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Running head

Alcohol-medication interactions

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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

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.

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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

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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
C_{max}: Peak plasma concentration
CNS: Central nervous system
CTs: Controlled trials
CV: Coefficient of variation
CYP: Cytochrome P450 enzymes
EMA: European Medicines Agency

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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
NNRTI: Non-nucleoside reverse-transcriptase inhibitor
NO: Nitric oxide
NRTI: Nucleoside analog 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 inhibitors
SD: Standard deviation
SEM: Standard error of the mean
SMD: Standardized mean difference
SMS: Serotonin modulator and stimulators
SNRI: Serotonin-norepinephrine reuptake inhibitors
SoF: Summary of findings
SSRIs: Selective serotonin reuptake inhibitors
TCA: Tricyclic antidepressants
THC: Delta (9)-tetrahydrocannabinol
T_{max}: Time to reach C_{max}
$T_{1/2}$: Elimination half-life
VAS: Visual analogue scale
WHO: World Health Organization

Key words: Alcohol, medications, interactions

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,

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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.

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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

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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 ($T_{1/2}$) for retigabine; Kruithof et al., (2017) provided peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), $T_{1/2}$ 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.

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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).

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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) C_{max}, (2) T_{max}, (3) $T_{1/2}$, and (4) AUC from time 0 (zero) to infinite ($AUC_{0\text{-}inf}$). When $AUC_{0\text{-}inf}$ 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.

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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).

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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 I^2 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: $CV_A = (SD_A/AM)*100 \Rightarrow SD_A = (CV_A*AM)/100$; Geometric CV were converted into SD using the following formula: $CV_G = (SD_G-1)*100 \Rightarrow SD_G = (CV_G/100)+1$. 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).

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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:

1 Medications 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

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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 C_{max} (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

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(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 C_{max}, in a shorter T_{max}, and had a longer $T_{1/2}$ of THC. We assigned a high grade of certainty to the higher C_{max} (cumulating data of almost 650 participants), a very low grade to the shorter T_{max} (more than 300 participants), and a moderate grade to the longer $T_{1/2}$ 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

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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 C_{max} (low certainty of evidence) and had a shorter T_{max} (moderate certainty of evidence) with opioids compared to those who received placebo. Analyzing single opioids, we found that patients who consumed alcohol achieved higher C_{max} and shorter T_{max} 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.

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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 C_{max} 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 C_{max} 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).

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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 C_{max} of bupropion, longer $T_{1/2}$ of SSRs, and longer T_{max} 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).

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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 C_{max}, and AUC, and longer $T_{1/2}$, T_{max} 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

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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.

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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 $T_{1/2}$ 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 C_{max} and AUD and shorter $T_{1/2}$ 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.

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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

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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 C_{max} 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.

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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 $T_{1/2}$ of theophylline without altering other PK outcomes of these medications. In addition, our results show that alcohol consumption reduced T_{max} 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 C_{max} 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).

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In our study, we found that participants who consumed alcohol achieved a higher C_{max} 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 $T_{1/2}$ of the medication and increased triglycerides blood concentrations),

cisapride (alcohol increased C_{max} and T_{max}), orlistat (alcohol increased fecal fat concentration), cyclosporine (alcohol reduced C_{max} and AUC and increased T_{max}), and ivermectin (alcohol increased C_{max}). 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.

4. 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

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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.

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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

Lorenzo Leggio is a U.S. government employee. Outside of his government work and employment, he receives royalties from Rutledge for having served as Editor of a textbook and he receives an honorarium from the U.K Medical Council on Alcoholism for serving as Editor-in-Chief for Alcohol and Alcoholism. Roberta Agabio, Pier Paolo Pani, Riccardo Presciuttini, Julia Sinclair, and Francesco Traccis have no interest to declare.

Clinical trial registration details

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REFERENCES

1. Agabio R, Campesi I, Pisanu C, Gessa GL, Franconi F. (2016). Sex differences in substance use disorders: focus on side effects. Addict Biol. 21: 1030-42.

2. Agabio R, Pisanu C, Gessa GL, Franconi F. (2017). Sex Differences in Alcohol Use Disorder. Curr Med Chem. 24: 2661-70. doi: 10.2174/0929867323666161202092908. PMID: 27915987.

3. Agabio R, Trogu E, Pani PP. (2018). Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. Cochrane Database Syst Rev. 4(4): CD008581. doi: 10.1002/14651858.CD008581.pub2. PMID: 29688573; PMCID: PMC6494437.

4. Agabio R, Traccis F, Presciuttini R, Leggio L Sinclair J. (2020). Clinically relevant alcohol- medication interactions: a systematic review and meta-analysis of placebo-controlled trials. PROSPERO 2020 CRD42020181411 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181411

5. Ali NA, Marshall RW, Allen EM, Graham DF, Richens A. (1985). Comparison of the effects of therapeutic doses of meptazinol and a dextropropoxyphene/paracetamol mixture alone and in combination with ethanol on ventilatory function and saccadic eye movements. Br J Clin Pharmacol. 20: 631-7 PubMed Central PMCID: PMC1400831.

6. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorder (DSM-5). Washington, DC: American Psychiatric Association.

7. Antila S, Jarvinen A, Akkila J, Honkanen T, Karlsson M, Lehtonen L. (1987). Studies on psychomotoric effects and pharmacokinetic interactions of the new calcium sensitizing drug levosimendan and ethanol. Arzneimittelforschung; 47: 816-20

8. Anton RF, Paladino JA, Morton A, Thomas RW. (1985). Effect of acute alcohol consumption on lithium kinetics, Clin Pharmacol Ther. 38: 52-5.

9. Asher M, Asnaani A, Aderka IM. (2017). Gender differences in social anxiety disorder: A review. Clin Psychol Rev. 56: 1-12. doi: 10.1016/j.cpr.2017.05.004.

10.Atkins, D., Eccles, M., Flottorp, S., Guyatt, G. H., Henry, D., Hill, S., ... & Williams, J. W. (2004). Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC health services research, 4(1), 1-7.

11.Avogaro, A., Beltramello, P., Gnudi, L., Maran, A., Valerio, A., Miola, M., ... & Tiengo, A. (1993). Alcohol intake impairs glucose counterregulation during acute insulin-induced hypoglycemia in IDDM patients: evidence for a critical role of free fatty acids. Diabetes, 42(11), 1626-1634.

Journal Pre-proof

12.Azcona O, Barbanoj MJ, Torrent J, Jane F. (1995). Evaluation of the central effects of alcohol and caffeine interaction, Br J Clin Pharmacol. 40: 393-400.

13.Bailey DG, Spence JD, Edgar B, Bayliff CD, Arnold JM. (1989). Ethanol enhances the hemodynamic effects of felodipine. Clin Invest Med. 12:357-62.

14.Bailey DG, Spence JD, Munoz C, Arnold JM. (1991). Interaction of citrus juices with felodipine and nifedipine. Lancet. 337(8736):268-269. doi:10.1016/0140-6736(91)90872-m

15.Bailey DG, Malcolm J, Arnold O, Spence JD. (1998). Grapefruit juice-drug interactions. Br J Clin Pharmacol. 46: 101-10. doi:10.1046/j.1365-2125.1998.00764.x

16.Bailey DG, Dresser GK, Bend JR. (2003). Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: comparison with grapefruit juice. Clin Pharmacol Ther. 73: 529-37.

17. Baldwin, D. S., Aitchison, K., Bateson, A., Curran, H. V., Davies, S., Leonard, B., ... & Wilson, S. (2013). Benzodiazepines: risks and benefits. A reconsideration. J Psychopharmacol. 27: 967-71. doi: 10.1177/0269881113503509.

18.Baraona E, Gentry RT, Lieber CS. (1994). Bioavailability of alcohol: role of gastric metabolism and its interaction with other drugs, Digestive diseases (Basel, Switzerland). 12: 351-67.

19.Benowitz NL, Jones RT, Jacob IP. (1986). Additive cardiovascular effects of nicotine and ethanol, Clinical Pharmacology and Therapeutics. 40: 420-24.

20.Blanco C, Volkow ND. (2019). Management of opioid use disorder in the USA: present status and future directions. Lancet, 393: 1760-72. doi: 10.1016/S0140-6736(18)33078-2.

21.Bodd E, Beylich KM, Christophersen AS, Mørland J. (1987). Oral administration of codeine in the presence of ethanol: a pharmacokinetic study in man. Pharmacol Toxicol, 61:297-300. doi:10.1111/j.1600-0773.1987.tb01822.x

22.Braithwaite RS, Bryant K J. (2010). Influence of alcohol consumption on adherence to and toxicity of antiretroviral therapy and survival. Alcohol Res Health, 33: 280-87.

23.Breslow RA, Dong C, White A. (2015). Prevalence of alcohol-interactive prescription medication use among current drinkers: United States, 1999 to 2010. Alcohol Clin Exp Res, 39: 371-79. doi:10.1111/acer.12633

24.Burge MR, Zeise TM, Sobhy TA, Rassam AG, Schade DS. (1999). Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. Diabetes Care, 22: 2037-43.

25.Cabarrocas X, Salva M, Pavesi M, Costa J. (2006). Ethanol does not significantly affect the bioavailability of almotriptan: an open, randomized, crossover, single-dose, phase I clinical trial in healthy volunteers. Int J Clin Pharmacol Ther, 44: 443-8.

26.Castells X, Blanco-Silvente L, Cunill R. (2018). Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev, 8: CD007813. doi: 10.1002/14651858.CD007813.pub3.

27.Chait LD, Perry JL. (1994). Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. Psychopharmacology (Berl), 115: 340-9.

Journal Pre-proof

28.Chan LN, Anderson GD. (2014). Pharmacokinetic and pharmacodynamic drug interactions with ethanol (alcohol). Clin Pharmacokinet; 53: 1115-36.

29.Chan P, Yomen K, Turcios J, Richman M. (2015). Prescription for antidepressant in reducing future alcohol-related readmission in patients suffering from depression and alcohol use disorder: a retrospective medical record review. Subst Abuse Treat Prev Policy, 10: 48. doi: 10.1186/s13011-015-0045-y.

30.Chen G, Nomikos GG, Affinito J, Zhao Z. (2016). Lack of Effect of Vortioxetine on the Pharmacokinetics and Pharmacodynamics of Ethanol, Diazepam, and Lithium. Clin Pharmacokinet, 55: 1115-27.

31.Chen M, Zhou SY, Fabriaga E, Zhang PH, Zhou Q. (2018). Food-drug interactions precipitated by fruit juices other than grapefruit juice: An update review. J Food Drug Anal. 2018; 26: S61-S71. doi:10.1016/j.jfda.2018.01.009

32.Cobin, R. H., Goodman, N. F., & AACE Reproductive Endocrinology Scientific Committee. (2017). American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause–2017 update. Endocrine practice, 23(7), 869-881.

33.Cooper ZD, Craft RM. (2018). Sex-Dependent Effects of Cannabis and Cannabinoids: A Translational Perspective. Neuropsychopharmacology, 43: 34-51. doi: 10.1038/npp.2017.140.

34.Crean CS, Tompson DJ. The effects of ethanol on the pharmacokinetics, pharmacodynamics, safety, and tolerability of ezogabine (retigabine). Clin Ther 2013; 35: 87-93.

35.D'Souza, S., Mayock, S., & Salt, A. (2017). A review of in vivo and in vitro aspects of alcohol-induced dose dumping. AAPS Open, 3(1), 1-20.

36.Dahan A, Altman H. Food-drug interaction: grapefruit juice augments drug bioavailability--mechanism, extent and relevance. Eur J Clin Nutr 2004; 58: 1-9. doi:10.1038/sj.ejcn.1601736

37.Dattani RG, Harry F, Hutchings AD, Routledge PA. (2004). The effects of acute ethanol intake on isoniazid pharmacokinetics, Eur J Clin Pharmacol, 60: 679-82.

38.De Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. (2006). Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med, 166: 2437–45.

39.de Miranda P, Blum MR. (1983). Pharmacokinetics of acyclovir after intravenous and oral administration. Journal of Antimicrobial Chemotherapy, 12(suppl_B), 29-37.

40.De Sanctis V, Soliman N, Soliman AT, Elsedfy H, Di Maio S, El Kholy M, Fiscina B. (2017). Caffeinated energy drink consumption among adolescents and potential health consequences associated with their use: a significant public health hazard. Acta Biomed, 23; 88(2):222-231. doi: 10.23750/abm.v88i2.6664. PMID: 28845841; PMCID: PMC6166148.

41.Deng S, Ni X, Shang D et al. (2018). Effects of Alcohol on the Pharmacokinetics of Blonanserin and N-Deethylated Blonanserin in Healthy Chinese Subjects. J Clin Psychopharmacol. 38(2):129-133.

42.Divoll M and Greenblatt DJ. (1981). Alcohol does not enhance diazepam absorption, Pharmacology, 22(4): 263-8

43.Doms M, Vanhulle G, Baelde Y, Coulie P, Dupont P and Rihoux JP. (1988). Lack of potentiation by cetirizine of alcohol-induced psychomotor disturbances, Eur J Clin Pharmacol, 34(6): 619-23

Journal Pre-proof

44.Dorian P, Sellers EM, Reed KL, Warsh JJ, Hamilton C, Kaplan HL, Fan T. (1983). Amitriptyline and ethanol: pharmacokinetic and pharmacodynamic interaction. Eur J Clin Pharmacol. 25(3):325-31

45.Dorian P, Sellers EM, Kaplan HL, Hamilton C, Greenblatt DJ and Abernethy D. (1985). Triazolam and ethanol interaction: kinetic and dynamic consequences, Clin Pharmacol Ther, 37(5): 558-62

46.Downey, L. A., King, R., Papafotiou, K., Swann, P., Ogden, E., Boorman, M., & Stough, C. (2013). The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. Accident; analysis and prevention, 50, 879–886. https://doi.org/10.1016/j.aap.2012.07.016

47.EMCDDA. Benzodiazepines drug profile, https://www.emcdda.europa.eu/publications/drug-profiles/benzodiazepines_en. (2020-10-16 12:07:42)

48.Erwin CW, Linnoila M, Hartwell J, Erwin A and Guthrie S. (1986). Effects of buspirone and diazepam, alone and in combination with alcohol, on skilled performance and evoked potentials, J Clin Psychopharmacol, 6(4): 199-209

49.Evans, S. M., & Levin, F. R. (2002). The effects of alprazolam and buspirone in light and moderate female social drinkers. Behavioural Pharmacology, 13(5), 427–439. doi:10.1097/00008877-200209000-00016

50.Faraone SV. (2018). The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehav Rev. 2018 Apr;87:255-270. doi: 10.1016/j.neubiorev.2018.02.001.

51. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. (2020). Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature. Adv Ther. 37(2):644-655. doi: 10.1007/s12325-019-01201-3. Epub 2019 Dec 23. PMID: 31873866.

52.Fiske WD, Jobes J, Xiang Q, Chang SC, Benedek IH. (2012). The effects of ethanol on the bioavailability of oxymorphone extended-release tablets and oxymorphone crush-resistant extended-release tablets. J Pain. 13(1):90-9

53.Food and Drug Administration. (2015). Guidance for Industry. Alcoholism: developing drugs for treatment Center for Drug Evaluation and Research (CDER). Rockville, MD.

54.Fraser AG. (1997). Pharmacokinetic interactions between alcohol and other drugs, Clinical Pharmacokinetics, 33(2): 79-90

55.Fukasawa T, Suzuki A, Otani K. (2007). Effects of genetic polymorphism of cytochrome P450 enzymes on the pharmacokinetics of benzodiazepines. Journal of clinical pharmacy and therapeutics, 32(4), 333-341.

56.Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, Longshore D, Morton SC, Orlando M, Shapiro M. (2002). The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. J Stud Alcohol, 63(2):179-86. doi: 10.15288/jsa.2002.63.179. PMID: 12033694.

57.Gardner JD, Mouton AJ. (2015). Alcohol effects on cardiac function. Compr Physiol. 5(2):791-802. doi: 10.1002/cphy.c140046. PMID: 25880513.

58.GBD. (2016). Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016 [published correction appears in Lancet.

Journal Pre-proof

2018 Sep 29;392(10153):1116] [published correction appears in Lancet. 2019 Jun 22;393(10190):e44]. Lancet. 2018;392(10152):1015-1035. doi:10.1016/S0140-6736(18)31310-2

59.Ginsburg ES, Walsh BW, Gao X, Gleason RE, Feltmate C, Barbieri RL. (1995a). The effect of acute ethanol ingestion on estrogen levels in postmenopausal women using transdermal estradiol. Journal of the Society for Gynecologic Investigation, 2(1), 26-29.

60.Ginsburg ES, Walsh BW, Shea BF, Gao X, Gleason RE, Barbieri RL. (1995b). The effects of ethanol on the clearance of estradiol in postmenopausal women. Fertility and sterility, 63(6), 1227-1230.

61.Ginsburg, E. S., Mello, N. K., Mendelson, J. H., Barbieri, R. L., Teoh, S. K., Rothman, M., ... & Sholar, J. W. (1996). Effects of alcohol ingestion on estrogens in postmenopausal women. Jama, 276(21), 1747-1751.

62.Graham K, Massak A. (2007). Alcohol consumption and the use of antidepressants. CMAJ, 176(5):633-7. doi: 10.1503/cmaj.060446. PMID: 17325328; PMCID: PMC1800314.

63.Greenblatt DJ, Shader RI, Weinberger DR, Allen MD, MacLaughlin DS (1978). Effect of a cocktail on diazepam absorption. Psychopharmacology, 57(2), 199-203.

64.Greenspan, K., & Smith, T. J. (1991). Perspectives on alcohol and medication interactions. Journal of Alcohol and Drug Education, 36(3), 103–107.

65.Gruber VA, Rainey PM, Lum PJ, Beatty GW, Aweeka FT and McCance-Katz EF. (2013). Interactions between alcohol and the HIV entry inhibitor Maraviroc, J Int Assoc Provid AIDS Care, 12(6): 375-7

66.Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence - publication bias. Journal of Clinical Epidemiology 2011;64:1277-82.

67.Haller C, Thai D, Jacob P, 3rd and Dyer J E (2006), GHB urine concentrations after single-dose administration in humans, J Anal Toxicol, 30(6): 360-4

68.Hartling, S. G., Faber, O. K., Wegmann, M. L., Wåhlin-Boll, E., & Melander, A. (1987). Interaction of ethanol and glipizide in humans. Diabetes Care, 10(6), 683-686.

69.Hartman RL, Brown TL, Milavetz G et al. (2015), Cannabis effects on driving lateral control with and without alcohol, Drug Alcohol Depend, 154: 25-37

70.Havier RG. (1991). The interaction of ethanol with drugs. Forensic Sci Rev 3:41–56.

71.Hayes SL, Pablo G, Radomski T and Palmer RF. (1977). Ethanol and oral diazepam absorption, Current Therapeutics, 18(9): 93-94

72.He G, Massarella J, Ward P. (1993). Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. Clin Pharmacokinet, 37(6):471–84.

73.He ZJ. (2005). Effects of food and alcohol on the pharmacokinetics of vardenafil, Zhonghua nan ke xue = National Journal of Andrology, 11(6): 477-479

74. Her L, Zhu HJ. (2020). Carboxylesterase 1 and Precision Pharmacotherapy: Pharmacogenetics and Nongenetic Regulators. Drug Metab Dispos, 48(3):230-244. doi: 10.1124/dmd.119.089680. Epub 2019 Dec 23. PMID: 31871135; PMCID: PMC7031766.

Journal Pre-proof

75.Hernandez-Lopez C, Farre M, Roset PN et al. (2002), 3,4-Methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics, J Pharmacol Exp Ther, 300(1): 236-44

76.Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. (2019). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, Available from www.training.cochrane.org/handbook.

77.Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

78.Holton AE, Gallagher P, Fahey T and Cousins G (2017), Concurrent use of alcohol interactive medications and alcohol in older adults: a systematic review of prevalence and associated adverse outcomes, BMC geriatrics, 17(1): 148

79.Hoyumpa AM, Patwardhan R, Maples M, Desmond PV, Johnson RF, Sinclair AP,Schenker S. (1981). Effect of short-term ethanol administration on lorazepam clearance. Hepatology, 1(1):47-53. PubMed PMID: 6116659.

80.Inoue T, Osada K, Tagawa M, Ogawa Y, Haga T, Sogame Y, Hashizume T, Watanabe T, Taguchi A, Katsumata T, Yabuki M, Yamaguchi N. (2012) Blonanserin, a novel atypical antipsychotic agent not actively transported as substrate by P-glycoprotein. Prog Neuropsychopharmacol Biol Psychiatry, 39(1):156-62. doi: 10.1016/j.pnpbp.2012.06.005. Epub 2012 Jun 9. PMID: 22691713.

81.Jang GR, Harris RZ. Drug interactions involving ethanol and alcoholic beverages. (2007) Expert Opin Drug Metab Toxicol, 3(5):719-31.

82.Jiao, X., Velez, S., Ringstad, J., Eyma, V., Miller, D., & Bleiberg, M. (2009). Myocardial infarction associated with Adderall XR and alcohol use in a young man. The Journal of the American Board of Family Medicine, 22(2), 197-201

83.Johnson F, Wagner G, Sun S and Stauffer J (2008), Effect of concomitant ingestion of alcohol on the in vivo pharmacokinetics of KADIAN (morphine sulfate extended-release) capsules, J Pain, 9(4): 330-6

84.Johnson FK, Ciric S, Boudriau S, Kisicki J and Stauffer J (2012), Effects of alcohol on the pharmacokinetics of morphine sulfate and naltrexone hydrochloride extended release capsules, J Clin Pharmacol, 52(5): 747-56

85.Johnson BA and Seneviratne C (2014), Alcohol-medical drug interactions, Handbook of clinical neurology, 125(): 543-559

86.Kaufman, D. W., Kelly, J. P., Wiholm, B. E., Laszlo, A., Sheehan, J. E., Koff, R. S., & Shapiro, S. (1999). The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. The American journal of gastroenterology, 94(11), 3189-3196

87.Kawano Y, Abe H, Kojima S, Takishita S and Omae T (2000), Interaction of alcohol and an alpha1-blocker on ambulatory blood pressure in patients with essential hypertension, Am J Hypertens, 13(3): 307-12

88.Kim BH, Yi S, Kim J et al. (2009), Influence of alcohol on the hemodynamic effects and pharmacokinetic properties of mirodenafil: a single-dose, randomized-sequence, open-label, crossover study in healthy male volunteers in Korea, Clin Ther, 31(6): 1234-43

Journal Pre-proof

89.Koziolek M, Alcaro S, Augustijns P, et al. (2019). The mechanisms of pharmacokinetic food-drug interactions - A perspective from the UNGAP group. Eur J Pharm Sci, 134:31-59. doi:10.1016/j.ejps.2019.04.003

90.Kresina TF, Flexner CW, Sinclair J et al. (2002) Alcohol use and HIV pharmacotherapy. AIDS Res Hum Retroviruses. 18(11):757–770.

91.Kruithof AC, Watanabe S, Peeters PA, de Kam ML, Zuiker RG, Stevens J, van Gerven JM, Stockis A. (2017). Pharmacological interactions between brivaracetam and ethanol in healthy males. J Psychopharmacol. 31(7):915-926. doi: 10.1177/0269881116665326.

92.Kuitunen T, Mattila MJ, Seppala T. (1990) Actions and interactions of hypnotics on human performance: single doses of zopiclone, triazolam and alcohol. Int Clin Psychopharmacol. 5 Suppl 2:115-30. PubMed PMID: 2201724.

93.Kumar S, Jin M, Ande A, Sinha N, Silverstein PS, Kumar A. (2012) Alcohol consumption effect on antiretroviral therapy and HIV-1 pathogenesis: role of cytochrome P450 isozymes. Expert Opin Drug Metab Toxicol. 8(11):1363-75.

94.Kupari M, Heikkilä J, Tolppanen EM, Nieminen MS, Ylikahri R. (1983) Acute effects of alcohol, beta blockade, and their combination on left ventricular function and hemodynamics in normal man. Eur Heart J. 4(7):463-71

95.LaGarcía Rodríguez and Jick, H. (1994). Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. The Lancet, 343(8900), 769-772.

96.Laisi U, Linnoila M, Seppala T, Himberg JJ, Mattila MJ (1979) Pharmacokinetic and pharmacodynamic interactions of diazepam with different alcoholic beverages. Eur J Clin Pharrnacol 16:263-270

97.Lane EA, Guthrie S, Linnoila M. (1985) Effects of ethanol on drug and metabolite pharmacokinetics. Clin Pharmacokinet. 10(3):228-47

98. Lebrec, D., De Fleury, P., Rueff, B., Nahum, H., & Benhamou, J. P. (1980). Portal hypertension, size of esophageal varices, and risk of gastrointestinal bleeding in alcoholic cirrhosis. Gastroenterology, 79(6), 1139-1144.

99.Lee JW, Morris JK, Wald NJ. Grapefruit Juice and Statins. Am J Med. 2016;129(1):26-29. doi:10.1016/j.amjmed.2015.07.036

100. Li, B., Wang, Y., Zhang, Y., & Liu, M. (2014). Effects of Ethanol on the Toxicokinetics of Methamphetamine in Rabbits. Iranian journal of pharmaceutical research: IJPR, 13(1), 329.

101. Liang, M., Liu, Y., Zheng, N., Ananda, S., & Liu, L. (2012). Distribution of methamphetamine and its metabolite amphetamine in acute and subacute ethanol-methamphetamine combination abuse model rats. Journal of analytical toxicology, 36(1), 30-35.

102. Lieber CS. (1990) Interaction of ethanol with drugs, hepatotoxic agents, carcinogens and vitamins. Alcohol Alcohol. 25: 157-176.

103. Lieber CS, Abittan CS. (1999). Pharmacology and metabolism of alcohol, including its metabolic effects and interactions with other drugs. Clin Dermatol. 17(4):365-379. doi:10.1016/s0738-081x(99)00020-6

Journal Pre-proof

104. Linas BP. (2016). Understanding Cost and Value in Hepatitis C Therapy. Top Antivir Med. 24(2):93-97. PMID: 27841979; PMCID: PMC6148929.

105. Lindberg RL, Huupponen RK, Viljanen S, Pihlajamäki KK. (1987) Ethanol and the absorption of oral penicillin in man. Int J Clin Pharmacol Ther Toxicol. 25(10):536-8.

106. Linnoila M, Otterstrom S and Anttila M (1974), Serum chlordiazepoxide, diazepam and thioridazine concentrations after the simultaneous ingestion of alcohol or placebo drink, Ann Clin Res, 6(1): 43561

107. Linnoila M, Mattila MJ, Kitchell BS. (1979) Drug interactions with alcohol. Drugs. 18(4):299-311. Review. PubMed PMID: 387374.

108. Linnoila M, Stapleton JM, Lister R, Moss H, Lane E, Granger A, Greenblatt DJ, (1990a) Eckardt MJ. Effects of adinazolam and diazepam, alone and in combination with ethanol, on psychomotor and cognitive performance and on autonomic nervous system reactivity in healthy volunteers. Eur J Clin Pharmacol. 38(4):371-7.

109. Linnoila M, Stapleton JM, Lister R, Moss H, Lane E, Granger A and Eckardt MJ (1990b), Effects of single doses of alprazolam and diazepam, alone and in combination with ethanol, on psychomotor and cognitive performance and on autonomic nervous system reactivity in healthy volunteers, Eur J Clin Pharmacol, 39(1): 21-8

110. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ. (2018). Alcohol and Cancer: A Statement of the American Society of Clinical Oncology. J Clin Oncol. 36(1):83-93. doi:10.1200/JCO.2017.76.1155

Lown, K. S., Bailey, D. G., Fontana, R. J., Janardan, S. K., Adair, C. H., Fortlage, L. A., ... & Watkins, P. B. (1997). Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. The Journal of clinical investigation, 99(10), 2545-2553.

111. Lukas SE, Orozco S. (2001) Ethanol increases plasma Delta(9)-tetrahydrocannabinol (THC) levels and subjective effects after marihuana smoking in human volunteers. Drug Alcohol Depend. 64(2):143-9.

112. Malhotra BK, Matschke K, Wang Q, Bramson C and Salageanu J (2015), Effects of ethanol on the pharmacokinetics of extended-release oxycodone with sequestered naltrexone (ALO-02), Clin Drug Investig, 35(4): 267-74

113. Mallach HJ, Moosmayer A, Gottwald K and Staak M (1975), [Pharmacokinetic studies on absorption and excretion of oxazepam in Combination with alcohol (author's transl)], Arzneimittelforschung, 25(11): 1840-5

114. Mattila MJ, Laisi U, Linnoila M, Salonen R (1982). Effect of alcoholic beverages on the pharmacokinetics of doxycycline in man. Acta pharmacologica et toxicologica, 50(5), 370-373.

