohol, medications, interactions

**Highlights**

* Alcohol consumption may interact and limit therapeutic effects of some medications
* Other xenobiotics in alcoholic beverages may interact with medications
* Other xenobiotics may influence alcohol-medication interactions (AMI)
* For certain medications, AMI persist after the exclusion of other xenobiotics
* Patients who use these medications should avoid alcohol consumption

**Abbreviations**

ADH: Alcohol dehydrogenase

ADHD: Attention-deficit/hyperactivity disorder

AIDS: Acquired immune deficiency syndrome

AM: Arithmetic mean

AMI: Alcohol-medication interactions

AUC: Area under the curve

AUD: Alcohol use disorder

BAC: Blood alcohol concentration

BP: Blood pressure

CES1: Carboxylesterase-1

CI: Confidence interval

Cmax: Peak plasma concentration

CNS: Central nervous system

CTs: Controlled trials

CV: Coefficient of variation

CYP: Cytochrome P450 enzymes

EMA: European Medicines Agency

FBF: Forearm blood flow

FDA: Food and Drug Administration

GHB: Gamma-hydroxybutyric acid

GI: Gastrointestinal events

GM: Geometric mean

GRADE: Grading of recommendations assessment, development, and evaluation

HAART: Highly active antiretroviral therapy

HIV: Human immunodeficiency virus infection

HR: Heart rate

MD: Mean difference

NAIs: Neuraminidase inhibitors

NDRI: [Norepinephrine-dopamine reuptake inhibitor](https://en.wikipedia.org/wiki/Norepinephrine%E2%80%93dopamine_reuptake_inhibitor)

NNRTI: [Non-nucleoside reverse-transcriptase inhibitor](https://en.wikipedia.org/wiki/Non-nucleoside_reverse_transcriptase_inhibitor)

NO: Nitric oxide

NRTI: [Nucleoside analog](https://en.wikipedia.org/wiki/Nucleoside_analog) [reverse-transcriptase inhibitor](https://en.wikipedia.org/wiki/Reverse-transcriptase_inhibitor)

NSAIDs: Non-steroidal anti-inflammatory drugs

PD: Pharmacodynamic effects

PDE5I: Phosphodiesterase type 5 inhibitor

PIs: Protease inhibitors

PK: Pharmacokinetic effects

RCTs: Randomized controlled trials

SARI: [Serotonin antagonist and reuptake inhibitor](https://en.wikipedia.org/wiki/Serotonin_antagonist_and_reuptake_inhibitor)s

SD: Standard deviation

SEM: Standard error of the mean

SMD: Standardized mean difference

SMS: Serotonin modulator and stimulators

SNRI: [Serotonin-norepinephrine reuptake inhibitor](https://en.wikipedia.org/wiki/Serotonin%E2%80%93norepinephrine_reuptake_inhibitor%22%20%5Co%20%22Serotonin%E2%80%93norepinephrine%20reuptake%20inhibitor)s

SoF: Summary of findings

SSRIs: Selective serotonin reuptake inhibitors

TCA: [Tricyclic antidepressant](https://en.wikipedia.org/wiki/Tricyclic_antidepressant%22%20%5Co%20%22Tricyclic%20antidepressant)s

THC: Delta (9)-tetrahydrocannabinol

Tmax:Time to reach Cmax

T1/2: Elimination half-life

VAS: Visual analogue scale

WHO: World Health Organization

**INTRODUCTION**

Alcohol consumption is a leading risk factor for morbidity and mortality (GBD 2016 Alcohol Collaborators, 2018) and risks of experiencing alcohol related harm, including trauma, physical and mental disorders, increase with the amount consumed (Di Castelnuovo et al., 2006; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; LoConte et al., 2018; Rehm et al., 2003; Taylor and Rehm, 2012). Negative consequences related to alcohol consumption also include its interactions with commonly used medications, otherwise known as alcohol-medication interactions (AMI) (Weathermon and Crabb, 1999). AMI are particularly frequent because, not only is alcohol one of the most widely used psychoactive substances worldwide, but also most people take medications, especially older adults (Holton et al., 2017; Moore et al., 2007). According to the World Health Organization (WHO), in 2016, 43% of the world population aged 15+ years consumed at least one alcoholic drink in the previous 12-month period; in some WHO regions (European Region and Region of Americas) almost 80% of the total adult population consumed alcohol at least occasionally (World Health Organization, 2018). In the US, between 1999 to 2010, more than 40% of adult population (aged ≥20 years) consumed alcohol and took prescribed medications and, among people aged ≥65, this rate almost doubled (78.6%) (Breslow et al., 2015).

Different AMI have been described. First, some medications can alter the pharmacokinetic (PK) parameters and/or the effects induced by alcohol consumption. For instance, some medications alter gastric emptying and/or inhibit the activity of gastric alcohol dehydrogenase (ADH) (Baraona et al., 1994; Fraser, 1997). Accordingly, people taking these medications who consume alcohol may achieve higher blood alcohol concentrations (BAC) compared to people not taking these medications at the same amount of alcohol.

Another typology of AMI consists in the increase of potentially serious medical consequences resulting from the combination of alcohol and some medications. For instance, the concomitant ingestion of alcohol and medications with sedative effects may result in an enhanced depression of the central nervous system (CNS) due to impaired metabolism of alcohol and/or the medications, a summation of sedative effects induced by alcohol and medications, or both effects simultaneously (Muhoberac et al., 1984). Alcohol can also alter PK and/or desired effects of therapeutic medications (Chan and Anderson, 2014; Weathermon and Crabb, 1999). For instance, it has been observed that acute alcohol consumption may decrease the metabolism of warfarin, an anticoagulant medication (Weathermon and Crabb, 1999). Accordingly, people taking this medication who consume alcohol may achieve a potentially dangerous increase of the anticoagulant effect compared to people taking the same dose of warfarin who are not consuming alcohol.

