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DRUG-DRUG INTERACTIONS IN THE TREATMENT FOR ALCOHOL USE DISORDERS: A COMPREHENSIVE REVIEW

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ABSTRACT

Drug interactions are one of the most common causes of side effects in polypharmacy. Alcoholics are a category of patients at high risk of pharmacological interactions, due to the presence of comorbidities, the concomitant intake of several medications and the pharmacokinetic and pharmacodynamic interferences of ethanol. However, the data available on this issue are limited. These reasons often frighten clinicians when prescribing appropriate pharmacological therapies for alcohol use disorder (AUD), where less than 15 % of patients receive an appropriate treatment in the most severe forms. The data available in literature regarding the relevant drug-drug interactions of the medications currently approved in United States and in some European countries for the

treatment of AUD (benzodiazepines, acamprosate, baclofen, disulfiram, nalmefene, naltrexone and sodium oxybate) are reviewed here. The class of benzodiazepines and disulfiram are involved in numerous pharmacological interactions, while they are not conspicuous for acamprosate. The other drugs are relatively safe for pharmacological interactions, excluding the opioid withdrawal syndrome caused by the combination of nalmefene or naltrexone with an opiate medication. The information obtained is designed to help clinicians in understanding and managing the pharmacological interactions in AUDs, especially in patients under multi-drug treatment, in order to reduce the risk of a negative interaction and to improve the treatment outcomes.

Keywords: drug interactions, alcohol use disorder, pharmacokinetics, pharmacodynamics, polypharmacy

1. Introduction

Drug-drug interactions are one of the most frequent causes of adverse events during polypharmacy, defined as the chronic co-prescription of several drugs [1]. Indeed, it is estimated that 6-30% of all side effects are caused by a pharmacological interaction. This can vary from 3-5% in subjects taking only few drugs, increasing to 20% in subjects treated with more than 10 drugs [2]. A drug-drug interaction is a change in a drug's effect, occurring when two or more drugs are administered during the same period. This effect can be synergistic (when the drug's effect is increased), antagonistic (when the drug's effect is decreased) or a new effect may appear, which doesn't depend on individual drug outcomes. Various mechanisms are involved in a drug-drug

interaction, and these are usually classified as “pharmacokinetic” or “pharmacodynamic” [3]. Pharmacokinetic interactions are the most frequent and engage all the stages of drug pharmacokinetics (absorption, distribution through the tissues, metabolism and elimination). The interactions that involve the metabolism stage are the most relevant; they are extremely numerous and often cause a decrease or an increase in the blood concentrations of the drugs. The system of hepatic cytochromes is generally involved, but other enzymes, such as those catalysing glucuronidation reactions, can be involved. Pharmacodynamic interactions, on the other hand, concern the effects of the drugs and their mechanism of action. Due to these reasons, the therapeutic effect of a drug may be reduced, or the drug’s influence may be stronger. However, not all interactions are clinically relevant. Some are merely interesting facts and have no influence on the pharmacological treatment, while, in other cases, they may even be used for therapeutic purposes. Drug-drug interactions are often predictably based on previous reports and clinical studies, as well as the knowledge of pharmacologic principles, but clinicians don’t often realize the outcome [4]. Moreover, limited information is available about the epidemiology of drug-drug interactions in clinical practice. Few studies have summarized the data in scientific literature on possible drug interactions in the field of drug addiction.

In this study, we have focused our attention on alcohol use disorder (AUD), one of the most common and undertreated mental disorders [5] and in the most severe forms, less than 15 % of patients receive appropriate treatment [6]. Every year, 3.3 million deaths and 5.1% of the global burden of disease is due to alcohol consumption [7]. The standard treatment for AUD includes

psychological and socio-rehabilitation therapies, associated with several pharmacological therapies. The latter are oriented to manage alcohol withdrawal [8], the relapse prevention and the reduction of alcohol consumption [9]. Despite the considerable progress regarding neurotransmission mechanisms, there is still no definitive therapy that satisfies the numerous and heterogeneous phenotypes involved in alcoholism. Several drugs have been tested in pre-clinical and clinical studies, the U.S. Food and Drug Administration (FDA) has approved naltrexone (oral and long-acting injectable), acamprosate and disulfiram [10]. In the European Union, nalmefene has also been approved for the reduction of alcohol consumption in alcoholic patients with a high drinking risk level, defined as > 60 g/day for men and > 40 g/day for women of alcohol intake [11]. In addition, sodium oxybate is approved in Austria and Italy [12], whilst in France baclofen is authorized as "temporary recommendation for use" [13]. Unfortunately, the prescription of these medications is difficult, due to the lack of knowledge of their availability, prescription guidelines and dosage [14]. The clinical attitude towards the medications also affects prescription, and the off-label use is high (topiramate, gabapentin, SSRI and ondansetron). The presence of comorbid conditions and associated polypharmacy further complicate the framework: most patients with AUD have tried or are actively using other drugs, and more than 33% of them present a drug use disorder [15]. Thus, the drug-drug interaction is an important and underestimated concern in patients with AUD, applying for pharmacological treatment. So far, the aim of this review is to recapitulate the pharmacological interactions reported in literature of the medications approved for

the treatment of AUD in U.S. and in some European states (benzodiazepines, acamprosate, baclofen, disulfiram, naltrexone, nalmefene and sodium oxybate).