115. Mattila MJ, Mattila ME, Konno K, Saarialho-Kere U. (1988) Objective and subjective effects of remoxipride, alone and in combination with ethanol or diazepam, on performance in healthy subjects. J Psychopharmacol. 2(3-4):138-49

116. Mattila MJ (1990), Alcohol and drug interactions, Annals of Medicine, 22(5): 363-369

117. Mattila MJ, Kuitunen T and Pletan Y (1992), Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects, Eur J Clin Pharmacol, 43(2): 179-84

Journal Pre-proof

118. Mattila MJ, Patat A, Seppala T, Kalska H, Jalava ML, Vanakoski J and Lavanant C (1996), Single oral doses of amisulpride do not enhance the effects of alcohol on the performance and memory of healthy subjects, Eur J Clin Pharmacol, 51(2): 161-6

119. McCance-Katz EF, Gruber VA, Beatty G, Lum PJ, Rainey PM. (2013) Interactions between alcohol and the antiretroviral medications ritonavir or efavirenz. J Addict Med. 7(4):264-70

120. McDowell JA, Chittick GE, Stevens CP, Edwards KD and Stein DS (2000), Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults, Antimicrob Agents Chemother, 44(6): 1686-90

121. Melander O, Liden A and Melander A (1995), Pharmacokinetic interactions of alcohol and acetylsalicylic acid, Eur J Clin Pharmacol, 48(2): 151-3

122. Melia AT, Zhi J, Zelasko R, Hartmann D, Guzelhan C, Guerciolini R and Odink J (1998), The interaction of the lipase inhibitor orlistat with ethanol in healthy volunteers, Eur J Clin Pharmacol, 54(43718): 773-7

123. Mendelson J, Jones RT, Upton R, and Jacob P 3rd (1995), Methamphetamine and ethanol interactions in humans, Clin Pharmacol Ther, 57(5): 559-68

Menkes, D. B., & Herxheimer, A. (2014). Interaction between antidepressants and alcohol: signal amplification by multiple case reports. International Journal of Risk & Safety in Medicine, 26(3), 163-170.

124. Mergenhagen, K. A., Wattengel, B. A., Skelly, M. K., Clark, C. M., & Russo, T. A. (2020). Fact versus Fiction: a Review of the Evidence behind Alcohol and Antibiotic Interactions. Antimicrobial Agents and Chemotherapy, 64(3).

125. Meyerholz, D. K., Edsen-Moore, M., McGill, J., Coleman, R. A., Cook, R. T., & Legge, K. L. (2008). Chronic alcohol consumption increases the severity of murine influenza virus infections. The Journal of Immunology, 181(1), 641-648.

126. Mezey, E. (1976). Ethanol metabolism and ethanol drug interactions. Biochem. Pharmac., 25, 869875.

127. Mintz J, Phipps CC, Arruda MJ, Glynn SM, Schneider NG and Jarvik ME (1991), Combined use of alcohol and nicotine gum, Addictive Behaviors, 16(43467): 43475

128. Modi NB, Dresser M, Desai D, Edgar C and Wesnes K (2007), Dapoxetine has no pharmacokinetic or cognitive interactions with ethanol in healthy male volunteers, J Clin Pharmacol, 47(3): 315-22

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine, 6(7), e1000097.

129. Morasso MI, Hip A, Márquez M, González C, Arancibia A (1988). Amoxicillin kinetics and ethanol ingestion. International journal of clinical pharmacology, therapy, and toxicology, 26(9), 428-431.

130. Morasso MI, Chavez J, Gai MN, Arancibia A (1990). Influence of alcohol consumption on erythromycin ethylsuccinate kinetics. International journal of clinical pharmacology, therapy, and toxicology, 28(10), 426-429.

131. Moore AA, Whiteman EJ and Ward KT (2007), Risks of combined alcohol/medication use in older adults, American Journal Geriatric Pharmacotherapy, 5(1): 64-74

Journal Pre-proof

132. Mouly, S., Lloret-Linares, C., Sellier, P. O., Sene, D., & Bergmann, J. F. (2017). Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort?. Pharmacological research, 118, 82-92.

133. Muhoberac, B. B., Roberts, R. K., Hoyumpa Jr, A. M., & Schenker, S. (1984). Mechanism (s) of ethanol-drug interaction. Alcoholism: Clinical and Experimental Research, 8(6), 583-593.

134. Murray, S., & Wooltorton, E. (2005). Alcohol-associated rapid release of a long-acting opioid. Cmaj, 173(7), 756-756.

135. Nafziger, A. N., & Barkin, R. L. (2018). Opioid therapy in acute and chronic pain. The Journal of Clinical Pharmacology, 58(9), 1111-1122.

136. National Institute on Alcohol Abuse and Alcoholism, 1995. Alcohol-Medication Interactions - Alcohol Alert No. 27 Available at: https://pubs.niaaa.nih.gov/publications/aa27.htm Accessed October 18, 2020

137. National Institute on Alcohol Abuse and Alcoholism (2014) Harmful interactions: mixing alcohol with medicines. NIH Publication No. 13-5329. National Institutes of Health, US Department of Health and Human Services. Available at: http://pubs.niaaa.nih.gov/publications/Medicine/medicine.htm. Accessed March 4, 2020

138. Neels HM, Sierens AC, Naelaerts K, Scharpé SL, Hatfield GM, Lambert WE. (2004). Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin Chem Lab Med. 42(11):1228-55. doi: 10.1515/CCLM.2004.245. PMID: 15576287.

139. Neutel, C. I., & Appel, W. C. (2000). The effect of alcohol abuse on the risk of NSAID-related gastrointestinal events. Annals of epidemiology, 10(4), 246-250

140. Newcorn JH, Stark JG, Adcock S, McMahen R, Sikes C (2017) A randomized phase I study to assess the effect of alcohol on the pharmacokinetics of an extended-release orally disintegrating tablet formulation of amphetamine in healthy adults. Clinical therapeutics, 39(8), 1695-1705.

141. Noureldin M, Krause J, Jin L, Ng V, Tran M. (2010) Drug-Alcohol Interactions: A Review of Three Therapeutic Classes. US Pharm. 35(11):29-40.

142. Ochs HR, Greenblatt DJ, Arendt RM, Hubbel W and Shader RI (1984), Pharmacokinetic noninteraction of triazolam and ethanol, J Clin Psychopharmacol, 4(2): 106-7

143. Offman EM, Freeman DJ, Dresser GK, Munoz C, Bend JR, Bailey DG. (2001) Red wine-cisapride interaction: comparison with grapefruit juice. Clin Pharmacol Ther. 70(1):17-23.

144. Oliver JA, Blank MD, Rensburg KJ Van, MacQueen DA, Brandon TH and Drobes DJ (2013), Nicotine interactions with low-dose alcohol: pharmacological influences on smoking and drinking motivation, J Abnorm Psychol, 122(4): 1154-65

145. Olsen, H., Bredesen, J. E., & Lunde, P. K. M. (1983). Effect of ethanol intake on disopyramide elimination by healthy volunteers. European journal of clinical pharmacology, 25(1), 103-105.

146. Parker RB, Hu ZY, Meibohm B and Laizure S C (2015), Effects of alcohol on human carboxylesterase drug metabolism, Clin Pharmacokinet, 54(6): 627-38

Journal Pre-proof

147. Paśko P, Rodacki T, Domagała-Rodacka R, Owczarek D. (2016). A short review of drug-food interactions of medicines treating overactive bladder syndrome. Int J Clin Pharm. 38(6):1350-1356. doi:10.1007/s11096-016-0383-5

148. Patat A, Stubbs D, Dunmore C, Ulliac N et al. (1995), Lack of interaction between two antihistamines, mizolastine and cetirizine, and ethanol in psychomotor and driving performance in healthy subjects, Eur J Clin Pharmacol, 48(2): 143-50

149. Patrick KS, Straughn AB, Minhinnett RR et al. (2007), Influence of ethanol and gender on methylphenidate pharmacokinetics and pharmacodynamics, Clin Pharmacol Ther, 81(3): 346-53

150. Patrick KS, Straughn AB, Reeves OT, Bernstein H, Bell GH, Anderson ER, Malcolm RJ (2013) Differential influences of ethanol on early exposure to racemic methylphenidate compared with dexmethylphenidate in humans. Drug metabolism and disposition, 41(1), 197-205.

151. Patrick KS, Straughn AB, Reeves III OT, Bernstein H, Malcolm R (2015) Comparative ethanol-induced potentiation of stimulatory responses to dexmethylphenidate versus methylphenidate. Journal of clinical psychopharmacology, 35(4), 464.

152. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. (2008). Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 49(7):1239-76. doi: 10.1111/j.1528-1167.2008.01561.x. PMID: 18397299.

153. Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, Giovino GA, West R, Hall W, Griffiths P, Ali R, Gowing L, Marsden J, Ferrari AJ, Grebely J, Farrell M, Degenhardt L. (2018). Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction.113(10):1905-1926. doi: 10.1111/add.14234. Epub 2018 Jun 4. PMID: 29749059.

154. Perez-Reyes M, Hicks RE, Bumberry J, Jeffcoat AR and Cook CE (1988), Interaction between marihuana and ethanol: effects on psychomotor performance, Alcohol Clin Exp Res, 12(2): 268-76

155. Perez-Reyes M, White WR, McDonald SA and Hicks RE (1992), Interaction between ethanol and dextroamphetamine: effects on psychomotor performance, Alcohol Clin Exp Res, 16(1): 75-81

156. Perkins KA, Sexton JE, DiMarco A, Grobe JE, Scierka A, Stiller RL. (1995) Subjective and cardiovascular responses to nicotine combined with alcohol in male and female smokers. Psychopharmacology (Berl). 119(2):205–212.

157. Pisanu C, Franconi F, Gessa GL, Mameli S, Pisanu GM, Campesi I, Leggio L, Agabio R. (2019). Sex differences in the response to opioids for pain relief: A systematic review and meta-analysis. Pharmacol Res. 148:104447. doi: 10.1016/j.phrs.2019.104447. PMID: 31499196.

158. Posner J, Bye A, Jeal S, Peck AW and Whiteman P (1984), Alcohol and bupropion pharmacokinetics in healthy male volunteers, Eur J Clin Pharmacol, 26(5): 627-30

159. Qureshi S, Laganiere S, Caille G, Gossard D, Lacasse Y and McGilveray I (1992), Effect of an acute dose of alcohol on the pharmacokinetics of oral nifedipine in humans, Pharm Res, 9(5): 683-6

160. Ramaekers JG, Theunissen EL, de Brouwer M, Toennes SW, Moeller MR, Kauert G. (2011) Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users. Psychopharmacology (Berl). 214(2):391-401.

Journal Pre-proof

161. Ranjan A, Nørgaard K, Tetzschner R, Steineck IIK, Clausen TR, Holst JJ, Madsbad S, Schmidt S. (2018) Effects of Preceding Ethanol Intake on Glucose Response to Low-Dose Glucagon in Individuals With Type 1 Diabetes: A Randomized, Placebo-Controlled, Crossover Study. Diabetes Care. 41(4):797-806.

162. Rehm, J., Room, R., Monteiro, M., Gmel, G., Graham, K., Rehn, N., ... & Jernigan, D. (2003). Alcohol as a risk factor for global burden of disease. European addiction research, 9(4), 157-164.

163. Riff DP, Jain AC, Doyle JT. (1969). Acute hemodynamic effects of ethanol on normal human volunteers. Am Heart J. 78(5):592-7. doi: 10.1016/0002-8703(69)90510-9. PMID: 5348743.

164. Rohatgi Ankit. WebPlotDigitizer Website: https://automeris.io/WebPlotDigitizer. Version: 4.3 Date: July, 2020 E-Mail: ankitrohatgi@hotmail.com Location: Pacifica, California, USA

165. Romaguera A, Torrens M, Papaseit E, Arellano AL, Farré M. Concurrent Use of Cannabis and Alcohol: Neuropsychiatric Effect Consequences. CNS Neurol Disord Drug Targets. 2017;16(5):592-597. doi: 10.2174/1871527316666170419161839. PMID: 28440194.

166. Ronen A, Chassidim HS, Gershon P, et al. (2010) The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accid Anal Prev. 42(6):1855-65.

167. Rose JE, Brauer LH, Behm FM, Cramblett M, Calkins K and Lawhon D (2004), Psychopharmacological interactions between nicotine and ethanol, Nicotine Tob Res, 6(1): 133-44

168. Sands, B. F., Knapp, C. M., & Ciraulo, D. A. (1993). Medical consequences of alcohol-drug interactions. Alcohol Health & Research World, 17(4), 316–320.

169. Sathyan G, Sivakumar K, Thipphawong J. (2008) Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence of alcohol. Curr Med Res Opin. 24(1):297-305.

170. Saxe TG. (1986) Drug-alcohol interactions. Am Fam Physician. 33(4):159-62.

171. Scavone JM, Greenblatt DJ, Harmatz JS, Shader RI. (1986) Kinetic and dynamic interaction of brotizolam and ethanol. Br J Clin Pharmacol. 21(2):197-204.

172. Schuckit MA (1987), Alcohol and drug interactions with antianxiety medications, Am J Med, 82(5a): 27-33

173. Schwartz JT, Brotman AW. (1992). A clinical guide to antipsychotic drugs. Drugs. 44(6):981-92. doi: 10.2165/00003495-199244060-00007. PMID: 1282868.

174. Seden K, Dickinson L, Khoo S, Back D. (2010). Grapefruit-drug interactions. Drugs. 70(18):2373-2407. doi:10.2165/11585250-000000000-00000

175. Seitz C, Garcia P, Arancibia A. (1995) Influence of ethanol ingestion on tetracycline kinetics. Int J Clin Pharmacol Ther. 33(8):462–464.

176. Sellers, E. M., & Busto, U. S. O. A. (1982). Benzodiazepines and ethanol: assessment of the effects and consequences of psychotropic drug interactions. Journal of Clinical Psychopharmacology, 2(4), 249-262.

177. Sellers EM, Giles HG, Greenblatt DJ, Naranjo CA. (1980). Differential effects of benzodiazepine disposition by disulfiram and ethanol. Arzneimittelforschung. 30(5a):882-886.

Journal Pre-proof

178. Sellers EM, Hamilton CA, Kaplan HL, Degani NC, Foltz RL. (1985) Pharmacokinetic interaction of propoxyphene with ethanol. Br J Clin Pharmacol. 19(3):398–401

179. Setnik B, Sokolowska M, Johnson F, Oldenhof J and Romach M. (2014). Evaluation of the safety, pharmacodynamic, and pharmacokinetic effects following oral coadministration of immediate-release morphine with ethanol in healthy male participants, Hum Psychopharmacol, 29(3): 251-65

180. Shimosato, K. (1988). Urinary excretion of p-hydroxylated methamphetamine metabolites in man. II. Effect of alcohol intake on methamphetamine metabolism. Pharmacology Biochemistry and Behavior, 29(4), 733-740.