This topic is of particular interest for clinicians, who should advise their patients to avoid the simultaneously consumption of alcohol when it may limit the therapeutic effects or increase the risk of potentially serious side effects of medications, as demonstrated by the large number of review articles on this topic (Baraona et al., 1994; Braithwaite and Bryant, 2010; Chan and Anderson, 2014; Fraser, 1997; Greenspan and Smith, 1991; “Harmful Interactions | National Institute on Alcohol Abuse and Alcoholism (NIAAA),” n.d.; Havier, 1991; Holton et al., 2017; Jang and Harris, 2007; Johnson and Seneviratne, 2014; Kresina et al., 2002; Kumar et al., 2012; Lane et al., 1985; LIEBER, 1990; Lieber and Abittan, 1999; Linnoila et al., 1979; Mattila, 1990; Mezey, 1976; Moore et al., 2007; Muhoberac et al., 1984; Noureldin et al., 2010; Sands et al., 1993; Saxe, 1986; Schuckit, 1987; Smith, 2009; Tanaka and Misawa, 1998; Vena and Cassano, 2012; Weathermon and Crabb, 1999; Weller and Preskorn, 1984; Zachariae, 1999).

Interestingly, certain non-alcoholic beverages like grapefruit, orange and apple juices may also interact with therapeutic medications (Dahan and Altman, 2004; Koziolek et al., 2019). For instance, it has been observed that grapefruit juice significantly increases the bioavailability of the calcium channel antagonist felodipine, an analogue of nifedipine. In detail, when felodipine was administered with 250 ml of grapefruit juice, the plasma felodipine area under the curve (AUC) resulted to be three times higher compared to the value achieved after its administration with water (Bailey et al., 1989). This effect induced a higher decrease in blood pressure (BP). Interestingly this interaction was discovered by chance, in a study aimed at investigating the interaction between felodipine and alcohol in which grapefruit juice was used to mask the taste of alcohol (Bailey et al., 1998, 1989; Lown et al., 1997). After this first evidence, several PK and/or pharmacodynamic (PD) interactions between different juices and therapeutic medications have been identified (Chen et al., 2018; Koziolek et al., 2019; Lee et al., 2016; Mouly et al., 2017; Paśko et al., 2016; Seden et al., 2010; Theile et al., 2017; Yu et al., 2017). Furthermore, certain alcoholic beverages (e.g., wine) contain xenobiotics other than alcohol, capable to interact with medications like resvetrol and gallic acid (Jang and Harris, 2007).

Considering that fruit juices are often used in clinical studies aimed at investigating AMI to mask alcohol taste, we hypothesized that the addition of juices and/or the lack of appropriate control group may have influenced some of the results obtained by clinical studies conducted in this field. Accordingly, we decide to conduct a systematic review and meta-analysis aimed at investigating potential AMI after the exclusion of the confounding effects induced by fruit juices or other substances. To achieve this goal, we selected only controlled studies in which participants received a therapeutic medication and consumed an alcohol-containing solution and the results obtained were compared to participants who received the same therapeutic medication together with an appropriate placebo solution (see Agabio et al., 2020 for methodological details). Studies in which the control group did not receive any solution were excluded and we specifically paid attention to establish whether participants of the control group received the appropriate placebo solution.

**2. Methods**

#### 2.1. Data sources

We conducted a systematic review and meta-analysis in line with PRISMA guidelines (Moher et al., 2009), the current recommendations of the Cochrane Collaboration (Higgins et al., 2019) and following an *a priori* protocol (Agabio et al., 2020). We searched Scopus, PubMed, EMBASE from database inception to 30th September 2019 with no language, date, country or publication type limitation, using the following search strategy: ("Ethanol"[Majr]) OR "Ethanol/pharmacokinetics"[Mesh] OR "Ethanol/pharmacology"[Mesh] OR ethanol[tiab]) OR ("Alcohols"[Majr]) OR "Alcohols/pharmacokinetics"[Mesh] OR "Alcohols/pharmacology"[Mesh] OR alcohols[tiab]) OR "Metabolism/Ethanol" AND "Drug Interactions"[Mesh] OR "interactions"[tiab]). References from the included and relevant on-topic excluded articles were reviewed to identify additional studies.

We contacted authors of studies published after the year 2000, by email, to request data on PK and/or PD outcomes that were not reported in their publications. If we did not receive a response to the first request, we attempted to contact the authors a second time. Three authors provided additional data. Crean and Tompson (2013) provided elimination half-life (T1/2) for retigabine; Kruithof et al., (2017) provided peak plasma concentration (Cmax), time to reach Cmax (Tmax), T1/2 and AUC for brivaracetam; Toennes et al. (2011) provided AUC for Delta (9)-tetrahydrocannabinol (THC). Authors of the other studies replied that they were not able to provide us these data or did not respond to our emails.

#### 2.2. Study selection

Three authors (F.T., R.A., R.P.) independently screened and assessed the titles and abstracts of retrieved studies, identifying candidates for further review and excluding irrelevant and/or duplicate studies. If eligibility could not be determined by title or abstract, the entire text of the study was retrieved and evaluated. Disagreements were resolved by discussions with another author (J.S., L.L.).

#### 2.3. Inclusion criteria

We included controlled clinical trials that: (1) enrolled subjects aged 18 or older who received a medication, (2) compared alcohol to alcohol-placebo on PK and/or PD outcomes of the investigated medication, and (3) included quantitative measures of these outcomes. We did not set limits to sample sizes, participant characteristics or types of intervention (e.g., parallel groups or crossover fashion). We included all medications that have, at present, diagnostic or therapeutic indications and are approved for clinical use by the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and/or other similar regulatory agencies. We also included cannabis, considering its common use as a therapeutic agent.

#### 2.4. Data collection

A custom data extraction spreadsheet was developed for recording all relevant details and outcomes from the included studies. All data extracted by one author were verified by a second investigator. Extracted data included: (1) name of medication, (2) dose of alcohol and medication, and (3) route of administration of alcohol and medication, (4) route of administration of alcohol and medication, and (5) timing of alcohol administration with respect to medication, (6) number and characteristics of participants (e.g., healthy volunteers, patients), (7) male/female ratio, (8) type of drinkers (e.g., patients affected by alcohol use disorder (AUD; see below), heavy drinkers, moderate drinkers), (9) characteristics of placebo solutions, (10) type of the study (e.g., controlled trial, randomized controlled trial, crossover), (11) potential conflict of interests of authors, and (12) outcomes available among the selected ones (see paragraph 5. Outcomes).