2. Methodological considerations

This comprehensive review summarises the well-known clinically relevant interactions concerning the approved drugs administered in the treatment of AUD. Although the hypothetical interactions considering pre-clinical studies are greater, we have chosen to report only those documented in the clinical setting. In addition, we have excluded the pharmacological interactions related to a drug use disorder, focusing on clinical interactions not considering the quantity and frequency intake. We search MEDLINE with the terms “interaction” OR “drug interaction” OR “drug-drug interaction” AND each of the following drugs: benzodiazepines, acamprosate, baclofen, disulfiram, sodium oxybate, naltrexone and nalmefene. We have included all papers with an abstract in English or in other European languages, that meet the inclusion criteria, up to and including 30 September 2017. Relevant articles were selected according to the professional judgement of the authors, no language restrictions were applied and there were no restrictions on the types of studies and articles reviewed. The results summarised in the following paragraphs are presented in Figure 1 and in Tables 1, 2, 3, 4 and 5.

3. Pharmacological treatment for alcohol withdrawal

3.1 Benzodiazepines

Benzodiazepines (BDZ) are GABAergic agonists with anxiolytic-hypnotic-sedative properties. They are administered in the treatment for AUD and, specifically, they are the gold standard for the treatment of alcohol withdrawal syndrome [8]. Chronic alcohol drinking affects numerous pathways of the central nervous system, in particular the glutamatergic system and the dopaminergic system, it increases the release of endocannabinoids and endogenous opioids and causes a down-regulation of GABA-A receptors. The modifications caused by alcohol to the GABA-A receptors contribute to numerous symptoms of the withdrawal syndrome, such as strong tremors of the hands and legs, agitation, insomnia, tachycardia and gastrointestinal symptoms [16]. Many different BDZ are effective because, like alcohol, they stimulate the inhibitory GABA-signalling pathways. Chlordiazepoxide, diazepam, lorazepam and oxazepam are the most commonly used, but none of them has been shown to be superior to the others [17].

3.1.1 Pharmacodynamic interactions

From a pharmacodynamic point of view, attention should be paid to the concomitant intake of BDZ with medicines having additive, depressive and sedative effects on the GABA-A receptors and on the central nervous system. They consist in opioids (analgesics, sedatives for coughs and replacement therapies), antidepressants, anticonvulsants, antihistamines H_1-sedative [18] and neuroleptics [19]. The concomitant intake of opiates with BDZ can even induce a “cross-tolerance” phenomena: this leads to a worsening of dependence, extremely difficult to overcome [20,21]. The association between alcohol and BDZ is also critical: the depressants effect of both drugs may

become synergistic rather than a merely additive effect, due to the competitive inhibition on hepatic metabolism of BDZ, following alcohol intake [22].

3.1.2 Pharmacokinetic interactions

Pharmacokinetic properties of BDZ play an important role in rationalising their prescription. Once absorbed by the gastrointestinal tract, BDZ and their metabolites generally have a high protein bound and are widely distributed in the body, accumulating in lipid-rich areas, such as the central nervous system and the adipose tissue. Most BDZ are metabolized by the P450 cytochrome enzymes (CYP3A4 and CYP2C19), then they are glucuronidated and excreted almost entirely in the urine. Of the BDZ most commonly used in clinical practice, midazolam is entirely metabolized by CYP3A4 and acts as a marker for evaluation of the activity of this cytochrome, while diazepam is mainly metabolized by CYP2C19 and to a lesser extent by CYP2C9 and CYP3A4 [23]. Other benzodiazepines, such as lorazepam and oxazepam, are directly glucuronidated and eliminated in the urine. Several drugs, metabolised by the same liver cytochromes, alter their blood concentrations or those of BDZ, when they are co-administered. A series of CYP3A4 inhibitors slow down the metabolism of BDZ, dangerously increasing their plasma concentrations. The most important are the azolic anti-fungal agents ketoconazole [24], itraconazole [25] and voriconazole [26], the macrolide antibiotics clarithromycin [27] and erythromycin [28], verapamil, diltiazem [29], aprepitant [30], grapefruit [31] and HIV protease inhibitors [32,33]. There are also a number of CYP3A4 inducers, which can lower plasma concentrations of BDZ to sub-therapeutic doses:

carbamazepine [34], phenytoin [34], phenobarbital [35], efavirenz [36] and nevirapine [37]. Referring to the influences on CYP2C19, phenytoin is a known inducer of the liver cytochrome. It is also metabolised by CYP2C9-dependent hepatic mechanism, and the interaction with a CYP2C19 substrate is not easy to predict. As example, the concomitant intake of diazepam and phenytoin resulted in a case of phenytoin toxicity [38]. Both phenytoin and diazepam were stopped, and the symptoms resolved. Diazepam is also conditioned by the co-taking of grapefruit juice, which increases its plasma concentrations [39]. Lorazepam, oxazepam and clobazam [40] are not metabolized by liver cytochromes: thus, they could represent ideal treatments in case of impaired liver function or cirrhosis. Anyway, they may encounter other pharmacological interactions. The most clinically relevant is valproate, which decreases lorazepam concentrations by up to 50%, slowing down the clearance of lorazepam glucuronides [41]. Concerning the protein bound-drug, the interaction of diazepam with digoxin is of clinical interest. The binding on albumins of both molecules induces a cooperative effect on digoxin binding, reducing its urinary excretion [42]. Co-administration of diazepam (5 mg) produced a moderate increase of digoxin half-life in plasma in five of the seven subjects, whereas urinary excretion of digoxin was substantially reduced in all subjects. Among medications at risk for combined pharmacokinetic-pharmacodynamic interactions, nefazodone is an antidepressant drug that increases the plasma concentrations of BDZ due to its inhibition activity on CYP3A4, especially for short half-life benzodiazepines (midazolam, alprazolam and triazolam) [43,44]. Venlafaxine, sertraline and fluoxetine have not shown the same significant effects, as their interference on CYP3A4 is limited [45,46]. The combination of BDZ

with oral contraceptives and statins, all competitive drugs on the liver cytochromes, appeared to be safe for therapeutic doses [47,48].