181. Shu EN, Onwujekwe EO and Okonkwo PO. (2000). Do alcoholic beverages enhance availability of ivermectin? [1], European Journal of Clinical Pharmacology, 56(5): 437-4384

182. Sinclair JM, Chambers SE, Shiles CJ, Baldwin DS. (2016). Safety and Tolerability of Pharmacological Treatment of Alcohol Dependence: Comprehensive Review of Evidence. Drug Saf. 39(7):627-45. doi: 10.1007/s40264-016-0416-y. PMID: 27023898.

183. Smit JW, Wijnne HJ, Schobben F, Sitsen A, de Bruin TW, Erkelens DW. (1995). Effects of alcohol consumption on pharmacokinetics, efficacy, and safety of fluvastatin. Am J Cardiol. 76(2):89A-96A.

184. Smith RG. (2009). An appraisal of potential drug interactions in cigarette smokers and alcohol drinkers, Journal of the American Podiatric Medical Association, 99(1): 81-88

185. Stevens DM, Weems JM, Brown L, Barbour KA, Stahl SM. (2017). The pharmacodynamic effects of combined administration of flibanserin and alcohol. J Clin Pharm Ther. 42(5):598–606.

186. Stromberg C and Mattila MJ. (1985). Acute and subacute effects on psychomotor performance of femoxetine alone and with alcohol, Eur J Clin Pharmacol, 28(6): 641-7

187. Stromberg C and Mattila MJ. (1987). Acute comparison of clovoxamine and mianserin, alone and in combination with ethanol, on human psychomotor performance, Pharmacol Toxicol, 60(5): 374-9

188. Subramanya, S. B., Stephen, B., Nair, S. S., Schäfer, K. H., & Lammers, W. J. (2015). Effect of ethanol exposure on slow wave activity and smooth muscle contraction in the rat small intestine. *Digestive diseases and sciences*, *60*(12), 3579-3589.

189. Szabo G, Saha B. (2015). Alcohol's Effect on Host Defense. Alcohol Res. 37(2):159-70. PMID: 26695755; PMCID: PMC4590613.

190. Tanaka E, Misawa S. (1998) Pharmacokinetic interactions between acute alcohol ingestion and single doses of benzodiazepines, and tricyclic and tetracyclic antidepressants -- an update. J Clin Pharm Ther. 23(5):331-6.

191. Taeuber K, Badian M, Brettel HF, Royen T, Rupp W, Sittig W and Uihlein M .(1979). Kinetic and dynamic interaction of clobazam and alcohol, Br J Clin Pharmacol, 7 Suppl 1(): 91s-97s

192. Thai D, Dyer JE, Benowitz NL and Haller CA. (2006). Gamma-hydroxybutyrate and ethanol effects and interactions in humans, J Clin Psychopharmacol, 26(5): 524-9

193. Tawakol A, Omland T and Creager MA. (2004). Direct effect of ethanol on human vascular function, Am J Physiol Heart Circ Physiol, 286(6): H2468-73

Journal Pre-proof

194. Taylor B, Rehm J. (2012). The relationship between alcohol consumption and fatal motor vehicle injury: high risk at low alcohol levels. Alcohol Clin Exp Res. 36(10):1827-1834. doi:10.1111/j.1530-0277.2012.01785.x

195. Theile, D., Hohmann, N., Kiemel, D., Gattuso, G., Barreca, D., Mikus, G., ... & Weiss, J. (2017). Clementine juice has the potential for drug interactions–in vitro comparison with grapefruit and mandarin juice. *European Journal of Pharmaceutical Sciences*, *97*, 247-256.

196. Thompson PJ (1992), Social nocturnal alcohol consumption and pharmacokinetics of theophylline, Chest, 101(1): 156-159

197. Toennes SW, Schneider K, Kauert GF, Wunder C, Moeller MR, Theunissen EL, Ramaekers JG. (2011) Influence of ethanol on cannabinoid pharmacokinetic parameters in chronic users. Anal Bioanal Chem. 400(1):145-52.

198. Toennes SW, Schneider K, Wunder C, Kauert GF, Moeller MR, Theunissen E L and Ramaekers J G (2013), Influence of ethanol on the pharmacokinetic properties of Delta9-tetrahydrocannabinol in oral fluid, J Anal Toxicol, 37(3): 152-8

199. Troy SM, Turner MB, Unruh M, Parker VD and Chiang ST (1997), Pharmacokinetic and pharmacodynamic evaluation of the potential drug interaction between venlafaxine and ethanol, J Clin Pharmacol, 37(11): 1073-81

200. Tsunoda SM, Harris RZ, Christians U, Velez RL, Freeman RB, Benet LZ, Warshaw A. (2001) Red wine decreases cyclosporine bioavailability. Clin Pharmacol Ther. 70(5):462-7.

201. U.S. Food and Drug Administration. (2013). Avoid food-drug interactions. U.S. Food and Drug Administration, White Oak, MD.

202. van de Wiel A. (2004). Diabetes mellitus and alcohol. Diabetes Metab Res Rev. 20(4):263-7. doi: 10.1002/dmrr.492. PMID: 15250029.

203. van Harten J, Stevens LA, Raghoebar M, Holland RL, Wesnes K, Cournot A. (1992) Fluvoxamine does not interact with alcohol or potentiate alcohol-related impairment of cognitive function. Clin Pharmacol Ther. 52(4):427-35.

204. van Steveninck AL, Gieschke R, Schoemaker HC, Pieters MS, Kroon J M, Breimer DD and Cohen AF (1993). Pharmacodynamic interactions of diazepam and intravenous alcohol at pseudo steady state, Psychopharmacology (Berl), 110(4): 471-8

205. van Steveninck AL, Gieschke R, Schoemaker RC, et al. (1996). Pharmacokinetic and pharmacodynamic interactions of bretazenil and diazepam with alcohol. Br J Clin Pharmacol.41(6):565–573.

206. Vena GA and Cassano N. (2012). The effects of alcohol on the metabolism and toxicology of anti-psoriasis drugs, Expert Opinion on Drug Metabolism and Toxicology, 8(8): 959-972

207. Vincent-Viry, M., Fournier, B., & Galteau, M. M. (2000). The effects of drinking and smoking on the CYP2D6 metabolic capacity. Drug Metabolism and Disposition, 28(6), 617-619.

208. Volkow N, Benveniste H, McLellan AT. (2018) Use and Misuse of Opioids in Chronic Pain. Annu Rev Med. 69:451-465. doi: 10.1146/annurev-med-011817-044739. Epub 2017 Oct 13. PMID: 29029586.

Journal Pre-proof

209. Walsh, J. S., Reese, M. J., & Thurmond, L. M. (2002). The metabolic activation of abacavir by human liver cytosol and expressed human alcohol dehydrogenase isozymes. Chemico-biological interactions, 142(1-2), 135-154.

210. Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology, 14(1), 1-13.

211. Warrington SJ, Ankier SI and Turner P. (1986). Evaluation of possible interactions between ethanol and trazodone or amitriptyline, Neuropsychobiology, 15 Suppl 1(): 31-7

212. Weathermon R and Crabb DW. (1999). Alcohol and medication interactions, Alcohol research & health: the journal of the National Institute on Alcohol Abuse and Alcoholism, 23(1): 40-54

213. Weller RA, Preskorn SH. (1984). Psychotropic drugs and alcohol: pharmacokinetic and pharmacodynamic interactions. Psychosomatics. 25(4):301-3, 305-6, 309. doi: 10.1016/S0033-3182(84)73047-7. PMID: 6144139.

214. Wensing G, Bauer R, Unger S, Rohde G and Heinig R. (2006). Simultaneous administration of vardenafil and alcohol does not result in a pharmacodynamic or pharmacokinetic interaction in healthy male subjects, Int J Clin Pharmacol Ther, 44(5): 216-24

215. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 313(24):2456-73. doi: 10.1001/jama.2015.6358. Erratum in: JAMA. 2015 Aug 4;314(5):520. Erratum in: JAMA. 2015 Aug 25;314(8):837. Erratum in: JAMA. 2015 Dec 1;314(21):2308. Erratum in: JAMA. 2016 Apr 12;315(14):1522. PMID: 26103030.

216. Wills RJ, Crouthamel WG, Iber FL, Perkal MB. (1982). Influence of alcohol on the pharmacokinetics of diazepam controlled-release formulation in healthy volunteers. J Clin Pharmacol. 22(11-12):557-61. PubMed PMID:7161409.

217. Wongrakpanich, S., Wongrakpanich, A., Melhado, K., & Rangaswami, J. (2018). A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging and disease, 9(1), 143.

218. World Health Organization, Global Status Report on Alcohol and Health 2018 (2018). www.who.int/substance_abuse/publications/global_alcohol_report/en

219. Yafi FA, Sharlip ID, Becher EF. (2018). Update on the Safety of Phosphodiesterase Type 5 Inhibitors for the Treatment of Erectile Dysfunction. Sex Med Rev. 6(2):242-252. doi: 10.1016/j.sxmr.2017.08.001. PMID: 28923561.

220. Yu J, Zhou Z, Tay-Sontheimer J, Levy RH, Ragueneau-Majlessi I. (2017). Intestinal Drug Interactions Mediated by OATPs: A Systematic Review of Preclinical and Clinical Findings. J Pharm Sci. 106(9):2312-2325. doi:10.1016/j.xphs.2017.04.004

221. Zachariae H. (1999). Alcohol interactions with drugs and its effect on the treatment of skin diseases. Clin Dermatol. 17(4):443-445. doi:10.1016/s0738-081x(99)00030-9

222. Zacny, J. P., Camarillo, V. M., Sadeghi, P., & Black, M. (1998). Effects of ethanol and nitrous oxide, alone and in combination, on mood, psychomotor performance and pain reports in healthy volunteers. Drug and alcohol dependence, 52(2), 115–123. https://doi.org/10.1016/s0376-8716(98)00056-8

Journal Pre-proof

223. Zhu, H. J., Patrick, K. S., Straughn, A. B., Reeves III, O. T., Bernstein, H., Shi, J., ... & Markowitz, J. S. (2017). Ethanol interactions with dexmethylphenidate and dl-methylphenidate spheroidal oral drug absorption systems in healthy volunteers. Journal of clinical psychopharmacology, 37(4), 419.

224. Ziedonis D, Das S, Larkin C. (2017). Tobacco use disorder and treatment: new challenges and opportunities. Dialogues Clin Neurosci. 19(3):271-280. doi: 10.31887/DCNS.2017.19.3/dziedonis. PMID: 29302224; PMCID: PMC5741110.

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FIGURE LEGENDS

Figure 1

Flow diagram of study selection

Figure 2

C_{max} of benzodiazepines: Forest plot of comparison - among participants taking benzodiazepines - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

Figure 3

C_{max} of diazepam: Forest plot of comparison - among participants taking diazepam - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation

Figure 4

C_{max} of THC: Forest plot of comparison - among participants taking THC - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation; THC: Δ^9-tetrahydrocannabinol

Figure 5

C_{max} of opioids: Forest plot of comparison - among participants taking opioids - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

Figure 6

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C_{max} of morphine: Forest plot of comparison - among participants taking morphine - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation

Figure 7

C_{max} of amphetamine: Forest plot of comparison - among participants taking amphetamine - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

Figure 8

C_{max} of methylphenidate: Forest plot of comparison - among participants taking methylphenidate - between those who assumed alcohol and those who assumed placebo

Abbreviations: C_{max}: Peak plasma concentrations; SD: Standard deviation; Std: Standardized

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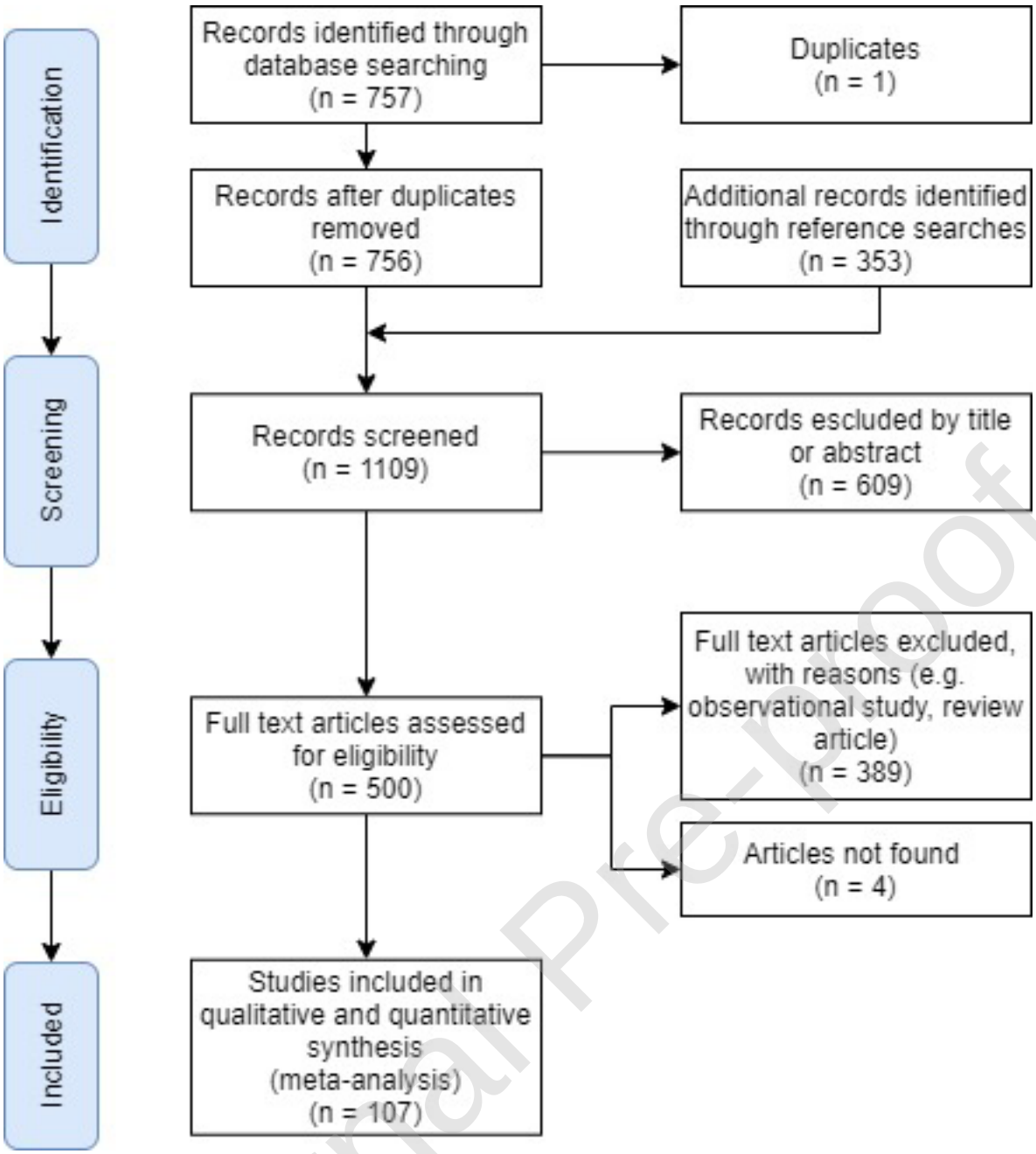