The numbers of participants provided in the Results section of the meta-analysis correspond to the numbers of individuals included in the analyses. These numbers can differ from those of participants recruited by primary studies based on the type of study (e.g., crossover or independent arms).

The latest draft of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has merged the two independent mental disorders ‘alcohol abuse’ and ‘alcohol dependence’ into a single mental disorder, defined AUD, whose diagnosis requires the fulfillment of two or more criteria out of a set of 11, comprised by joined sets of the previous disorders (APA, 2013).

#### 2.5. Outcomes

PK outcomes included in the meta-analysis were the following: (1) Cmax, (2) Tmax, (3) T1/2, and (4) AUC from time 0 (zero) to infinite (AUC 0-inf). When AUC 0-inf was not available, we used AUC from time 0 (zero) to the longest time provided by the authors. Regarding PD outcomes, we aimed at evaluating AMI that may interfere with the expected therapeutic effect of that medication. Therefore, we collected any outcome related with the therapeutic aims of medications evaluated using objective scales (e.g., score for pain relief in case of opioids) or other objective measures (e.g., heart rate (HR), diastolic and systolic BP, body weight). When reported as graphs, we extracted data using WebPlotDigitalizer software (Rohatgi, 2020). We did not include outcomes that explored the safety or toxicity profile of medications.

2.6. Exclusion criteria

Studies were excluded if: (a) they were preclinical studies, review articles, observational studies, case reports, and/or letters; (b) participants did not receive approved medications; (c) participants received medications removed by the market; (d) participants did not receive alcohol; (e) a control group was not available; (f) participants of the control group did not receive a placebo solution; (g) the number of participants was not available; (h) the dose of the medication was not available; (i) participants were < 18-years-old; (j) participants received a combination of medications; or (k) data on the outcomes selected were not available.

#### 2.7. Assessment of risk of bias

Three authors (F.T., R.A., R.P.) independently assessed the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). In details, we assessed random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Regarding the risk of bias in the random sequence generation and allocation concealment, we judged at low-risk studies with a crossover design, as the same subjects were included in both the groups (experimental and control groups) after an adequate period of washout. Regarding the risk of bias due to the knowledge of the allocation by participants and personnel during the study, we considered that PK outcomes were not likely to be influenced by lack of blinding and, accordingly, we assigned a low risk of bias to the studies in which these outcomes were evaluated. Conversely, these PD outcomes were considered to be likely influenced by these sources of risk of bias.

Regarding the influence of other xenobiotics, for both PK and PD outcomes, we judged at high risk of bias the studies in which the placebo solution differed from the one used for alcoholic solution. For those studies in which the description of the placebo solution was not provided, we judged at unclear risk of bias. In detail, we assigned a low risk of bias to those studies in which the alcoholic and placebo solutions only differed for the presence or absence of alcohol (e.g., grapefruit juice with pure alcohol compared to grapefruit juice without alcohol). On the other hand, we assigned a high risk of bias to those studies in which the two solutions differed for other substances that may interact with therapeutic medications (e.g., alcoholic solution consisting of grapefruit juice and pure alcohol compared to a placebo solution consisting of water). Finally, we assigned an unclear risk of bias to those studies in which, in the alcoholic solution, the presence of other xenobiotics could be not excluded (e.g., when vodka or whisky were compared to water). We also collected data regarding potential conflicts of interest (e.g., whether the study was sponsored or executed by a commercial entity).

#### 2.8. Data analysis

We used Cochrane RevMan software [Review Manager (RevMan) Version 5.4 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] for our statistical analysis. We analyzed continuous outcomes by calculating the mean difference (MD) and dichotomous outcomes by calculating the risk ratio (RR) with the uncertainty result expressed 95% confidence interval (CI). We considered a significant difference between alcohol and placebo when CIs excluded 0 (P-values <0.05) and the lack of difference in cases where CIs included 0 (P-values ≥0.05). The presence of significant heterogeneity will be defined as I² value > 50% or P-value for the test ≤ 0.1 (Higgins and Green, 2011). Random effects model was used for all the analyses.

When available, data were collected as Arithmetic Mean (AM) and Standard Deviation (SD) or Standard Error of the Mean (SEM), and SEM were converted into SD. When AM, SD or SEM were not available, Geometric Mean (GM) and Coefficient of Variation (CV) were collected, depending on the Authors’ choices. Arithmetic CV were converted into SD using the formulas: CVA = (SDA/AM)\*100 ⇨ SDA = (CVA\*AM)/100; Geometric CV were converted into SD using the following formula: CVG = (SDG-1)\*100 ⇨ SDG = (CVG/100)+1. When AM was not available, we collected Geometric Means (GM) and included these means in the meta-analysis considering that the use of GM instead of AM may only reduce the hypothetical results range as GM is always lower than AM. When data were not available as AM, SD, SEM, GM, and CV, we collected median, range and/or an interquartile range. In this case, mean and range were converted into AM and SD through the framework proposed by Wan and colleagues (Wan et al., 2014). In case of missing data on the SD, we used the mean of the SD of the other data. We used the Standardized Mean Difference (SMD) when different medications were included in the same analysis.

We elaborated the “Summary of Findings (SoF)” for those medications or class of medications for which data were collected from at least 3 independent studies, in which at least 200 participants were recruited. SoF were elaborated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Atkins et al., 2004; Guyatt et al., 2011).