4. Pharmacological treatment for alcohol dependence

4.1 Acamprosate

Acamprosate (or calcium acetyl-homotaurinate) has a similar structure to the neurotransmitters taurine or gamma-aminobutyric acid (GABA), and its acetylation allows it to pass through the blood-brain barrier [49]. Its mechanism of action has not been fully clarified: the main neurochemical effects are the antagonization of the NMDA and mGluR5 receptors, the agonism of the GABA-A receptors at high concentrations [50], the decrease of the voltage-dependent calcium channels activity and the decrease of the cerebral expression of c-*fos*, a gene immediately expressed at the onset of alcohol withdrawal syndrome [51]. This drug was registered in 2004, by the FDA, for the treatment of withdrawal symptoms in alcohol-dependent patients [52]. Usually, 666 mg oral are administered, three times daily. Acamprosate achieved the best results in reducing alcohol relapse in the long-term, in association with psychotherapy and with a cycle of detoxification before beginning therapy [53,54].

4.1.1 Pharmacodynamic interactions

Acamprosate is a safe medicine regarding pharmacological interactions. The literature reports that it has been administered in association with tricyclic antidepressants, selective serotonin

reuptake inhibitors (SSRI), anxiolytics, sedative-hypnotic drugs, and non-opiate analgesics [55]. The temporary dose reduction utilized in case of gastrointestinal side effects, especially diarrhoea, does not appear to influence the incidence of drug-drug interactions. The latest pharmacovigilance data do not report serious adverse events in more than one million people who assumed the drug [56].

4.1.2 Pharmacokinetic interactions

The absorption of acamprosate through the digestive tract is limited and slow, and varies considerably from individual to individual; the only data available on its absorption reports that, when taken with meals, the bioavailability of the drug decreases from 42% to 23% [57]. However, the effect of food on absorption has no clinical repercussions and it is therefore not necessary to adjust the dose. Studies carried out with a radio-marked tracer, ^{14}C-acamprosate, show that the body does not metabolize the drug: it is not metabolized in the liver and does not represent an inhibitor, an inducer or a substrate for the hepatic enzymes [57]. This means that the potential for any metabolic interaction is very low, even in patients with impaired liver function. Acamprosate does not bind to plasma proteins; its half-life is longer than 20 hours [57]. Accordingly, no reciprocal pharmacokinetic interaction occurred between acamprosate and diazepam [58], imipramine [59], oxazepam [60], disulfiram [61], naltrexone [62] and alcohol [63].

4.2 Baclofen

Baclofen is a selective GABA-B receptor agonist administered in the treatment of paraplegia, multiple sclerosis and serious central or spinal neurological diseases. A series of trials have demonstrated the effectiveness of baclofen in alcohol-dependent patients [64-66], but these results have not been confirmed by other authors [67,68]; consequently, overall conclusions cannot be made. The current recommendations suggest that the daily intake should not exceed 75-80 mg, although long-term studies have shown that doses superior to 250 mg/day are often necessary to obtain the craving–suppressing effects [69,70]. Currently, it has a temporary recommendation for use in alcohol dependence in France [71]. There is no definitive evidence that actions on GABA-B receptor are involved in its clinical effects, which include central depressant properties, such as sedation, ataxia, respiratory and cardiovascular depression.

4.2.1 Pharmacodynamic interactions

The pharmacological interactions of baclofen are generalizable in sedatives effects, epileptogenic effects, or in muscle relaxant effects. The risk of sedation and respiratory depression increases when baclofen is administered in combination with opiate medications [72]. The same effect, although not reported in the literature, may be caused by the concomitant intake of benzodiazepines. The most relevant drug-drug interactions concern the association of baclofen with epileptogenic drugs. As example, seizure-like phenomenon was reported during induction of anaesthesia with propofol, in a patient with syringomyelia, receiving baclofen for flexor spasms [73]. This effect was probably

due to the occurrence of epileptic discharges mediated by propofol stimulation on GABA-A receptors, because of desensitization of GABA-B receptors that failed to control the release of GABA. The influence of the GABA-B receptor on GABA-A mediated epileptic discharges has been identified only recently [74]. A similar mechanism could explain the adverse reaction experienced by a 15-year-old male patient, under a long-term treatment with intrathecal baclofen. He developed dyskinesia affecting the head and upper limbs two days after the concurrent administration of intrathecal ziconotide, suggesting a presumable interaction between baclofen and ziconotide [75]. In addition, an increased muscle relaxant effect was observed in a single patient receiving baclofen, with two different tricyclic drugs (amitriptyline and doxepin) [76]. Baclofen is relatively well tolerated and safe when given in combination with intoxicating doses of alcohol [77]; in a cohort of 253 subjects with alcohol dependence, using baclofen for their disorder, the level of sedation appears to depend on the doses of both the baclofen and the alcohol [78]. Only a single case of a 46-year-old alcoholic patient without any history of neurological disorders was reported, who had experienced two episodes of seizures while undergoing treatment with up to 240 mg/day of baclofen [79].