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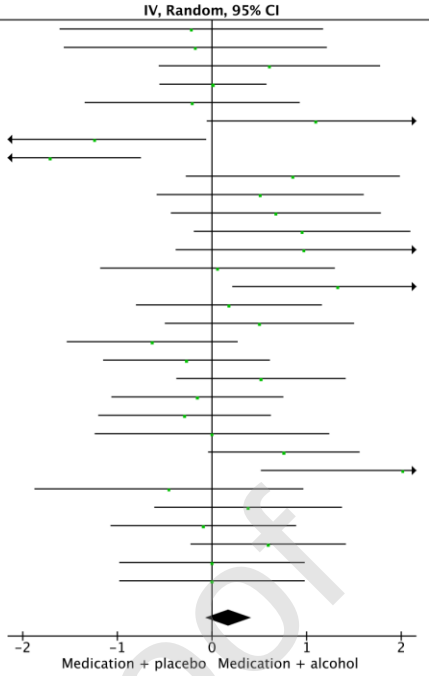
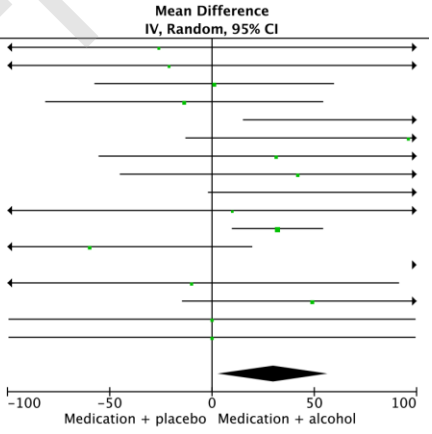
Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Divoll et al., 1981a	140	109.25	6	166	97.45	3	2.2%	−0.22 [−1.61, 1.17]
Divoll et al., 1981b	145	109.25	6	166	97.45	3	2.2%	−0.18 [−1.57, 1.21]
Dorian 1985	2.2	0.5	6	1.8	0.7	6	2.8%	0.61 [−0.56, 1.78]
Erwin et al., 1986	375.42	109.25	24	374.34	97.45	24	5.6%	0.01 [−0.56, 0.58]
Greenblatt et al., 1978	207.5	72.7498	6	221.1	43.8459	6	2.9%	−0.21 [−1.35, 0.93]
Hayes et al., 1977	392	154	7	249	78	7	2.9%	1.10 [−0.06, 2.25]
Hoyumpa 1981	16	4	7	22	5	7	2.8%	−1.24 [−2.42, −0.06]
Kuitonen 1990	1.3	0.4157	12	2.1	0.485	12	3.6%	−1.71 [−2.67, −0.75]
Laisi 1979a	260	109.25	10	164	97.45	5	2.9%	0.85 [−0.28, 1.99]
Laisi 1979b	195.3627	25	10	164	97.45	5	3.1%	0.51 [−0.58, 1.60]
Laisi 1979c	230.9239	26.7	10	189	97.45	5	3.0%	0.68 [−0.43, 1.78]
Laisi 1979d	296	109.25	10	189	97.45	5	2.9%	0.95 [−0.19, 2.10]
Linnoila et al., 1974a1	2,287.43	564.4	5	1,600.02	706.6	5	2.3%	0.97 [−0.38, 2.33]
Linnoila et al., 1974a2	400.026	195.9	5	390.108	92.2	5	2.6%	0.06 [−1.18, 1.30]
Linnoila et al., 1990a	264	23.7	8	232	21.8	8	3.0%	1.33 [0.21, 2.44]
Linnoila et al., 1990a1	74.23	29.4156	8	68.71	28.85	8	3.5%	0.18 [−0.80, 1.16]
Linnoila et al., 1990a2	148.47	65.9024	8	117.79	48.3661	8	3.4%	0.50 [−0.50, 1.50]
Linnoila et al., 1990b	268.22	55.9723	10	328.04	115.4231	10	3.8%	−0.63 [−1.53, 0.27]
Linnoila et al., 1990b1	6.36	2.846	10	7.16	2.846	10	3.9%	−0.27 [−1.15, 0.61]
Linnoila et al., 1990b2	29.69	7.2732	10	25.49	8.2219	10	3.9%	0.52 [−0.38, 1.41]
Mallach et al., 1975a	1,028	239	14	1,064	187	7	3.8%	−0.15 [−1.06, 0.75]
Mallach et al., 1975b	972	346	14	1,064	187	7	3.8%	−0.29 [−1.20, 0.62]
Ochs 1984	5.4	2.4597	5	5.4	2.6833	5	2.6%	0.00 [−1.24, 1.24]
Scavone et al., 1986	5.3	1.4422	13	4.3	1.0817	13	4.3%	0.76 [−0.04, 1.56]
Seller et al., 1980 b	796.98	109.25	6	570.85	97.45	6	2.0%	2.02 [0.52, 3.52]
Sellers et al., 1980	338.5	84.33	4	377.5	63.2	4	2.1%	−0.46 [−1.88, 0.97]
Taeuber et al., 1979	388.75	444.5156	8	243.75	245.1398	8	3.4%	0.38 [−0.61, 1.37]
van Steveninck et al., 1993	126	109.25	8	136	97.45	8	3.5%	−0.09 [−1.07, 0.89]
van Steveninck et al., 1993b	367	107	12	318	35	12	4.2%	0.59 [−0.23, 1.42]
Wills 1982a	215	109.25	12	215	97.45	6	3.5%	0.00 [−0.98, 0.98]
Wills 1982b	215	109.25	12	215	97.45	6	3.5%	0.00 [−0.98, 0.98]
Total (95% CI)			**286**			**234**	**100.0%**	**0.18 [−0.06, 0.42]**

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 51.30$, df = 30 (P = 0.009); $I^2 = 42\%$
Test for overall effect: Z = 1.46 (P = 0.15)



Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Divoll et al., 1981a	140	109.25	6	166	97.45	3	3.0%	−26.00 [−166.72, 114.72]
Divoll et al., 1981b	145	109.25	6	166	97.45	3	3.0%	−21.00 [−161.72, 119.72]
Erwin et al., 1986	375.42	109.25	24	374.34	97.45	24	9.5%	1.08 [−57.49, 59.65]
Greenblatt et al., 1978	207.5	72.7498	6	221.1	43.8459	6	8.2%	−13.60 [−81.57, 54.37]
Hayes et al., 1977	392	154	7	249	78	7	3.5%	143.00 [15.12, 270.88]
Laisi 1979a	260	109.25	10	164	97.45	5	4.4%	96.00 [−13.00, 205.00]
Laisi 1979b	195.3627	25	10	164	97.45	5	6.1%	31.36 [−55.45, 118.17]
Laisi 1979c	230.9239	26.7	10	189	97.45	5	6.1%	41.92 [−45.08, 128.93]
Laisi 1979d	296	109.25	10	189	97.45	5	4.4%	107.00 [−2.00, 216.00]
Linnoila et al., 1974a2	400.026	195.9	5	390.108	92.2	5	1.8%	9.92 [−179.86, 199.70]
Linnoila et al., 1990a3	264	23.7	8	232	21.8	8	15.5%	32.00 [9.69, 54.31]
Linnoila et al., 1990b3	268.22	55.9723	10	328.04	115.4231	10	6.8%	−59.82 [−139.33, 19.69]
Seller et al., 1980 b	796.98	109.25	6	570.85	97.45	6	4.0%	226.13 [108.99, 343.27]
van Steveninck et al., 1993	126	109.25	8	136	97.45	8	4.9%	−10.00 [−111.45, 91.45]
van Steveninck et al., 1993b	367	107	12	318	35	12	8.7%	49.00 [−14.70, 112.70]
Wills 1982a	215	109.25	12	215	97.45	6	5.1%	0.00 [−99.50, 99.50]
Wills 1982b	215	109.25	12	215	97.45	6	5.1%	0.00 [−99.50, 99.50]
Total (95% CI)			**162**			**124**	**100.0%**	**29.89 [3.29, 56.50]**

Heterogeneity: $Tau^2 = 1056.76$; $Chi^2 = 27.39$, df = 16 (P = 0.04); $I^2 = 42\%$
Test for overall effect: Z = 2.20 (P = 0.03)



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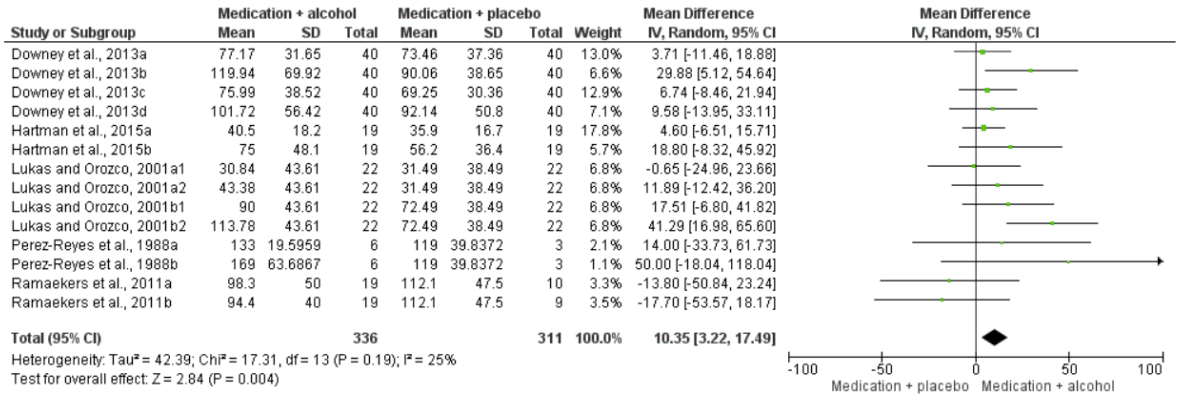
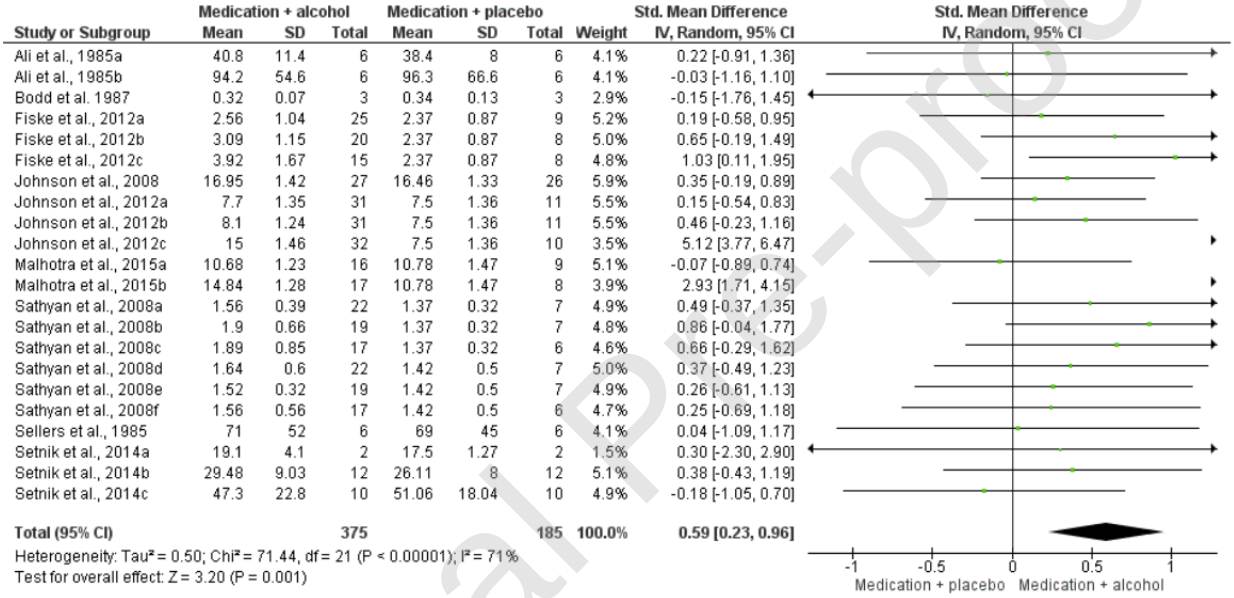