**3. RESULTS AND DISCUSSION**

Our search identified a total of 757 records from which duplicates were removed, leaving 756 records (see Fig. 1). We selected another 353 articles through manual search. Screening the titles and abstracts of these records provided information that led to the exclusion of 609 articles; 389 were excluded through full-text review and 4 articles were not retrieved (see S References). Globally, we identified 107 articles that met our inclusion criteria, with no exclusion criteria, in which 3097 participants were recruited. Their characteristics are described in the following paragraphs and in the Supplementary tables and Supplementary results, divided into the following different medications or class of medications:

1Medications that affect the Central Nervous System (CNS)

1.1 Benzodiazepines and other anxiolytics

1.2 Cannabis

1.3 Opioids

1.4 Psychostimulants

1.5 Antidepressants and mood stabilizers

1.6 Antipsychotics

1.7 Medications used for the treatment of alcohol and substances use disorders

1.8 Medications used for the treatment of seizures

2 Medications for the treatment of infectious diseases

2.1 Antibiotics

2.2 Antiviral medications

3 Antinflammatory medications

4 Medications used for the treatment of cardiovascular disease

5 Medications used for the treatment of diabetes

6 Medications used for the treatment of respiratory diseases

7 Estrogens

8 Medications used for the treatment of erectile dysfunction

9 Miscellaneous medications

9.1 Statins (fluvastatin)

9.2 Gastric acid-reducing agents (cisapride)

9.3 Medications used for the treatment of obesity (orlistat)

9.4 Medications used for the treatment of migraine (almotriptan)

9.5 Medications used for the treatment of hypoactive sexual desire disorder in women (flibanserin)

9.6 Medications used for anesthesia (nitrous oxide)

9.7 Immunosuppressant medications (cyclosporine)

9.8 Medications used for the treatment of filariasis and onchocerciasis (ivermectin)

3.1 Medications that affect the Central Nervous System (CNS)

*3.1.1 Benzodiazepines* (see S Table 1, S Results 1.1, Tables 1-2, SoF 1-2, and Figures 2-3)

Benzodiazepines are approved for the treatment of anxiety, insomnia, epilepsy, and managing alcohol withdrawal. Alcohol and benzodiazepines produce similar pharmacological effects and their simultaneous use increases CNS depressant effects, impairs driving abilities, and increases the risk of fatal overdose (see Schuckit, 1987; Baldwin et al., 2013; EMCDDA, 2020). Based on PK properties, benzodiazepines can be divided into different groups: those that are mainly metabolized by CYP3A4 and CYP2C19 (e.g., alprazolam, diazepam, clobazam, or chlordiazepoxide) and benzodiazepines that undergo to glucuronidation reactions by UGT (e.g., lorazepam and oxazepam) (Fukasawa et al, 2007). Alcohol is converted into acetaldehyde by two different enzymatic systems: the first one comprises different ADH enzymes and the second one, called the microsomial ethanol-oxidizing system (MEOS), that includes different CYP enzymes, mainly CYP2E1 and other CYPs, like 1A2 and 3A4 (Chan and Anderson, 2014; Johnson and Seneviratne, 2014). Accordingly, acute consumption of alcohol may compete with the metabolism of those benzodiazepines metabolized by CYP enzymes and increase their blood concentrations (Chan and Anderson, 2014; Johnson and Seneviratne, 2014; Sellers and Busto, 1982). Consistent with this hypothesis, we found that, among participants taking diazepam, those who consumed alcohol achieved higher Cmax (low grade of certainty; almost 290 participants) and AUC (very low grade of certainty; 270 participants) of this medication compared to those who consumed placebo (see Tables 1 and 2), while we did not find any effect of alcohol on PK parameters of oxazepam and lorazepam (i.e., benzodiazepines mainly metabolized by UGT). Our results add further evidence for interactions between alcohol and certain benzodiazepines, suggesting that physicians should advise patients who use these specific benzodiazepines to avoid alcohol consumption. However, the low grades of certainty assigned to these AMI emphasize the need for further studies, with appropriate control groups included.

*3.1.2 Cannabis* (see S Table 2, S Results 1.2, Tables 1-2, SoF 3, and Figure 4)

Alcohol and cannabis are among the most common used psychoactive substances (Peacock et al., 2018), frequently consumed in combination, with worrying consequences (Romaguera et al., 2017). In addition, medical use of cannabis is approved in some countries for the treatment of nausea and vomiting, appetite stimulation, chronic pain and spasticity in patients affected by severe disorders (Whiting et al., 2015). In these patients, an increased risk of side effects due to the interaction between alcohol and medical cannabis should be taken into account. Accordingly, physicians and patients should be aware of these interactions and the evidence from the present study may be useful to increase our knowledge on this topic.

In the present study, we found that, among participants taking cannabis, those who consumed alcohol compared to placebo, achieved higher Cmax, in a shorter Tmax, and had a longer T1/2 of THC. We assigned a high grade of certainty to the higher Cmax (cumulating data of almost 650 participants), a very low grade to the shorter Tmax (more than 300 participants), and a moderate grade to the longer T1/2 of THC (almost 250 participants). In all the studies included in these analyses, THC was consumed through inhalation, and in the majority, alcohol was consumed before THC inhalation. These interactions resulted to be statistically significant, when alcohol was administered either in fed or fasting conditions. In other words, the results of our study show that, when consumed in combination with alcohol, THC blood concentrations are higher and longer than when it is consumed alone. Subsequently, when consumed with alcohol, psychoactive and therapeutic effects, as well as any negative effects of THC, may be higher and longer than when it is consumed alone. The mechanism of these interactions is behind the scope of the present study. However, it has been proposed that alcohol consumption ameliorates THC absorption through increased pulmonary capillary flow (Hartman et al., 2015a) because alcohol improves cardiac output and increases HR (Riff et al., 1969). It would be of interest to evaluate whether these interactions tend to disappear with chronic alcohol consumption and whether alcohol consumption interacts with PK outcomes of THC also when THC is orally consumed instead of through inhalation.