4.2.2 Pharmacokinetic interactions

Baclofen is absorbed by the gastrointestinal tract, the peak plasma concentration appears within 1.5 hours. It is metabolized by the liver only to a small extent, giving rise to inactive metabolites. The terminal half-life is about 3-4 hours and it is eliminated mainly in an unmodified form, more than

70% through the kidney. However, pharmacokinetics of high dose baclofen may vary from the conventional 80 mg daily [80]. Time-to-peak plasma levels and plasma half-lives were substantially longer than conventional doses. In addition, baclofen levels were observed to rise gradually over time in some patients on a stable dosing regimen, probably a result of impaired renal clearance. Currently, no pharmacokinetic interactions are known between baclofen and other drugs. Also when taken with tizanidine, a muscle relaxant, baclofen was safe in fifteen healthy men. They were administered for seven consecutive doses, without the occurrence of any clinical interaction [81].

4.3 Disulfiram

Disulfiram was approved in 1994 by the FDA for the pharmacological treatment of alcoholism [82]. It is considered an aversion drug which interferes with alcohol metabolism, preventing the transformation of acetaldehyde (a toxic metabolite). Alcohol is metabolized in the liver by the enzyme alcohol dehydrogenase to acetaldehyde, which is in turn converted to the harmless acetic acid by the enzyme acetaldehyde dehydrogenase. Disulfiram prevents the second reaction, blocking the activity of acetaldehyde dehydrogenase. The maintenance dose is 250 mg per day (range, 125 to 500 mg), it should not exceed 500 mg daily. When the patient drinks alcohol and has recently taken a tablet of disulfiram, the concentration of acetaldehyde in the blood can be up to 5-10 times higher. This mechanism is responsible for the onset of the acetaldehyde syndrome or Disulfiram-Ethanol Reaction (DER): flushing, headache, respiratory distress, nausea, vomiting, tachycardia, syncope and hypotension [83,84]. These symptoms last for several minutes and may

compromise the patients' health. Disulfiram is therefore contraindicated in patients taking products that contain alcohol, also as an excipient in parenteral medicinal products [85].

4.3.1 Pharmacodynamic interactions

According to the pharmacological activities of disulfiram, the most relevant interaction concerns medicinal products containing alcohol (drops formulation, e.g. diazepam solution). This association is capable of triggering DER. Most DERs are mild and patients recover without serious sequelae, but some lethal DERs have been documented. Disulfiram is also capable to inhibit the enzyme dopamine β-hydroxylase (DBH), which converts dopamine to norepinephrine. This mechanism has been advanced as a possible explanation for the appearance of psychosis during disulfiram treatment, either in monotherapy or in combination therapy, when interaction-emergent psychosis could occur. In literature, the onset of psychotic symptoms is reported with the concomitant intake of mixed amphetamine salts [86], methylphenidate [87], buspirone [88], marijuana [89], isoniazid [90], metronidazole [91] and medicines that have impact on the dopaminergic neurotransmitter. In all cases, the psychotic symptoms resolved after the discontinuation of both medications, without the use of antipsychotic drugs. Moreover, disulfiram reinforces the action of coumarinic anticoagulants, augmenting warfarin hypoprothombinemia by chelating the metal cations necessary for the synthesis of active prothrombin [92].

4.3.2 Pharmacokinetic interactions

Disulfiram is almost entirely absorbed in the gastrointestinal tract, and it is metabolized in the liver to diethyldithiocarbamate (DTC), which in turn breaks down into carbon disulphide and diethylamine. Disulfiram requires about 12 hours reaching a pharmacological effect and its half-life is estimated between 60 to 120 hours.

Different drugs metabolised by the cytochrome P450 system show pharmacokinetic interference, if the patient is taking disulfiram. Disulfiram increases the plasma levels and extends the half-life of drugs that are substrates of the isoenzyme CYP2E1, such as anaesthetics [93-95], theophylline [96] and paracetamol: theoretically, disulfiram might reduce the toxic effect of paracetamol on the liver [97]. Disulfiram also interacts with different CYP3A4 substrates. A case of probable disulfiram-clarithromycin interaction has been reported, with the onset of fulminating hepatitis and severe toxic epidermal necrolysis [98]. Since both drugs inhibit CYP3A4, an accumulation of the toxic metabolites of disulfiram probably occurred, especially that of carbon disulphur, recognised as an inducer of hepatic toxicity. The influence of disulfiram on the metabolism of carbamazepine is negligible [99], whilst when it is administered for a long period, it inhibits the metabolism of diazepam and chlordiazepoxide, leading to a reduction in plasma clearance and extending their half-life, with an increased patient's drowsiness. Lorazepam or oxazepam are not metabolised by liver cytochromes, so they could be the drugs of choice, if benzodiazepine therapy is assumed concurrently with disulfiram [100]. Colchicine and antiretroviral medications (ARV) are other CYP3A4 substrates, a single case of acute colchicine intoxication following co-administration of disulfiram was described [101]. The ARV could influence the therapeutic efficacy of disulfiram,

because efavirenz and atazanavir respectively increase and decrease the disulfiram effect on enzymes of alcohol metabolism [102].