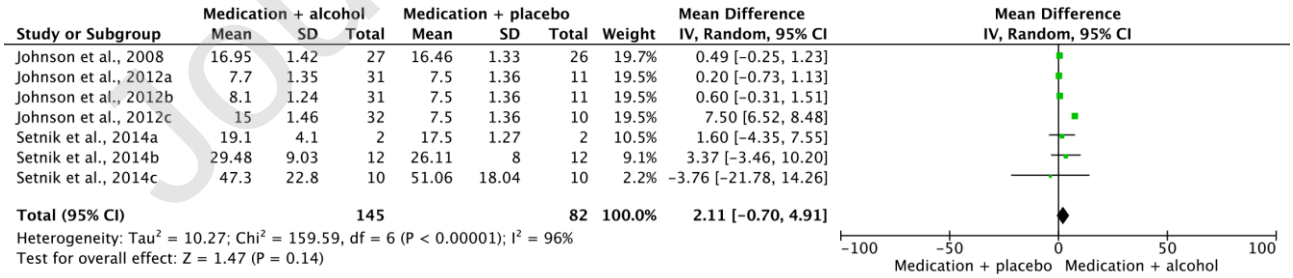
Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Downey et al., 2013a	77.17	31.65	40	73.46	37.36	40	13.0%	3.71 [-11.46, 18.88]
Downey et al., 2013b	119.94	69.92	40	90.06	38.65	40	6.6%	29.88 [5.12, 54.64]
Downey et al., 2013c	75.99	38.52	40	69.25	30.36	40	12.9%	6.74 [-8.46, 21.94]
Downey et al., 2013d	101.72	56.42	40	92.14	50.8	40	7.1%	9.58 [-13.95, 33.11]
Hartman et al., 2015a	40.5	18.2	19	35.9	16.7	19	17.8%	4.60 [-6.51, 15.71]
Hartman et al., 2015b	75	48.1	19	56.2	36.4	19	5.7%	18.80 [-8.32, 45.92]
Lukas and Orozco, 2001a1	30.84	43.61	22	31.49	38.49	22	6.8%	-0.65 [-24.96, 23.66]
Lukas and Orozco, 2001a2	43.38	43.61	22	31.49	38.49	22	6.8%	11.89 [-12.42, 36.20]
Lukas and Orozco, 2001b1	90	43.61	22	72.49	38.49	22	6.8%	17.51 [-6.80, 41.82]
Lukas and Orozco, 2001b2	113.78	43.61	22	72.49	38.49	22	6.8%	41.29 [16.98, 65.60]
Perez-Reyes et al., 1988a	133	19.5959	6	119	39.8372	3	2.1%	14.00 [-33.73, 61.73]
Perez-Reyes et al., 1988b	169	63.6867	6	119	39.8372	3	1.1%	50.00 [-18.04, 118.04]
Ramaekers et al., 2011a	98.3	50	19	112.1	47.5	10	3.3%	-13.80 [-50.84, 23.24]
Ramaekers et al., 2011b	94.4	40	19	112.1	47.5	9	3.5%	-17.70 [-53.57, 18.17]
Total (95% CI)			**336**			**311**	**100.0%**	**10.35 [3.22, 17.49]**

Heterogeneity: Tau² = 42.39; Chi² = 17.31, df = 13 (P = 0.19); I² = 25%
Test for overall effect: Z = 2.84 (P = 0.004)



Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ali et al., 1985a	40.8	11.4	6	38.4	8	6	4.1%	0.22 [-0.91, 1.36]
Ali et al., 1985b	94.2	54.6	6	96.3	66.6	6	4.1%	-0.03 [-1.16, 1.10]
Bodd et al. 1987	0.32	0.07	3	0.34	0.13	3	2.9%	-0.15 [-1.76, 1.45]
Fiske et al., 2012a	2.56	1.04	25	2.37	0.87	9	5.2%	0.19 [-0.58, 0.95]
Fiske et al., 2012b	3.09	1.15	20	2.37	0.87	8	5.0%	0.65 [-0.19, 1.49]
Fiske et al., 2012c	3.92	1.67	15	2.37	0.87	8	4.8%	1.03 [0.11, 1.95]
Johnson et al., 2008	16.95	1.42	27	16.46	1.33	26	5.9%	0.35 [-0.19, 0.89]
Johnson et al., 2012a	7.7	1.35	31	7.5	1.36	11	5.5%	0.15 [-0.54, 0.83]
Johnson et al., 2012b	8.1	1.24	31	7.5	1.36	11	5.5%	0.46 [-0.23, 1.16]
Johnson et al., 2012c	15	1.46	32	7.5	1.36	10	3.5%	5.12 [3.77, 6.47]
Malhotra et al., 2015a	10.68	1.23	16	10.78	1.47	9	5.1%	-0.07 [-0.89, 0.74]
Malhotra et al., 2015b	14.84	1.28	17	10.78	1.47	8	3.9%	2.93 [1.71, 4.15]
Sathyan et al., 2008a	1.56	0.39	22	1.37	0.32	7	4.9%	0.49 [-0.37, 1.35]
Sathyan et al., 2008b	1.9	0.66	19	1.37	0.32	7	4.8%	0.86 [-0.04, 1.77]
Sathyan et al., 2008c	1.89	0.85	17	1.37	0.32	6	4.6%	0.66 [-0.29, 1.62]
Sathyan et al., 2008d	1.64	0.6	22	1.42	0.5	7	5.0%	0.37 [-0.49, 1.23]
Sathyan et al., 2008e	1.52	0.32	19	1.42	0.5	7	4.9%	0.26 [-0.61, 1.13]
Sathyan et al., 2008f	1.56	0.56	17	1.42	0.5	6	4.7%	0.25 [-0.69, 1.18]
Sellers et al., 1985	71	52	6	69	45	6	4.1%	0.04 [-1.09, 1.17]
Setnik et al., 2014a	19.1	4.1	2	17.5	1.27	2	1.5%	0.30 [-2.30, 2.90]
Setnik et al., 2014b	29.48	9.03	12	26.11	8	12	5.1%	0.38 [-0.43, 1.19]
Setnik et al., 2014c	47.3	22.8	10	51.06	18.04	10	4.9%	-0.18 [-1.05, 0.70]
Total (95% CI)			**375**			**185**	**100.0%**	**0.59 [0.23, 0.96]**

Heterogeneity: Tau² = 0.50; Chi² = 71.44, df = 21 (P < 0.00001); I² = 71%
Test for overall effect: Z = 3.20 (P = 0.001)



Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Johnson et al., 2008	16.95	1.42	27	16.46	1.33	26	19.7%	0.49 [−0.25, 1.23]
Johnson et al., 2012a	7.7	1.35	31	7.5	1.36	11	19.5%	0.20 [−0.73, 1.13]
Johnson et al., 2012b	8.1	1.24	31	7.5	1.36	11	19.5%	0.60 [−0.31, 1.51]
Johnson et al., 2012c	15	1.46	32	7.5	1.36	10	19.5%	7.50 [6.52, 8.48]
Setnik et al., 2014a	19.1	4.1	2	17.5	1.27	2	10.5%	1.60 [−4.35, 7.55]
Setnik et al., 2014b	29.48	9.03	12	26.11	8	12	9.1%	3.37 [−3.46, 10.20]
Setnik et al., 2014c	47.3	22.8	10	51.06	18.04	10	2.2%	−3.76 [−21.78, 14.26]
Total (95% CI)			**145**			**82**	**100.0%**	**2.11 [−0.70, 4.91]**

Heterogeneity: Tau² = 10.27; Chi² = 159.59, df = 6 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.47 (P = 0.14)

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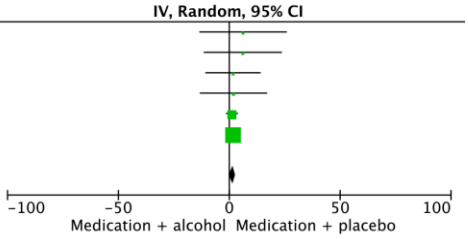
Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Patrick et al., 2007a	21.5	31.7	19	15.3	22	10	0.6%	6.20 [−13.53, 25.93]
Patrick et al., 2007b	21.4	22.7	19	15.3	22	9	0.7%	6.10 [−11.53, 23.73]
Patrick et al., 2013a	12.4	23	24	10.7	21	24	1.5%	1.70 [−10.76, 14.16]
Patrick et al., 2013b	12	22	24	10.1	31	24	1.0%	1.90 [−13.31, 17.11]
Zhu et al., 2017a	10.3	4.33	14	9.1	2.82	14	31.8%	1.20 [−1.51, 3.91]
Zhu et al., 2017b	12.4	2.85	14	10.7	2.25	14	64.4%	1.70 [−0.20, 3.60]
Total (95% CI)			**114**			**95**	**100.0%**	**1.60 [0.08, 3.13]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.56$, df = 5 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 2.06 (P = 0.04)



Study or Subgroup	Medication + alcohol Mean	SD	Total	Medication + placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mendelson et al., 1995	91.2048193	12.36	8	83.4939759	11.52654	8	8.5%	0.61 [−0.40, 1.62]
Newcorn et al., 2017a	42.9	5.56	32	42.2	5.59	10	12.1%	0.12 [−0.59, 0.83]
Newcorn et al., 2017b	40.4	6.51	31	42.2	5.59	10	12.1%	−0.28 [−1.00, 0.44]
Newcorn et al., 2017c	39.5	5.63	29	42.2	5.59	9	11.5%	−0.47 [−1.23, 0.29]
Newcorn et al., 2017d	13.8	1.87	32	13.5	1.82	10	12.1%	0.16 [−0.55, 0.87]
Newcorn et al., 2017e	13.1	2.1	31	13.5	1.82	10	12.1%	−0.19 [−0.91, 0.52]
Newcorn et al., 2017f	12.6	1.77	29	13.5	1.82	9	11.5%	−0.49 [−1.25, 0.26]
Perez-Reyes et al., 1992a1	15.7	2.7713	12	18.3	4.8497	12	10.6%	−0.64 [−1.46, 0.19]
Perez-Reyes et al., 1992a2	25.5	3.1177	12	21.4	2.4249	12	9.5%	1.42 [0.50, 2.33]
Total (95% CI)			**216**			**90**	**100.0%**	**−0.01 [−0.39, 0.37]**

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 17.13$, df = 8 (P = 0.03); $I^2 = 53\%$
Test for overall effect: Z = 0.07 (P = 0.94)

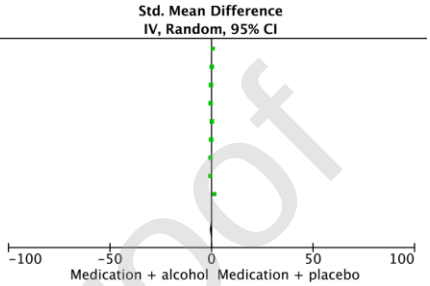


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Table 1. Alcohol-medications Interactions: Results of the meta-analyses

	Studies	N Patients	MD (CI)	*P*	I^2
1. MEDICATIONS THAT AFFECT THE CENTRAL NERVOUS SYSTEM (CNS)					
1.1 BENZODIAZEPINES AND OTHER ANXIOLYTICS					
Cmax[a]	31	520	0.18 (-0.06, 0.42)	0.15	42
Tmax[a]	30	491	0.08 (-0.11, 0.26)	0.41	1
$T_{1/2}$[a]	26	430	0.08 (-0.24, 0.40)	0.63	56
AUC[a]	28	466	-0.03 (-0.49, 0.43)	0.90	79
Adinazolam					
Cmax	2	32	10.62 (-14.88, 36.11)	0.41	0
Tmax	2	32	-0.25 (-1.04, 0.54)	0.54	0
$T_{1/2}$	2	32	-2.31 (-5.38, 0.76)	0.14	0
AUC	2	32	4.51 (-15.27, 24.30)	0.65	89
Alprazolam					
Cmax	2	40	0.66 (-3.80, 5.11)	0.77	45
Tmax	2	40	0.00 (-0.71, 0.71)	1.00	0
$T_{1/2}$	2	40	-0.46 (-3.20, 2.29)	0.75	0
AUC	2	40	-5.88 (-11.68, -0.07)	0.05	0
Brotizolam					
Cmax	1	26	1.00 (0.02, 1.98)	0.05	N.A.
Tmax	1	26	-0.06 (-0.77, 0.65)	0.87	N.A.
$T_{1/2}$	1	26	0.80 (-0.18, 1.78)	0.11	N.A.
AUC	1	26	2.58 (-4.61, 9.77)	0.48	N.A.
Chlordiazepoxide					
Cmax	1	10	687.41 (-105.26, 1480.08)	0.09	N.A.
Tmax	1	10	1.00 (-0.42, 2.42)	0.17	N.A.
$T_{1/2}$	1	10	-42.23 (-47.73, -36.73)	**< 0.00001**	N.A.
AUC	1	10	-51.09 (-62.69, -39.49)	**< 0.00001**	N.A.
Clozabam					
Cmax	1	16	145.00 (-206.76, 496.76)	0.42	N.A.
Tmax	1	16	0.00 (-1.12, 1.12)	1.00	N.A.
$T_{1/2}$	1	16	9.71 (5.36, 14.06)	**< 0.00001**	N.A.
AUC	1	16	34.70 (-13.78, 83.18)	0.16	N.A.
Diazepam					
Cmax	17	286	29.89 (3.29, 56.50)	**0.03**	42
Tmax	17	274	0.03 (-0.39, 0.45)	0.89	60
$T_{1/2}$	14	234	0.67 (-1.79, 3.13)	0.59	79
AUC	16	270	38.22 (23.57, 52.86)	**< 0.00001**	100
Diazepam (without studies at high risk of bias)					
Cmax	13	227	17.25 (-11.46, 45.96)	0.24	41
Tmax	13	215	0.31 (0.02, 0.60)	**0.03**	0
$T_{1/2}$	10	175	2.61 (0.42, 4.80)	**0.02**	62
AUC	12	211	51.18 (34.21, 68.15)	**< 0.00001**	100
Lorazepam					
Cmax	1	14	-6.00 (-10.74, -1.26)	**0.01**	N.A.
Tmax	1	14	2.20 (0.77, 3.63)	**0.003**	N.A.
Oxazepam					
Cmax	3	50	-48.58 (-129.60, 38.44)	0.29	0
Tmax	3	50	-0.02 (-0.58, 0.54)	0.94	0
$T_{1/2}$	3	50	-0.41 (-2.77, 1.94)	0.73	0
AUC	3	50	-007 (-0.78, 0.64)	0.85	0
Triazolam					
Cmax	3	46	-0.22 (-1.26, 0.82)	0.68	78
Tmax	2	22	0.17 (-0.46, 0.80)	0.60	0
$T_{1/2}$	2	22	0.09 (-0.56, 0.74)	0.78	0
AUC	2	22	1.44 (-0.07, 2.94)	0.06	0