*3.1.3 Opioids* (see S Table 3, S Results 1.3, Tables 1-2, SoF 4-5, and Figures 5-6)

Opioids are approved for the treatment of severe, acute or chronic pain, not responsive to other medications (Nafziger and Barkin, 2018). In the last years, their widespread use for chronic pain has contributed to the recent opioid epidemic with substantial increases of overdoses and addiction among people taking prescribed opioids (Volkow et al., 2018). Interactions between alcohol and opioids have been already described by previous studies (Chan and Anderson, 2014; Johnson and Seneviratne, 2014). In detail, it was observed that the simultaneously ingestion of alcohol with an extended-release formulation of hydromorphone hydrochloride resulted in an unintended rapid release of the opioids (Jang and Harris, 2007). Therefore, the FDA promoted clinical trials aimed at investigating the risk of this interaction.

Alcohol impairs the medication slow-release mechanism leading to the entire dose of hydroxymorphone being rapidly released from its matrix due to the intake of alcohol (D’Souza et al., 2017). It has been hypothesized that alcohol interacted with the capsule, causing an excessive release of the medication (Murray and Wooltorton, 2007). Such interactions with alcohol were not observed for other extended-release formulations of other opioids, including morphine. Subsequently, the extended-release formulation of hydromorphone hydrochloride was withdrawn from the market. In agreement with these findings, we found that patients who consumed alcohol achieved higher Cmax (low certainty of evidence) and had a shorter Tmax (moderate certainty of evidence) with opioids compared to those who received placebo. Analyzing single opioids, we found that patients who consumed alcohol achieved higher Cmax and shorter Tmax with hydromorphone compared to those who consumed placebo, and there were no differences between alcohol and placebo in PK outcomes of other opioids, including morphine. Nevertheless, the low certainty of evidence assigned to this AMI and the large use of alcohol and opioids underline the need to conduct further studies to ameliorate our knowledge of these potential interactions.

*3.1.4 Psychostimulants and methylphenidate* (see S Table 4, S Results 1.4, Tables 1-2, SoF 6-7, and Figures 7-8)

Methylphenidate is among the first-line medications for the treatment of individuals with attention-deficit/hyperactivity disorder (ADHD; see Faraone, 2017). Methylphenidate is mainly metabolized into a pharmacologically inactive metabolite, ritalinic acid, by an esterase but, when alcohol is available, it may also be transformed into the active metabolite ethylphenidate (Chan and Anderson, 2014; Patrick et al., 2007). Regarding the interactions between alcohol and methylphenidate, previous review articles have described the contrasting results obtained by different clinical trials (Chan and Anderson, 2014; Weller and Preskorn, 1984). Our study, using a meta-analytic approach and cumulating data coming from more than 200 participants, allows us to establish with moderate certainty that, among participants taking methylphenidate, those who consumed alcohol achieved higher Cmax and AUC of this medication compared to those who consumed placebo (see Tables 1 and 2). These findings suggest that patients with ADHD should abstain from alcohol consumption, at least at the beginning of methylphenidate treatment, because alcohol consumption may increase the concentration of this medication to levels higher than desired and, subsequently, the risk of side effects related to these higher levels. In our study, we were not able to evaluate potential differences in blood concentrations of ethylphenidate. However, this metabolite has been detected in people who consumed methylphenidate and alcohol (Chan and Anderson, 2014). It may be postulated that the increase of Cmax and AUC values found in the present study among participants who were taking methylphenidate and consumed alcohol is consistent with the hypothesis that alcohol acts as an inhibitor of the esterase-mediated hydrolysis of methylphenidate and/or that the active metabolite ethylphenidate may act as an inhibitor of this enzyme (Patrick et al., 2007).

Together with methylphenidate, amphetamine is one of the main pharmacological interventions for ADHD in adulthood (Castells et al., 2018). In general, alcohol consumption should be avoided in combination with amphetamines because it may potentiate cardiovascular side effects (e.g., tachycardia, myocardial infarction) by increasing cardiac work and myocardial oxygen consumption (Mendelson et al., 1995; Jiao et al., 2009). Furthermore, clinical and preclinical studies report that alcohol intake can induce changes in metabolism of methamphetamine (Shimosato, 1988; Lian et al., 2012; Li et al., 2014).

In our study, we did not find any effect of acute alcohol on PK properties of amphetamines. However, the low or very low grades of evidence assigned to these AMI underline the need to conduct additional studies to better evaluate whether the efficacy of amphetamines may be affected by alcohol.

*3.1.5 Antidepressants and mood stabilizers* (see S Table 5, S Results 1.5, and Tables 1-2)

The prevalence of AUD in patients taking anti-depressants and/or mood stabilizers is higher than compared to the control population (Graham and Massak, 2007; Troy et al., 1997), and patients with mood disorders who take antidepressants often present with comorbid AUD (Agabio et al., 2018; Chan et al., 2015). Several reports indicate that alcohol intake may increase the risk of side effects due to antidepressant therapies (Menkes and Herxheimer, 2014; Weathermon et al., 1999). It has also been suggested that alcohol may interfere with antidepressant efficacy, even if the mechanism underlying this potential AMI is not completely understood (Menkes and Herxheimer, 2014). Interestingly, nearly all antidepressants (e.g., amitriptyline, SSRIs) have a hepatic oxidative metabolism by CYP2D6 enzyme. The lack of clear AMI with antidepressants may be due to the fact that alcohol has not been found to significantly induce or inhibit CYP2D6 (Vincent-Viry et al., 2000). Unfortunately, our results do not clarify this controversial topic. Our study found some PK differences between alcohol and placebo for some antidepressants. Specifically, we found that, compared to participants who received placebo, those who consumed alcohol achieved a lower Cmax of bupropion, longer T1/2 of SSRs, and longer Tmax of trazodone. However, the limited number of available studies did not allow us to assign the grades of certainty to these AMI. Furthermore, we found no differences in the other PK parameters of these antidepressants and no difference in any PK outcomes of other antidepressants and mood stabilizers like amytriptiline, mianserin, venlafaxine, vortioxetine, or lithium carbonate.