Disulfiram interferes even with the cytochrome CYP2C9 activity: when it is administered together with amitriptyline, it increases the risk of a confusional and/or psychotic state due to the toxic effects of the tricyclic antidepressant, which accumulates in the blood [103]. Similar considerations can be made with other tricyclic antidepressants, such as imipramine and desipramine [104]. In the same way, when disulfiram is taken with phenytoin or fosphenytoin, it reduces their biotransformation affecting the elimination rate by non-competitive mechanisms, increasing their toxicity [105,106]. Finally, disulfiram may alter methadone disposition, but in the doses used for the management of alcoholism, there was no clinical interaction between the two drugs [107]. Neither rifampicin [108] nor tolbutamide [109] interact with disulfiram at therapeutic doses.

4.4 Nalmefene

Nalmefene is a selective opioid receptor antagonist authorised by the European Medicines Agency in February 2013 [110] to reduce alcohol consumption in alcohol-dependent patients, with high levels of consumption (more than 60 grams/daily for men and more than 40 grams/daily for women), in accordance to the World Health Organisation guidelines [111]. Nalmefene acts as a μ and δ receptor antagonist and a partial k receptor agonist [112], it is structurally similar to naltrexone but it has a higher bioavailability and a longer plasma half-life, with a lower risk of liver toxicity [113]. Nalmefene has been shown to be effective in reducing alcohol consumption in

alcohol-dependent patients when it is taken as-needed [114-115], presumably modulating the activity of the opioid system and counteracting the activation of the dopaminergic mesolimbic pathway, induced by a chronic alcohol consumption [116]. Nalmefene is taken as needed, a tablet (18 mg) should be taken preferably 1-2 hours prior to the anticipated time of drinking.

4.4.1 Pharmacodynamic interactions

Due to its activity on opioid receptors, nalmefene assumption with opioid agonists inhibits its pharmacological effect: this applies to all opioid analgesics, but also to cough medicines containing codeine. Furthermore, the unintentional prescription of nalmefene associated with an opioid can trigger off a withdrawal syndrome [117,118]. Although caution is advised in administering nalmefene in patients who also take neuroleptics, such as haloperidol and droperidol, medicines associated with a possible, albeit rare, occurence of cardiac arrhythmias [119], the drug has shown (at doses of 20 mg/daily and 80 mg/daily) to have no effect on the QT interval and T wave morphology [120]. No clinically interactions between nalmefene and alcohol have been reported [121]: changes in cognitive and psychomotor performance may occur, but the effects of the concomitant assumption of nalmefene and alcohol do not exceed the sum of the effects of each of these substances taken separately.

4.4.2 Pharmacokinetic interactions

Nalmefene does not show relevant pharmacokinetic differences between males and females, young people and the elderly, or different ethnic groups [122]. Oral bioavailability of nalmefene after a single administration is nearly 41 %, the peak plasma concentration is rapidly reached after about 1.5 hours and the terminal half-life is estimated at about 12 hours [123]. Nalmefene is largely metabolized in the liver and transformed into nalmephene 3-O-glucuronide, mainly by the enzyme UGT2B7 and, to a lesser extent, by the enzymes UGT1A3 and UGT1A8. A small proportion of nalmefene is converted into 3-O-sulphate nalmefene and nornalmefene by CYP3A4. Metabolites do not have a pharmacological effect, renal excretion is the main route of their elimination. Despite the high liver metabolism, the drug is not a hepatotoxin, therefore it doesn't compromise liver function or alter the laboratory values, even for prolonged periods of time [124]. However, the administration of a single dose of nalmefene in twelve patients with hepatic impairment increased the drug exposure, compared to healthy volunteers. Nalmefene clearance was reduced by 31 %, while the half-life of the drug increased by 32 %, indicating the presence of an inverse relationship between nalmephene clearance and the degree of liver impairment [125].

No relevant pharmacokinetic interactions have been reported, but possible interactions with powerful inhibitors of the enzyme UGT2B7, such as diclofenac and naproxene [126], ketoconazole [127] and low concentrations of amitriptyline [128], cannot be excluded. Problems are unlikely to occur with occasional use, but there is no data on a long-term therapy. Conversely, the concomitant

administration of a UGT2B7 inducer, such as different chemotherapeutic agents [129] or di-hydroartethmisine [130], may reduce nalmefene plasma concentrations to sub-therapeutic ranges.

4.5 Naltrexone

Naltrexone is an opioid receptor antagonist. It is a competitive antagonist of μ receptors, and to a lesser extent of δ e k receptors. In AUD, several studies have demonstrated its efficacy in reducing the rate of recidivism and the craving levels [131]. Currently, the FDA recommends 50 mg/daily of naltrexone for treating AUDs, but some findings suggest that higher doses (up to 150 mg/day) may be effective in reducing alcohol consumption [132]. Blocking the activation of opioid receptors, naltrexone reduces the release of dopamine into the alcohol-induced reward circuit and the gratifying effects [133]. For these reasons, naltrexone is one of the most suitable drugs for reducing the alcohol desire, while other medications, such as acamprosate, are more effective in maintaining abstinence [134].