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Benzodiazepines mainly metabolized by CYP3A4					
Cmax[a]	4	76	0.44 (-0.08, 0.96)	0.10	19
Tmax[a]	4	76	0.07 (-0.38, 0.52)	0.76	0
$T_{1/2}$[a]	4	76	-0.29 (-1.48, 0.90)	0.64	78
AUC[a]	4	76	-0.74 (-1.83, 0.35)	0.18	75
Benzodiazepines mainly metabolized by CYP3A4 and CYP2C19					
Cmax[a]	18	302	0.33 (0.05, 0.60)	**0.02**	22
Tmax[a]	18	290	0.06 (-0.22, 0.34)	0.66	22
$T_{1/2}$[a]	15	250	0.24 (-0.23, 0.71)	0.32	64
AUC[a]	17	286	0.09 (-0.62, 0.79)	0.81	84
Benzodiazepines mainly metabolized by CYP2C19					
Cmax[a]	5	78	-0.11 (-0.99, 0.78)	0.81	71
Tmax[a]	4	54	-0.04 (-0.58, 0.50)	0.88	0
$T_{1/2}$[a]	4	54	-0.26 (-0.80, 0.28)	0.35	0
AUC[a]	4	54	0.39 (-0.62, 1.40)	0.45	67
Benzodiazepines mainly metabolized by UGT					
Cmax[a]	4	64	-0.46 (-0.98, 0.07)	0.09	0
Tmax[a]	4	64	0.30 (-0.38, 0.98)	0.39	37
$T_{1/2}$[a]	3	50	-0.07 (-0.65, 0.51)	0.81	0
AUC[a]	3	50	-0.04 (-0.62, 0.54)	0.89	0
OTHER ANXIOLYTICS					
Buspirone					
Cmax	2	48	0.03 (-0.55, 0.61)	0.92	0
NONBENZODIAZEPINE HYPNOTIC MEDICATION					
Zoplicone					
Cmax	1	24	2.00 (-19.11, 23.11)	0.85	N.A.
1.2 CANNABIS (THC)					
Cmax	14	647	10.35 (3.22, 17.49)	**0.004**	25
Tmax	10	308	-0.03 (-0.05, -0.01)	**0.006**	97
$T_{1/2}$	8	243	0.39 (0.2, 0.58)	**< 0.0001**	0
AUC	10	308	8.09 (-2.78, -18.95)	0.14	59
VAS (hungry) [a]	2	52	0.15 (-0.39, 0.70)	0.59	0
1.3 OPIOIDS					
Cmax[a]	22	560	0.59 (0.23, 0.96)	**0.001**	71
Tmax[a]	21	554	-0.37 (-0.67, -0.07)	**0.02**	59
$T_{1/2}$[a]	19	417	-0.02 (-0.25, 0.21)	0.89	14
AUC[a]	22	530	-0.78 (-1.60, 0.05)	0.07	92
Codeine					
Cmax	1	6	-0.2 (-0.19, 0.15)	0.81	N.A.
$T_{1/2}$	1	6	0.80 (-0.02, 1.62)	0.05	N.A.
AUC	1	6	-1.45 (-35.54, 32.64)	0.93	N.A.
Dextropropoxyphene					
Cmax	1	12	-2.10 (-71.01, 66.81)	0.95	N.A.
Tmax	1	12	0.00 (-1.07, 1.07)	1.00	N.A.
$T_{1/2}$	1	12	0.10 (-0.52, 0.72)	0.75	N.A.
AUC	1	12	-66.60 (-355.12, 221.92)	0.65	N.A.
Hydromorphone					
Cmax	6	156	0.27 (0.11, 0.43)	**0.0009**	0
Tmax	6	156	-2.65 (-4.59, -0.70)	**0.008**	0
$T_{1/2}$	6	144	-0.56 (-2.42, 1.30)	0.55	0
AUC	6	196	0.29 (-2.90, 3.48)	0.86	0
Meptizol					
Cmax	1	12	2.40 (-8.74, 13.54)	0.67	N.A.
Tmax	1	12	-0.20 (-0.72, 0.32)	0.45	N.A.
$T_{1/2}$	1	12	0.16 (-0.07, 0.39)	0.18	N.A.
AUC	1	12	-11.60 (-39.72, 16.52)	0.42	N.A.
Morphine					
Cmax	7	227	2.11 (-0.70, 4.91)	0.14	96

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Tmax	7	227	-0.32 (-0.90, 0.27)	0.29	82
$T_{1/2}$	4	100	-0.17 (-0.52, 0.17)	0.32	0
AUC	7	162	-6.59 (-25.91, 12.73)	0.50	100
Oxycodone					
Cmax	2	50	1.98 (-2.10, 6.05)	0.34	96
Tmax	2	50	-0.98 (-2.93, 0.97)	0.32	55
$T_{1/2}$	2	50	0.26 (-0.26, 0.79)	0.33	0
AUC	2	50	5.45 (-32.08, 42.98)	0.78	100
Oxymorphone					
Cmax	3	85	0.74 (0.02, 1.46)	0.05	56
Tmax	3	85	-0.75 (-2.13, 0.62)	0.28	15
$T_{1/2}$	3	85	-0.20 (-2.30, 1.91)	0.86	0
AUC	3	85	1.96 (-3.77, 7.70)	0.50	0
Propoxyphene					
Cmax	1	12	2.00 (-53.02, 57.02)	0.94	N.A.
Tmax	1	12	0.34 (-2.88, 3.56)	0.84	N.A.
$T_{1/2}$	1	12	-25.81 (-29.11, -22.52)	**< 0.0001**	N.A.
AUC	1	12	20.00 (-88.64, 128.64)	0.72	N.A.
1.4 PSYCHOSTIMULANTS					
Methylphenidate					
Cmax	6	209	1.60 (0.08, 3.13)	**0.04**	0
Tmax	6	209	2.26 (-2.70, 7.23)	0.37	94
$T_{1/2}$	6	209	-0.01 (-0.29, 0.26)	0.92	0
AUC	6	209	13.53 (6.56, 20.50)	**0.0001**	0
VAS[a]	6	209	0.48 (0.20, 0.76)	**0.0007**	96
Amphetamine					
Cmax[a]	9	306	-0.01 (-0.39, 0.37)	0.94	53
Tmax[a]	9	306	0.11 (-0.14, 0.37)	0.40	0
$T_{1/2}$[a]	9	306	-0.01 (-0.26, 0.25)	0.96	0
AUC[a]	9	306	0.05 (-0.42, 0.51)	0.84	67
1.5 ANTIDEPRESSANTS AND MOOD STABILIZERS					
ANTIDEPRESSANTS					
Tricyclic antidepressants (TCA; amytriptiline)					
Cmax	3	44	1.66 (-6.87, 10.19)	0.70	31
Tmax	2	22	-19.43 (-83.83, 44.97)	0.55	46
$T_{1/2}$	2	18	-1.87 (-7.64, 3.90)	0.52	6
AUC	2	22	0.08 (-1.58, 1.74)	0.93	71
Norepinephrine-dopamine reuptake inhibitor (NDRI; bupropion)					
Cmax	1	16	-101.50 (-148.35, -54.65)	**< 0.0001**	N.A.
Tmax	1	16	0.20 (-0.42, 0.82)	0.53	N.A.
$T_{1/2}$	1	16	0.26 (-0.32, 0.84)	0.38	N.A.
AUC	1	16	16.80 (-152.84, 186.44)	0.85	N.A.
Selective serotonin reuptake inhibitors (SSRIs)					
Cmax[a]	4	110	0.18 (-0.20, 0.55)	0.35	0
Tmax[a]	2	64	-0.50 (-1.16, 0.15)	0.13	38
$T_{1/2}$[a]	1	40	1.12 (0.45, 1.79)	**0.001**	N.A.
AUC[a]	2	64	-0.07 (-0.56, 0.42)	0.78	0
Tetracyclic antidepressant (mianserin)					
Cmax	1	24	6.30 (-29.40, 42.00)	0.73	N.A.
Serotonin antagonist and reuptake inhibitors (SARI; trazodone)					
Cmax	1	12	-0.06 (-0.48, 0.36)	0.78	N.A.
Tmax	1	12	43.37 (5.39, 81.35)	**0.03**	N.A.
$T_{1/2}$	1	12	-0.47 (-2.15, 1.21)	0.58	N.A.
AUC	1	12	0.00 (-3.24, 3.24)	1.00	N.A.
Serotonin-norepinephrine reuptake inhibitors (SNRI; venlafaxine)					
Cmax	1	32	1.00 (-33.68, 35.68)	0.95	N.A.
Tmax	1	32	-0.30 (-0.85, 0.25)	0.28	N.A.
AUC	1	32	-5.00 (-172.80, 162.80)	0.95	N.A.

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Serotonin modulator and stimulators (SMS; vortioxetine)					
Cmax	2	134	0.76 (-14.33, 15.86)	0.92	0
AUC	2	134	24.87 (-70.43, 120.17)	0.61	0
MOOD STABILIZERS					
Lithium carbonate					
Cmax	1	20	0.08 (-0.05, 0.21)	0.22	N.A.
Tmax	1	20	0.20 (-0.63, 1.03)	0.64	N.A.
$T_{1/2}$	1	20	4.50 (-2.51, 11.51)	0.21	N.A.
AUC	1	20	1.00 (-1.16, 3.16)	0.37	N.A.
1.6 ANTIPSYCHOTICS					
Atypical antipsychotics					
Cmax[a]	4	116	0.45 (-0.28, 1.19)	0.23	72
Tmax[a]	4	116	-0.44 (-3.25, 2.36)	0.76	97
$T_{1/2}$	1	20	9.00 (4.84, 13.16)	**< 0.0001**	N.A.
AUC[a]	3	92	0.79 (-0.25, 1.82)	0.14	81
Amisulpride					
Cmax	2	72	3.99 (-5.77, 13.75)	0.42	0
Tmax	2	72	-1.25 (-7.62, 5.12)	0.70	100
AUC	2	72	20.11 (-21.03, 61.25)	0.34	0
Blonserin					
Cmax	1	20	663.00 (387.11, 938.89)	**< 0.00001**	N.A.
Tmax	1	20	1.00 (0.38, 1.62)	**0.002**	N.A.
$T_{1/2}$	1	20	9.00 (4.84, 13.16)	**< 0.0001**	N.A.
AUC	1	20	5593.00 (3539.11, 7646.89)	**< 0.00001**	N.A.
Remoxipiride					
Cmax	1	24	-0.06 (-0.73, 0.61)	0.86	N.A.
Tmax	1	24	0.00 (-0.57, 0.57)	1.00	N.A.
1.7 MEDICATIONS FOR THE TREATMENT OF ALCOHOL USE DISORDER AND SUBSTANCES USE DISORDERS					
Baclofen					
Craving for alcohol	2	72	0.57 (-0.15, 11.54)	0.06	0
Gamma-hydroxybutyric acid					
Cmax	1	32	11.40 (-3.53, 26.33)	0.13	N.A.
Tmax	1	32	-3.20 (-18.18, 11.78)	0.68	N.A.
$T_{1/2}$	1	32	15.20 (-10.71, 41.11)	0.25	N.A.
AUC	1	32	2030.00 (-847.78, 4907.78)	0.17	N.A.
Mecamylamine					
Cigarette smoked	1	48	-0.21 (-1.66, 1.24)	0.78	N.A.
Nicotine					
Plasma levels	1	36	-1.30 (-4.64, 2.04)	0.45	N.A.
$T_{1/2}$	2	16	-1.57 (-21.82, 18.67)	0.88	0
Craving for cigarettes[a]	4	282	0.44 (-0.17, 1.05)	0.16	78
Cigarette smoked	1	48	-0.6 (-1.63, 0.41)	0.24	N.A.
Craving for alcohol	1	174	0.30 (-3.46, 4.06)	0.88	N.A.
1.8 MEDICATIONS FOR THE TREATMENT OF SEIZURES					
Briviracetam					
Cmax	1	36	-0.58 (-1.27, 0.11)	0.10	N.A.
Tmax	1	36	0.71 (-0.15, 1.57)	0.11	N.A.
$T_{1/2}$	1	36	-0.12 (-0.96, 0.72)	0.78	N.A.
AUC	1	36	0.83 (-2.94, 4.60)	0.67	N.A.
Retigabine					
Cmax	1	48	120.60 (23.96, 217.24)	0.88	N.A.
$T_{1/2}$	1	34	-0.50 (-1.36, 0.36)	0.26	N.A.
AUC	1	48	1061.00 (655.86, 1466.14)	**< 0.00001**	N.A.

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	Studies	N Patients	MD (CI)	*P*	I^2
2. MEDICATIONS FOR THE TREATMENT OF INFECTIOUS DISEASES					
2.1 ANTIBIOTICS					
PENICILLINS					
Cmax[a]	4	42	-0.16 (-0.81, 0.49)	0.62	0
Tmax[a]	4	42	0.52 (-0.71, 1.74)	0.41	0
$T_{1/2}$[a]	4	42	0.72 (0.03, 1.40)	**0.04**	0
AUC[a]	4	42	0.30 (-0.35, 0.94)	0.37	0
Amoxicilline					
Cmax	2	24	0.15 (-1.36, 1.66)	0.84	0
Tmax	2	24	35.48 (18.24, 52.73)	**< 0.0001**	0
$T_{1/2}$	2	24	22.65 (10.27, 35.04)	**0.0003**	0
AUC	2	24	115.08 (-78.71, 308.87)	0.24	0
Phenoxymethylpenicillin					
Cmax	2	18	-2.50 (6.93, 1.92)	0.27	0
Tmax	2	18	-0.15 (-0.32, 0.02)	0.09	0
$T_{1/2}$	2	18	0.04 (-0.19, 0.27)	0.73	0
AUC	2	18	0.84 (-4.17, 5.86)	0.74	0
Tetracyclines					
Cmax[a]	6	68	-0.31 (-1.14, 0.52)	0.47	54
Tmax[a]	6	68	0.10 (-0.41, 0.62)	0.69	0
$T_{1/2}$[a]	6	68	0.42 (-0.11, 0.95)	0.12	0
AUC[a]	6	68	-0.28 (-1.18, 0.62)	0.54	60
Doxycycline					
Cmax	5	50	-0.97 (-1.55, -0.38)	**0.001**	0
Tmax	5	50	0.39 (-5.87, 6.66)	0.90	0
$T_{1/2}$	5	50	2.69 (0.16, 5.22)	**0.04**	15
AUC	5	50	-12.89 (-21.62, -4.16)	**0.004**	0
Tetracycline					
Cmax	1	18	3.04 (0.95, 5.14)	**0.004**	N.A.
Tmax	1	18	0.45 (-1.02, 1.92)	0.55	N.A.
$T_{1/2}$	1	18	0.47 (-1.74, 2.68)	0.68	N.A.
AUC	1	18	31.63 (13.12, 50.14)	**0.0008**	N.A.
Macrolides (erythromycin)					
Cmax	1	18	-0.13 (-0.41, 0.15)	0..37	N.A.
Tmax	1	18	0.11 (-0.30, 0.52)	0.60	N.A.
$T_{1/2}$	1	18	-0.62 (-1.56, 0.32)	0.19	N.A.
AUC	1	18	-0.90 (-1.76, -0.04)	0.04	N.A.
Isoniazid					
Cmax	1	32	0.76 (-0.08, 1.60)	0.08	N.A.
Tmax	1	32	-1.50 (-23.32, 20.32)	0.89	N.A.
$T_{1/2}$	1	32	-16.00 (-75.19, 43.19)	0.60	N.A.
AUC	1	32	54.00 (-83.67, 191.67)	0.44	N.A.
2.2 ANTIVIRAL MEDICATIONS					
Nucleoside analog reverse-transcriptase inhibitors (NRTIs; abacavir)					
Cmax	1	49	0.53 (-0.10, 1.16)	0.10	N.A.
$T_{1/2}$	1	49	0.37 (0.22, 0.52)	**< 0.00001**	N.A.
AUC	1	49	4.55 (2.87, 6.28)	**< 0.00001**	N.A.
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs; efavirenz)					
Cmax	1	20	-0.20 (-0.74, 0.34)	0.47	N.A.
Tmax	1	20	0.75 (-0.81, 2.31)	0.35	N.A.
$T_{1/2}$	1	20	1.10 (-0.43, 2.63)	0.16	N.A.
AUC	1	20	-0.13 (-4.65, 4.39)	0.96	N.A.
CCR5 receptor antagonists (maraviroc)					
Cmax	1	20	34.00 (-136.16, 204.16)	0.70	N.A.
Tmax	1	20	-0.63 (-1.71, 0.46)	0.26	N.A.