*3.1.6 Antipsychotics* (see S Table 6, S Results 1.6, and Tables 1-2)

Antipsychotic drugs are a widely prescribed group of medications with a range of clinical applications that include psychosis, severe depression, and bipolar disorder (Schwartz and Brotman, 1992). The combination of antipsychotics (especially for typical neuroleptics) with alcohol should be avoided, given the increased risk of neurologic and psychiatric adverse reactions due to addictive effects on CNS depression (NIAAA, 1995). However, only a few studies have directly assessed the interaction between alcohol and antipsychotic drugs. In this analysis, we found that, among participants taking the atypical antipsychotic medication blonanserin, those who consumed alcohol achieved higher Cmax, and AUC, and longer T1/2, Tmax and AUC, compared to those who received placebo. The mechanism by which alcohol may alter blonanserin plasma levels is not completely clear and therefore future investigations are needed. However, these results were observed in an analysis in which only one study (20 participants) was included. Accordingly, we did not assign the certainty grade of evidence to this AMI. It may be speculated that the increase in blood concentration of this medication was due to generic effects induced by alcohol consumption on gastrointestinal motility, mucosal permeability, and solubility of medications (Ionue et al., 2012; Subramanya et al., 2015). On the other hand, we found no differences between alcohol and placebo in PK outcomes of other atypical antipsychotic medications, like amisulpiride and remoxipiride. These results tentatively suggest that alcohol consumption may induce different effects on specific antipsychotic medications. Considering the high prevalence of alcohol consumption in patients taking antipsychotics, further well-designed RCTs should be conducted to unveil the real effects of alcohol on this class of medications.

*3.1.7 Medications used for the treatment of alcohol and substance use disorders* (see S Table 7, S Results 1.7, and Tables 1-2)

Alcohol use disorder is a severe mental disorder characterized by the inability to control alcohol consumption (APA, 2013). Patients affected often consume large amounts of alcohol (APA, 2013). Accordingly, patients taking pharmacotherapies approved for these disorders (Blanco and Volkow, 2019; FDA, 2015; Sinclair et al., 2016; Ziedonis et al., 2017) should be aware of potential interactions between alcohol and these medications. In our study we found that among participants taking nicotine, there were no differences between alcohol and placebo in craving for cigarettes, but we assigned a very low grade of certainty to this finding (i.e., one study was at high risk of bias and after its exclusion, the analysis did not find difference between alcohol and placebo). The limited number of studies available to evaluate potential AMI for medications approved for the treatment of diseases characterized by excessive alcohol consumption is surprising and represents one of the most important finding of our study. This result underlines the urgent need to conduct studies with appropriate control groups to improve our knowledge on this field.

*3.1.8 Medications used for the treatment of seizures* (see S Table 8, S Results 1.8, and Tables 1-2)

Due to their narrow therapeutic index, almost all antiepileptic medications are under laboratory monitoring and several interactions with other medications have been described (Neels et al, 2004; Patsalos et al, 2008). As a rule, the contemporary consumption of alcohol and antiepileptic medications should be avoided for the risk of additive effects on motor and cognitive functions (NIAAA, 2014). Beside the presence of these harmful sequelae, few clinical studies have investigated potential interactions between alcohol and these medications. In our study, we found that, compared to placebo, those who consumed alcohol achieved higher bioavailability of retigabine. However, we found no differences in the other PK outcomes of retigabine or in all the PK outcomes of brivacetam. Unfortunately, the limited number of studies did not allow us to draw any definitive conclusion.

3.2 Medications for the treatment of infectious diseases

*3.2.1 Antibiotics* (see S Table 9, S Results 2.1, and Tables 1-2)

Concomitant use of antibiotics and alcohol is contraindicated to avoid the risk of certain side effects like disulfiram-like reactions (NIH, 2014; FDA, 2013; Mergenhagen et al., 2020). However, evidence regarding interactions between alcohol and these medications is sparse and often discordant (Mergenhagen et al., 2020). In our study, we found that among participants taking some antibiotics (e.g., penicillins, amoxicillin, doxycycline), those who consumed alcohol differed from those who consumed placebo in some PK values. However, we judged some studies included in these analyses at high risk of bias and after their exclusion, no differences were found between alcohol and placebo. In addition, we found no differences in other PK parameters of the same antibiotics and in PK parameters of other antibiotics (e.g., erythromycin and isoniazid). A sufficient number of studies and participants were not available to assign the grade of evidence to the AMI for any of these medications. Accordingly, the results of our study do not allow us to draw clear conclusions, either pros or cons, regarding the existence of PK interactions between alcohol and antibiotics.

*3.2.2 Antiviral medications* (see S Table 10, S Results 2.2, and Tables 1-2)

As a general recommendation, alcohol consumption should be avoided during therapy for viral infections as it may increase the risk of side effects (e.g., dizziness) and worsening disease progression (Meyerholz et al., 2008; Szabo and Saha, 2015). Nevertheless, alcohol consumption is common in patients affected by acquired immune deficiency syndrome (AIDS) under highly active antiretroviral therapy (HAART) (Galvan et al., 2002). More importantly, HIV-infected AUD patients are usually under multi-drug therapy, thus the neurotoxicological effects of consuming alcohol could be extremely severe.

In our study, we found that among HIV-infected individuals taking abacavir, those who consumed alcohol had longer T1/2 and higher AUC of abacavir compared to placebo. Notably, ADH, the main enzymatic system involved in alcohol metabolism, is also involved in the metabolism of some antiviral agents such as acyclovir and abacavir (Walsh et al., 2002; de Miranda and Blum, 1983). Accordingly, the mechanism of this AMI may be due to a competitive action of both alcohol and abacavir on ADH enzymes (Mcdowell et al., 2000), that may have resulted in the increased plasma concentrations of the antiviral medication found by our study.