4.5.1 Pharmacodynamic interactions

Naltrexone is contraindicated in patients taking opioid drugs because of its antagonism activity, both in antalgic therapy, in replacement therapy and/or during anaesthesia. Although this combination is not recommended in the package leaflet of opioid medications, approximately 1.8% of the patients receiving opioid maintenance therapy have assumed naltrexone in their lifetime [135]. Consequently, co-administration with morphine and its derivatives, oxycodone,

buprenorphine, fentanyl [136], codeine and methadone [137], but also with opioid analgesics such as pentazocin and nalbufin, should be avoided. Before administering naltrexone, it is advisable to have stopped opioid therapy for at least ten days: in the case of concomitant assumption, the patient is at high risk of a withdrawal syndrome; a hypersensitivity reaction to the opioid agonist may occur in rare cases [138]. In addition, two cases of lethargy and drowsiness were reported after concomitant use of naltrexone with tioridazine, a phenothiazine [139]. Although concurrent intake of naltrexone and antidepressants (tricyclic, SSRI and serotonin-norepinephrine reuptake inhibitor or SNRI), neuroleptics and benzodiazepines is not recommended, for the risk of lengthening the QT interval to the electrocardiogram and possible cardiac arrhythmias, no cardiovascular events have been reported in the literature. In the ultra-short opiate detoxification, the QTc interval was significantly lengthened (median value 420 msec vs. 453 msec) in combination with clonidine, but this was probably due to hypopotassiemia and clonidine itself [140]. In the case of a simultaneous administration with disulfiram or baclofen, no interactions are expected [141,142]. The PTX3003 experimental product, a combination of baclofen, naltrexone and sorbitol, is actually being tested in a phase III clinical trial for patients with Charcot-Marie-Tooth type 1A disease, showing good efficacy and an excellent tolerability profile [142]. Regarding acamprosate, the administration with naltrexone in healthy volunteers significantly increases the maximum plasma concentration and the area under the plasma concentration-time curve of acamprosate, but no adverse effects have been documented; on the contrary, it has been hypothesized that this effect may have a positive and "reinforcing" role in alcohol-dependent patients [62]. No relevant interactions among naltrexone

and alcohol were described. The co-administration of the drug and 240 ml solution at the increasing concentrations of alcohol did not change the pharmacokinetic profile of naltrexone [143].

4.5.2 Pharmacokinetic interactions

There are no data supporting pharmacokinetic interactions of naltrexone. Some in vitro studies have highlighted that neither naltrexone, nor its main metabolite, 6-β-naltrexol, are metabolized through human CYP450 enzymes [144]. They are mainly metabolized by hepatic di-hydrodiol dehydrogenase (DD1, DD2 and DD4), which are inhibited competitively by testosterone and di-hydrotestosterone, but this interaction remains of an uncertain clinical significance. As a result, there are several studies that show the reliability of naltrexone administration in different categories of patients. In particular, it has been safely administered in 215 patients with multiple sclerosis [145] and 46 Crohn's disease patients [146], while the protracted-release formulation was effective and well tolerated in 23 HIV-positive patients with a concurrent alcohol and/or opiate use disorder [147]. Precisely, naltrexone had already been shown to have no effect on the bioavailability of zidovudine, as it did not modify the area under the curve (AUC) when co-administered with the anti-retroviral drug [148]. The administration of naltrexone (50 mg/daily) was well tolerated also in twelve arachnophobic patients treated with alprazolam (1 mg/daily) [149], and in 14 opioid dependent patients treated with prazepam (10 mg, twice daily) [150]. Moreover, the simultaneous intake of naltrexone and citalopram [151] or sertraline [152] did not produce any side effects.

4.6 Sodium oxybate

Sodium oxybate is the sodium salt of γ-hydroxybutyric (GHB) acid, a short-chain fatty acid derived from γ-aminobutyric acid (GABA). The latter is a prominent inhibitory neurotransmitter of the central nervous system, which acts as a neuromodulator of the dopaminergic, GABAergic and opioidergic pathways [153]. The terms GHB and sodium oxybate are often used indifferently, but only the sodium oxybate (i.e. the sodium salt of GHB) has a clinical application. Sodium oxybate was approved in Italy in 1992 for the treatment of alcohol dependence; in 1999 it was also approved in Austria. It is considered effective and safe for the treatment of alcohol dependence, alcohol withdrawal syndrome, and for the prevention of relapse [154], not necessarily as the second or third choice. A safe approach to use sodium oxybate is to fraction it into three to six daily administrations (50 to 100 mg/kg/day). It has an alcohol-mimicking effect, comparable to an alcohol "substitute": acting on the GABA-B receptors, it causes an increase in the release of dopamine in the nucleus accumbens [155]. Fortunately, episodes of craving and abuse of the drug in alcoholic patients are very limited (around 10%), and no cases of death from sodium oxybate overdose have been reported [156].

4.6.1 Pharmacodynamic interactions

Sodium oxybate is a central nervous system depressant. When it is co-administered with medications impairing the central nervous system, it showed synergistic effects only with few of them. When sodium oxybate and lorazepam were coadministered, increased sleepiness was

observed, whereas it was safely administered with tramadol (100 mg), methadone, protriptyline (10 mg) and duloxetine (60 mg) [157-158]. Even the association between sodium oxybate and disulfiram was safe: the number and type of adverse events of each drug is comparable in the group treated with both drugs, to those patients treated with just one drug [159]. However, a possible additive effect cannot be excluded, when higher dosages of sodium oxybate (up to 9 g/day) are coadministered with higher dosages of hypnotics, opioids or antidepressants [160]. The co-administration of modest doses of GHB (50 mg/Kg) and ethanol resulted in increased episodes of vomiting, hypotension, and a greater decrease in O_2 saturation, but only minimal pharmacokinetic interactions were observed [161]. Moreover, recent studies with a new formulation of sodium oxybate showed a different profile compared to alcohol, the sedative effects are less marked and there is no reciprocal reinforcement between the two substances; the co-administration was safe [162].