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AUC	1	20	-26.00 (-256.33, 204.33)	0.82	N.A.
Neuraminidase inhibitors (NAIs; oseltamivir)					
Cmax	1	34	23.00 (22.32, 23.68)	**< 0.00001**	N.A.
Tmax	1	34	0.00 (-0.65, 0.65)	1.00	N.A.
$T_{1/2}$	1	34	-0.70 (-1.38, -0.02)	**0.04**	N.A.
AUC	1	34	79.00 (78.33, 79.67)	**< 0.00001**	N.A.
Protease inhibitors (PIs; ritonavir)					
Cmax	1	34	-0.20 (-1.45, 1.05)	0.75	N.A.
Tmax	1	34	1.13 (0.04, 2.21)	**0.04**	N.A.
$T_{1/2}$	1	34	17.00 (-6.25, 40.55)	0.16	N.A.
AUC	1	34	2.00 (-26.00, 30.00)	0.89	N.A.

	Studies	N Patients	MD (CI)	*P*	I^2
3. ANTINFLAMMATORY MEDICATIONS					
Acetylsalicylic acid					
Cmax	2	60	-6.37 (-23.19, 10.45)	0.46	72
Tmax	2	60	-0.23 (-0.69, 0.24)	0.34	0
$T_{1/2}$	2	60	0.19 (-0.32, 0.70)	0.46	0
AUC	2	60	-5.20 (-16.64, 6.25)	0.37	100

	Studies	N Patients	MD (CI)	*P*	I^2
4. MEDICATIONS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES					
Beta blockers (atenolol)					
Cmax	1	32	-0.03 (-0.20, 0.14)	0.73	N.A.
Tmax	1	32	0.00 (-0.81, 0.81)	1.00	N.A.
DBP	1	32	-5.00 (-10.54, 0.54)	0.08	N.A.
SBP	1	32	8.00 (2.46, 13.54)	0.005	N.A.
Heart rate	1	32	5.00 (0.62, 9.38)	**0.03**	N.A.
Antiarrhythmic medications (sodium channel blockers; disopyramide)					
$T_{1/2}$	1	12	-0.55 (-1.38, 0.28)	0.19	N.A.
AUC	1	12	-1.08 (-9.00, 6.84)	0.79	N.A.
Calcium channel blockers					
Cmax[a]	2	36	0.25 (-0.41, 0.90)	0.46	0
Tmax[a]	2	36	0.57 (-0.63, 1.77)	0.35	66
$T_{1/2}$[a]	2	36	-0.48 (-1.14, 0.19)	0.16	0
AUC[a]	2	36	0.92 (-1.38, 3.22)	0.43	89
DBP	1	20	13.94 (4.11, 23.77)	0.19	N.A.
SBP	1	20	5.68 (-0.26, 11.62)	0.06	N.A.
Heart rate	1	20	22.86 (12.09, 33.63)	**< 0.0001**	N.A.
FBF	1	20	5.00 (2.60, 7.40)	**< 0.0001**	N.A.
Calcium-sensitizer and ATP-dependent potassium channel openers (levosimendan)					
$T_{1/2}$	1	24	-0.04 (-0.22, 0.14)	0.66	N.A.
AUC	1	24	-0.30 (-9.15, 8.55)	0.95	N.A.
α_1-bockers (prazosin)					
DBP	1	20	-3.90 (-9.75, 1.95)	0.19	N.A.
SBP	1	20	-5.70 (-14.30, 2.90)	0.19	N.A.
Heart rate	1	20	3.50 (-2.88, 9.88)	0.28	N.A.
Precursor of nitric oxide (NO; sodium nitroprusside)					
FBF	1	18	2.90 (1.14, 4.66)	**0.001**	N.A.

	Studies	N Patients	MD (CI)	*P*	I^2
5. MEDICATIONS FOR THE TREATMENT OF DIABETES					
Glucagone					
Glucose nadir	2	32	-0.54 (-1.10, 0.01)	0.05	20

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Glucose AUC	2	32	-151.68 (-248.64, -54.73)	**0.002**	97
Insulin					
Glucose nadir	2	36	-0.50 (-1.92, 0.93)	0.49	93
Sulfonylureas					
Glucose nadir[a]	2	40	-0.15 (-0.78, 0.47)	0.63	0
Glyburibe					
Glucose AUC	1	20	-0.50 (-0.72, -0.28)	**< 0.0001**	N.A.

	Studies	N Patients	MD (CI)	*P*	I^2
6. MEDICATIONS FOR THE TREATMENT OF RESPIRATORY DISEASES					
Methylxanthines and dimethylxanthines					
Cmax[a]	2	32	0.42 (-0.28, 1.13)	0.24	0
Tmax[a]	2	32	0.26 (-0.60, 1.12)	0.55	32
$T_{1/2}$	1	16	2.00 (0.06, 3.94)	**0.04**	N.A.
AUC[a]	2	32	0.88 (0.14, 1.62)	**0.02**	0
Caffeine					
Cmax	1	16	0.73 (-1.19, 2.65)	0.46	N.A.
Tmax	1	16	25.00 (-7.52, 57.52)	0.13	N.A.
AUC	1	16	605.45 (75.53, 1135.37)	**0.03**	N.A.
Theophylline					
Cmax	1	12	0.70 (-0.61, 2.01)	0.30	N.A.
Tmax	1	12	-0.10 (-0.65, 0.45)	0.72	N.A.
$T_{1/2}$	1	12	2.00 (0.06, 3.94)	**0.04**	N.A.
AUC	1	12	27.00 (-7.66, 61.66)	0.13	N.A.
Histamine H1 receptor antagonists					
Cmax[a]	4	168	0.14 (-0.17, 0.44)	0.38	0
Tmax	1	24	-1.50 (-2.27, -0.73)	**0.0001**	N.A.
AUC	1	24	6.00 (-224.48, 236.48)	0.96	N.A.
Cetirizine					
Cmax	2	108	2.90 (-10.02, 15.82)	0.66	20
Ebastine					
Cmax	1	24	0.10 (-13.90, 14.10)	0.99	N.A.
Tmax	1	24	-1.50 (-2.27, -0.73)	**0.0001**	N.A.
AUC	1	24	6.00 (-224.48, 236.48)	0.96	N.A.
Mizolastine					
Cmax	1	36	0.50 (-3.67, 4.67)	0.81	N.A.
Muscarinic receptor agonist (methacholine)					
FBF	1	20	5.00 (2.60, 7.40)	**< 0.0001**	N.A.

	Studies	N Patients	MD (CI)	*P*	I^2
7. ESTROGENS					
Estradiol (E2)					
Cmax	3	62	97.94 (38.54, 157.34)	**0.001**	63
$T_{1/2}$	1	24	133.00 (-26.38, 292.38)	0.10	N.A.
AUC	2	38	29.45 (-4.73, 63.62)	0.09	0

	Studies	N Patients	MD (CI)	*P*	I^2
8. MEDICATIONS FOR THE TREATMENT OF ERECTILE DYSFUNCTION					

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Cmax[a]	3	72	0.28 (-0.29, 0.85)	0.34	27
Tmax[a]	2	60	-0.20 (-0.71, 0.31)	0.43	0
$T_{1/2}$[a]	2	60	-0.17 (-0.89, 0.54)	0.64	47
AUC[a]	3	72	-0.07 (-0.54, 0.39)	0.75	0
Verdanafil					
Cmax	2	36	0.90 (0.08, 1.72)	**0.03**	0
Tmax	1	24	-0.38 (-1.03, 0.28)	0.26	N.A.
$T_{1/2}$	1	24	0.24 (-0.57, 1.05)	0.56	N.A.
AUC	2	36	-0.20 (-1.02, 0.62)	0.63	0

	Studies	N Patients	MD (CI)	*P*	I^2
9. MISCELLANEOUS MEDICATIONS					
Statins (fluvastatin)					
Cmax	1	16	-104.20 (-279.38, 70.98)	0.24	N.A.
Tmax	1	16	0.18 (-0.14, 0.50)	0.27	N.A.
$T_{1/2}$	1	16	-0.71 (-0.93, -0.49)	**< 0.0001**	N.A.
AUC	1	16	-0.04 (-0.22, 0.14)	0.67	N.A.
Cholesterol blood concentration	1	16	-0.16 (-0.74, 0.42)	0.59	N.A.
Triglycerides blood concentration	1	16	0.57 (0.23, 0.91)	**0.001**	N.A.
Gastric acid-reducing agents (cisapride)					
Cmax	1	24	2.00 (-6.32, 10.32)	0.64	N.A.
Tmax	1	24	0.70 (0.26, 1.14)	**0.002**	N.A.
$T_{1/2}$	1	24	0.70 (-1.42, 2.82)	0.52	N.A.
AUC	1	24	39.00 (-27.75, 105.75)	0.25	N.A.
Medications for the treatment of obesity (orlistat)					
Fecal fat	1	20	1.30 (0.16, 2.44)	**0.03**	N.A.
Medications for the treatment of migraine (almotriptan)					
Cmax	1	32	0.70 (-5.54, 6.94)	0.83	N.A.
AUC	1	32	1.75 (-24.94, 28.44)	0.90	N.A.
Medications for the treatment of hypoactive sexual desire disorder in women (fibanserin)					
AUC	2	71	-64.62 (-238.43, 109.19)	0.47	0
Medications for anesthesia (nitrous oxide)					
Pain assessment with a cold pressor test	2	33	0.20 (-0.42, 0.82)	0.52	19
Immunosuppressant medications (cyclosporine)					
Cmax	1	24	-479.00 (-689.92, -268.08)	**< 0.00001**	N.A.
Tmax	1	24	2.70 (1.81, 3.59)	**< 0.00001**	N.A.
$T_{1/2}$	1	24	-0.80 (-3.42, 1.82)	0.55	N.A.
AUC	1	24	-2472.00 (-4129.64, -814.36)	**0.003**	N.A.
Medications for the treatment of filariasis and onchocerciasis (ivermectin)					
Cmax	1	20	41.50 (28.54, 54.46)	**< 0.00001**	N.A.

Legend [a]: SMD instead of MD is reported; AUC: Area under the curve; CI: Confidence interval; C_{max}: Peak plasma concentrations; DBP: Diastolic blood pressure; MD: Mean difference; N: Number; N.A.: Not Applicable; SMD: Standardized mean difference; SBP: Systolic blood pressure; T_{max}: Time to reach C_{max} peak plasma concentrations; T ½: Half-life. In bold: Significant differences between alcohol and placebo.

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Table 2. Significant alcohol-medications interactions

Medication	Interactions	Certainty of the evidence (grade)
Abacavir	↑ $T_{½}$ ↑ AUC	N.A. N.A.
Amoxicillina	↑ T_{max} ↑ $T_{½}$	N.A. N.A.
Atenolol	↑ Heart rate	N.A.
Atypical antipsychotics	↑ $T_{½}$	N.A.
Benzodiazepines mainly metabolized by CYP3A4 and CYP2C19	↑C_{max}	Low
Blonserin	↑C_{max} ↑ T_{max} ↑ $T_{½}$ ↑ AUC	N.A. N.A. N.A. N.A.
Bupropion	↓ C_{max}	N.A.
Caffeine	↑ AUC	N.A.
Cannabis	↑ C_{max} ↓ T_{max} ↑ $T_{½}$	High Very low Moderate
Cisapride	↑ $T_{½}$	N.A.
Chlordiazepoxide	↓ $T_{½}$ ↓ AUC	N.A. N.A.
Clobazam	↑ $T_{½}$	N.A.
Cyclosporine	↓ C_{max} ↑ $T_{½}$ ↓ AUC	N.A. N.A. N.A.
Diazepam	↑ C_{max} ↑AUC	Low Very low
Doxycycline	↓ C_{max} ↑ $T_{½}$ ↓ AUC	N.A. N.A. N.A.
Ebastine	↓ $T_{½}$	N.A.
Estradiol	↑ C_{max}	N.A.
Fluvastatin	↓ $T_{½}$ ↑ Triglycerides blood concentrations	N.A. N.A.
Glucagone	↓ Glucose AUC	N.A.
Glyburide	↓ Glucose AUC (or ↑ decrease in glucose AUC)	N.A.
Hydromorphone	↑ C_{max} ↓ T_{max}	N.A. N.A.
Ivermectin	↑ C_{max}	N.A.
Lorazepam	↓ C_{max} ↑ T_{max}	N.A. N.A.
Methylphenidate	↑ C_{max} ↑ AUC ↑ VAS stimulated	Moderate Moderate Moderate
Methylxanthines and dimethylxanthines	↑ $T_{½}$ ↑ AUC	N.A. N.A.
Nifedipine	↑ Heart rate	N.A.

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Opioids	↑ C_{max} ↓ $T_{½}$	Low Moderate
Orlistat	↑ Fecal fat concentrations	N.A.
Oseltamivir	↑ C_{max} ↓ $T_{½}$ ↑ AUC	N.A. N.A. N.A.
Penicillins	↑ $T_{½}$	N.A.
Propoxyphene	↓ $T_{½}$	N.A.
Retigabine	↑ AUC	N.A.
Ritonavir	↑ T_{max}	N.A.
SSRIs	↑ $T_{½}$	N.A.
Theophylline	↑ AUC	N.A.
Tetracycline	↑ C_{max} ↑ AUC	N.A. N.A.
Trazodone	↑ T_{max}	N.A.
Verdanafil	↑ C_{max}	N.A.

Summary of relevant pharmacodynamic and pharmacokinetic interactions with alcohol. Abbreviations:

AUC: Area under the curve; C_{max}: Peak plasma concentrations; $T_{max:}$ Time to reach C_{max} ; $T_{½}$: Half-life; VAS: Visual analogue scale; N.A.: Not available.

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