Our study also found that among healthy participants taking oseltamivir, those who consumed alcohol achieved higher Cmax and AUD and shorter T1/2 compared to placebo. Other studies have observed an interaction between oseltamivir and alcohol (He et al., 1999; Parker et al., 2015). Specifically, the bioavailability of oseltamivir, an antiviral agent approved for the treatment and prevention of Influenza A and B, has been found to be impaired by acute alcohol consumption (Parker et al., 2015). In this AMI, it was proposed that another enzyme, the human carboxylesterase-1 (CES1), is responsible for the activation of several medications, including oseltamivir (He et al., 1999; Parker et al., 2015). As alcohol inhibits CES1 (Her and Zhu, 2020), alcohol consumption may interfere with the conversion of oseltamivir into its active compound (oseltamivir carboxylate), resulting in its increased blood concentration and potential toxicity, but decreased therapeutic effects (He et al., 1999; Parker et al., 2015). Thus, the contemporary intake of these medications and alcohol is potentially concerning for the risk to develop PK interactions. In this scenario, special attention should be paid to HIV+ patients. However, in our study we also found that alcohol induces minimal or no changes in PK properties of other antiviral medications like ritonavir, maraviroc and efavirenz. Increasing our knowledge on potential AMI would be extremely useful considering the high cost of some antiviral therapies (Linas, 2016). Unfortunately, we could not draw a definitive conclusion, or assign the grade of certainty to the AMI found, due to the selection of a limited number of studies on this topic in our meta-analysis.

3.3 Anti-inflammatory medications (see S Table 11, S Results 3, and Tables 1-2)

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the class of medications most commonly prescribed for the treatment of pain and inflammatory disorders, especially among the elderly population (Wongrakpanich et al., 2018). NSAIDs use is associated with increased risk of gastrointestinal (GI) events (LaGarcía Rodríguez and Jick, 1994) and alcohol consumptions represents an independent risk factor for similar GI complications, like GI bleeding and gastric ulcer (Lebrec et al., 1980). Accordingly, NSAIDs use among people with AUD significantly elevates the risk to develop GI events (Nautel & Appel, 2000; Kaufman et al., 1999). On the other hand, only a few clinical studies have directly evaluated the impact of acute alcohol ingestion on NSAIDs PK or PD properties. Our study did not find differences between alcohol and placebo in any PK outcomes evaluated for aspirin. These findings suggest that alcohol consumption does not affect the efficacy of aspirin. However, to the best of our knowledge, no RCT has evaluated whether the therapeutic effects of other NSAIDs are modified by alcohol. Therefore, we believe that it is still wise to advise patients not to consume alcohol while they are taking NSAIDs.

3.4 Medications used for the treatment of cardiovascular diseases (see S Table 12, S Results 4, and Tables 1-2)

Alcohol produces several effects on the cardiovascular system in a dose dependent manner (Gardner and Mouton, 2015). Low to moderate alcohol intake is associated with a reduced risk of cardiovascular morbidity and mortality, on the other hand binge drinking and severe alcohol consumption lead to increased risk. Notably, the prevalence of alcohol consumption is particularly high (around 25%) in patients taking cardiovascular agents (Breslow et al., 2015). Our results suggest that alcohol does not induce any PK changes when combined with beta blockers (atenolol), antiarrhythmic medications (disopyramide), calcium channel blockers (felodipine, nifedipine, verapamil), calcium-sensitizer or ATP-dependent potassium channel openers (levosimendan). On the other hand, we found that alcohol consumption significantly affected some PD outcomes of calcium channel blockers and beta blockers, specifically increased HR and systolic BP compared to placebo. Finally, we found no differences between alcohol and placebo in any PD outcomes evaluated for prazosin. Unfortunately, the limited number of studies for this class of medications prevented us from drawing clear conclusions.

3.5 Medications used for the treatment of diabetes (see S Table 13, S Results 5, and Tables 1-2)

The relationship between alcohol and diabetes is complex and controversial (van de Wiel, 2004). Regarding potential AMI, it has been observed that acute alcohol consumption without food may induce hypoglycemia, especially in patients taking sulphonylurea, while light-to moderate drinking improves insulin sensitivity (van de Wiel, 2004). In our study, we found that among patients with diabetes mellitus type II taking the sulfonylurea glyburide, those who consumed alcohol achieved a higher decrease of glycaemia compared to those who received placebo. This AMI may be due to an increase in insulin sensitivity in response to alcohol consumption (Burge et al., 1999). We also observed that, among patients with diabetes mellitus type II taking the glucokinase activator piragliatin, those who consumed alcohol achieved a lower Cmax of this medication compared to those who consumed placebo. It has been proposed that this effect may be mediated by competitive metabolism of ADH and CYP3A enzymes involved in the metabolite of both piragliatin and alcohol (Zhi et al., 2016). Finally, we found that, among patients with diabetes mellitus type I taking glucagon, those who consumed alcohol had a smaller glucose AUC compared to those who received placebo. Since alcohol inhibits both gluconeogenesis and glycogenolysis (van de Wiel, 2004), its acute consumption may reduce the glucose response to glucagon. Conversely, in patients with diabetes mellitus type I taking insulin, we found no differences in glucose nadir between alcohol and placebo. Our results confirm the existence of interactions between alcohol and at least some medications for the treatment of diabetes. However, the limited number of studies selected prevented us from assigning the grades of evidences to these AMI and drawing any conclusions. Globally, these findings suggest appropriate studies to be conducted to clearly establish these AMI.

3.6 Medications used for the treatment of respiratory diseases (see S Table 14, S Results 6, and Tables 1-2)

In our study, we found that alcohol consumption interferes with PK methylxanthines and dimethylxanthines. In detail, alcohol consumption increased AUC of caffeine and T1/2 of theophylline without altering other PK outcomes of these medications. In addition, our results show that alcohol consumption reduced Tmax of ebastine without modifying other PK outcomes of this medication or the other antihistamine medications. These results may be of interest in clinical practice, for instance to explain the worsening effects performed by alcohol in caffeine intoxication.

In the last years, the large use of caffeinated energy drinks among adolescents has become an important cause of concern because of the risk of tachycardia, vomiting, cardiac arrhythmias, seizures, and even death induced by caffeine intoxication (De Sanctis et al., 2017). It has been observed that consuming alcohol with these beverages may further worsen caffeine intoxication. Our results suggest that the worsening effects may be mediated by an increase of caffeine AUC induced by alcohol consumption. Nevertheless, the scarce number of studies prevented us from assigning the grade of evidence or drawing clear conclusions about these AMI.