4.6.2 Pharmacokinetic interactions

Sodium oxybate is largely absorbed after oral administration in healthy volunteers with a history of recreational use [163] and in alcohol-dependent patients [164]. It acts rapidly, sodium oxybate reaches the plasma concentration peak in 30-120 minutes and the terminal half-life is around 30-60 minutes. It is mainly metabolised in the liver; only a small part (around 2-5%) being excreted unchanged in the urine. Despite the drug being metabolised in the liver, the literature contains no reports of pharmacokinetic interactions between sodium oxybate and other medications.

In vitro, sodium oxybate did not significantly inhibit the cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A, at higher concentrations than therapeutic levels [157]. Sodium oxybate does not interfere with anti-retroviral drugs and/or interferon: the hepatic pathways involved in the metabolism of sodium oxybate [160] are different from those that metabolise the drugs used in the treatment for HIV, HBV and HCV [165]. Even omeprazole did not affect the pharmacokinetics of sodium oxybate to a clinically significant extent [166]. A single, supposed pharmacokinetic interaction has been reported in a case of chronic cluster headache, where the concomitant intake of sodium oxybate and topiramate resulted in a neurological coma [157].

5. Conclusion

Polypharmacy is a high-risk condition, due to the pharmacokinetic and pharmacodynamic properties of the medications being assumed at the same time. In recent years, interest in pharmacological treatments for AUD and their safety have been increasing, but pharmacological interactions are insufficiently considered [14,167]. Patients with alcoholism may be treated concomitantly with antihypertensives, diuretics, antibiotics, antivirals and lipid-lowering drugs, some of which have shown to interact with the pharmacological treatment of AUD. This implies that when it is necessary to start treatment with an aversive or an anti-craving medication, all the possible drug-drug interactions should be carefully considered. Most of the interactions documented in literature have been reported for the BDZ class and disulfiram. It is widely supported that no member of benzodiazepines exceeds the others for the treatment of alcohol withdrawal, but their

different pharmacokinetic properties may justify the use of a specific molecule, especially in patients at risk of drug interactions. The pharmacokinetic profile of diazepam has unique advantages in alcoholic patients, such as the short time to peak effect and a long elimination half-life, resulting in a lower incidence and severity of withdrawal symptoms and rebound phenomena [168]. However, interactions with drugs metabolized by the CYP2C19, CYP2C9 and CYP3A4 enzymes are possible and its prescription should in any case be assessed on a case-by-case approach. Disulfiram is one of the most commonly used drugs in alcohol dependence and, in this class of drugs, it has the greatest risk of pharmacological interactions. Its dangerous association with more than 40 drugs, five organic solvents, one pesticide and at least one species of mushroom had already been reported several years ago [169]. It is characterised by serious pharmacodynamic interactions, which concern both medications containing alcohol and specific medicines associated with the onset of psychiatric events. Nevertheless, it may interact with various liver enzymes, including CYP2E1, CYP2C9 and CYP3A4. Baclofen and sodium oxybate are relatively safer drugs for co-administration, as well as nalmefene and naltrexone, without forgetting that the opioid withdrawal syndrome due to their association with an opioid may be fatal. On the other hand, acamprosate is devoid of pharmacological interactions, being successfully prescribed in association with antidepressants, BDZ, non-opiate analgesics, naltrexone and disulfiram. The accumulated information should contribute to a greater safety in the use of the drugs prescribed for AUDs in patients undertaking multi-drug treatment, in order to reduce the risk of a negative interaction and to optimize the clinical outcomes.

Conflict of Interest

All other authors declare that they have no conflicts of interest.

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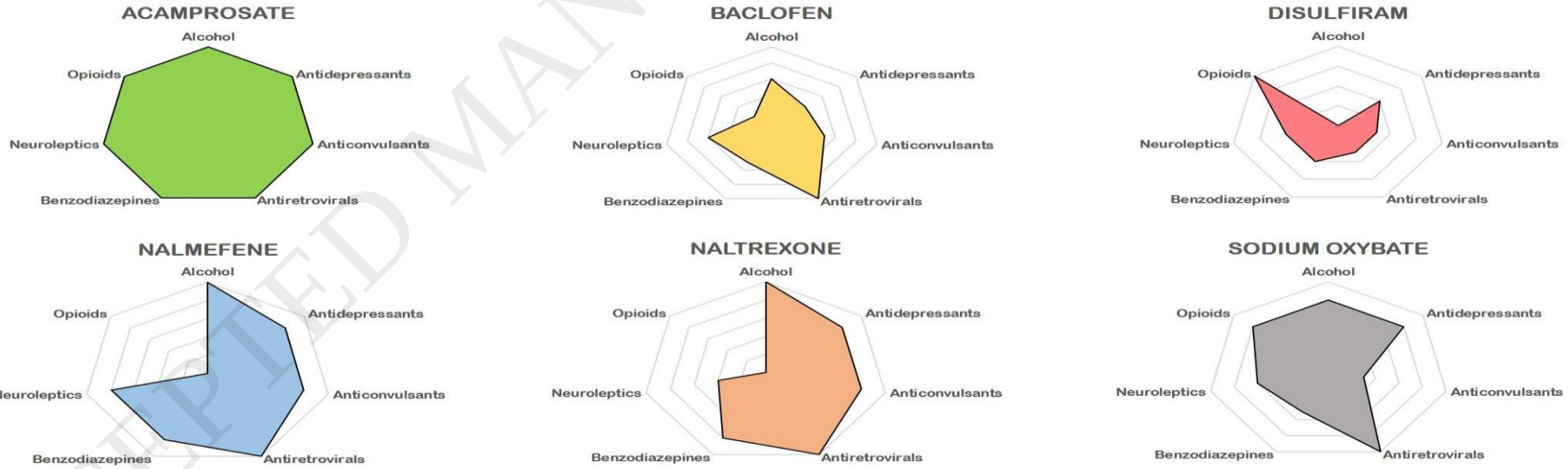
Figures captions

Figure 1. Radar charts showing the potential combination of pharmacological treatments of alcohol dependence with several classes of medications. The data length of a spoke is proportional to the magnitude of the potential association between the two drugs. A line connect the data values for each spoke.