3.7 Estrogens (see S Table 15, S Results 7, and Tables 1-2)

We found that participants who consumed alcohol achieved higher Cmax of estradiol compared to placebo, and there were no differences in other PK outcomes of this estrogen. Nevertheless, the limited number of studies we selected prevented us from assigning the grade of certainty to this finding. The lack of appropriate studies to evaluate these potential AMI underlines the urgent need to ameliorate our knowledge on the possible risks and benefits of therapies available for the treatment of menopausal symptoms (Cobin et al., 2017).

3.8 Medications used for the treatment of erectile dysfunction (see S Table 16, S Results 8, and Tables 1-2)

Vardenafil is a phosphodiesterase type 5 inhibitor (PDE5I) approved for the treatment of erectile dysfunction (Yafi et al., 2018). Case reports of seizures and myocardial infarction have been reported in men who abused PDE5Is with alcohol and other psychoactive substances (Yafi et al., 2018).

In our study, we found that participants who consumed alcohol achieved a higher Cmax of vardenafil compared to those who consumed placebo, and there were no differences in other PK outcomes of this medication. This result was obtained by data collected by only one study. Again, the limited number of studies available prevented us from drawing a conclusion on this topic.

3.9 Miscellaneous medications (see S Table 17, S Results 9, and Tables 1-2)

Our study identified other interactions between alcohol and other medications like fluvastatin (alcohol reduced T1/2 of the medication and increased triglycerides blood concentrations),

cisapride (alcohol increased Cmax and Tmax), orlistat (alcohol increased fecal fat concentration), cyclosporine (alcohol reduced Cmax and AUC and increased Tmax), and ivermectin (alcohol increased Cmax). However, these findings were obtained by single studies, which prevented us from drawing clear conclusions.

For a few medications (almotriptan, flibanserin, and NO), we found no differences between alcohol and placebo in any outcome evaluated.

1. **Conclusions**

The results of our systematic review and meta-analysis show that, after the exclusion of the confounding effects of other xenobiotics, alcohol consumption is responsible for significant interactions with misused drugs and medications of frequent use like diazepam, cannabis, methylphenidate, and opioids. These results are important from a pharmacological, clinical and public health standpoint, given the wide use of these medications as well as of alcohol. The knowledge of these interactions is essential for physicians to advise their patients to avoid alcohol consumption when they prescribe medications for which AMI have been demonstrated.

However, only for certain medications (diazepam, cannabis, methylphenidate, and opioids), we have collected enough data to assign the certainty grades to these AMI. For most medications, we found some significant differences in one or more PK parameters between alcohol and placebo, but the limited number of available studies did not allow us to assign them the certainty grades. These medications include SSRIs and two other antidepressants (bupropion and trazodone), one antipsychotic (blonserin), one medication for the treatment of seizures (retigabine), three antibiotics (amoxicillin, doxycycline, and tetracycline), three antiviral medications (abacavir, oseltamivir, and ritonavir), estradiol, one medication for the treatment of cardiovascular diseases (atenolol), two medications approved for the treatment of diabetes (glucagon and glyburide), two medications for the treatment of respiratory diseases (ebastine, methacholine), and some other miscellaneous medications (verdanafil, fluvastatin, cisapride, orlistat, cyclosporine and ivermectin).

It is surprising that our knowledge on this topic is also limited for medications approved for the treatment of diseases characterized by excessive alcohol consumption, like AUD, or frequently associated with excessive alcohol consumption, like mood disorders, psychotic disorders, and viral diseases.

Interestingly, sex and gender differences have been described in the PK and/or PD parameters of alcohol (Agabio et al., 2016; Agabio et al., 2017), as well as diazepam (Farkouh et al., 2020), cannabis (Cooper and Craft, 2018), methylphenidate (Patrick et al., 2007), and opioids (Pisanu et al., 2019). Accordingly, it may be speculated that interactions between alcohol and these medications are prevalent and more intense among women than men. Unfortunately, in our study we could not evaluate possible gender differences in the AMI found because most studies recruited only male participants and the very few studies in which both men and women were recruited did not provide data broken down for men and women, except for a couple of studies.

Furthermore, considering the high risk of AMI among the elderly, it would have been of interest to evaluate which medications may be limited in their effectiveness if consumed together with alcohol. Nevertheless, we could not draw any conclusion regarding this specific topic because we did not find enough studies conducted in elder populations.

The lack of data representative of the female and elderly population represents another important result of the present study and reflects an important limitation of the current knowledge and published literature. From a clinical point of view, these findings suggest to advice patients who need to take medications to avoid alcohol consumption at least for the first days of the pharmacological treatment, to prevent potential confounding effects due to AMI. Similarly, alcohol consumption should be avoided by patients who do not respond to specific pharmacological treatments to exclude the role of alcohol in reducing the therapeutic effects of medications.

These findings underline the critical need to conduct further studies with appropriate control groups, with enough female participants to enable the data to be broken down into male and female participants to analyze sex differences, and with elderly population to expand our knowledge of this field.

*Declarations of competing interest*

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*Clinical trial registration details*

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**FIGURE LEGENDS**

**Figure 1**

Flow diagram of study selection

**Figure 2**

Cmax of benzodiazepines: Forest plot of comparison - among participants taking benzodiazepines - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

**Figure 3**

Cmax of diazepam: Forest plot of comparison - among participants taking diazepam - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation

**Figure 4**

Cmax of THC: Forest plot of comparison - among participants taking THC - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation; THC: ∆9-tetrahydrocannabinol

**Figure 5**

Cmax of opioids: Forest plot of comparison - among participants taking opioids - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

**Figure 6**

Cmax of morphine: Forest plot of comparison - among participants taking morphine - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation

**Figure 7**

Cmax of amphetamine: Forest plot of comparison - among participants taking amphetamine - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

**Figure 8**

Cmax of methylphenidate: Forest plot of comparison - among participants taking methylphenidate - between those who assumed alcohol and those who assumed placebo

Abbreviations: Cmax: Peak plasma concentrations; SD: Standard deviation; Std: Standardized