Tables

Table 1. Pharmacodynamic interactions among BDZ and different classes of medications

Drug class	Generic name	Availability	Interaction
Opioids	Codeine Fentanyl Idromorphone Morphine Methadone Oxycodone Tramadole	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and respiratory depression Co-administration increases the risk of addiction to these medications, through a "cross-tolerance" phenomenon
Antidepressants	Bupropione IMAO Mirtazapine Nefazodone SSRI SNRI Trazodone Tryciclic antidepressants	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances
Anticonvulsants	Carbamazepine Ethosuccimide Felbamate Gabapentin Lacosamide Lamotrigine	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances

	Levetiracetam Oxcarbazepine Phenytoin Phenobarbital Pregabalin Topiramate Valproic acid Vigabatrin Zonisamide		
Antihistamines	First-generation Antihistamines	OTC and medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances
Neuroleptics	Classical neuroleptics Atypical neuroleptics	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Table 2. Pharmacokinetic interactions among BDZ and different classes of medications

Target		Drug class	Generic name	Availability
CYP3A4	Inhibitors	Azolic anti-fungal agents	Itraconazole Ketoconazole Voriconazole	OTC and Medical prescription
		Macrolids antibiotics	Erythromycin Clarithromycin	Medical prescription
		HIV protease inhibitors	Saquinavir Ritonavir Lopinavir	Medical prescription
		Calcium antagonists	Diltiazem Verapamil	Medical prescription
		Antiemetics	Aprepitant	Medical prescription
		Antidepressants	Nefazodone	Medical prescription
		Grapefruit juice		OTC
	Inducers	Anticonvulsants	Carbamazepine Phenytoin	Medical prescription
		Barbiturates	Phenobarbital	Medical prescription
		Antiretrovirals	Efavirenz Nevirapine	Medical prescription
CYP2C19	Inhibitors	Grapefruit juice		OTC

Substrate and Inducer	Anticonvulsants	Phenytoin	Medical prescription
Glucuronidation enzymes	Anticonvulsants	Valproic acid	Medical prescription
Protein bound-drug	Digital glycosides	Digoxin	Medical prescription

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Table 3. Interactions between baclofen and sodium oxibate with different classes of medications

Drug class	Generic name	Availability	Interaction
Baclofen			
Opioids	Buprenorphine Codeine Fentanyl Idromorphone Morphine Methadone Nalbuphine Oxycodone Pentazocin Tramadole	Medical prescription	Co-administration could increase the sedative effect and the risk of a respiratory depression
Anesthetic	Propofol	Medical prescription	A single case of recurrent generalized seizures with the concomitant intake of propofol has been reported
Analgesic	Ziconotide	Medical prescription	A single case of dyskinetic syndrome with the concomitant intake of intrathecal ziconotide has been reported
Tryciclic antidepressants	Amitriptyline Doxepin	Medical prescription	Co-administration could increase the muscle relaxant effect
Sodium oxibate			
Anticonvulsants	Topiramate	Medical prescription	A single case of high plasma concentrations of topiramate with the concomitant intake of sodium oxybate has been reported

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Table 4. Interactions between disulfiram with different classes of medications

Pharmacodynamic interactions

Drug class	Generic name	Availability	Interaction
Drugs containing alcohol		Medical prescription and OTC	The association is capable of triggering the disulfiram-ethanol reaction, with serious consequences for patients
Anticoagulants	Warfarin	Medical prescription	Disulfiram may augment warfarin hypoprothombinemia by chelating the metal cations necessary for the synthesis of active prothrombin
Antibiotics	Isoniazid Metronidazole	Medical prescription	These compounds, when administered in combination, may significantly alter metabolism of brain catecholamines
Psychostimulants	Amphetamine Methylphenidate Buspirone Marijuana	Medical prescription	Disulfiram interferes with the mechanism of action of these drugs, inhibiting the dopamine β-hydroxylase activity, resulting in hallucinations, behavioural disorders and/or psychosis

Pharmacokinetic interactions

Target		Drug class	Generic name	Availability
CYP2E1	Disulfiram inhibition	Anaesthetics	Halothane Isoflurane Sevoflurane	Medical prescription
		Methylxanthine	Theophylline	Medical prescription and OTC
		Analgesic	Paracetamol	Medical prescription and OTC
CYP3A4	Inhibitor	Antibiotics	Clarithromycin	Medical prescription

		Anti-rheumatic	Colchicine	Medical prescription
		Antiretrovirals	Atazanavir	Medical prescription
	Inducer	Antiretrovirals	Efavirenz	Medical prescription
	Disulfiram inhibition	Benzodiazepines	Chlordiazepoxide Diazepam	Medical prescription
CYP2C9	Inhibitor	Tryciclic antidepressants	Amitriptyline Desipramine Imipramine	Medical prescription
		Anticonvulsants	Phenytoin Fosphenytoin	Medical prescription

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Table 5. Interactions between naltrexone and nalmefene with different classes of medications

Drug class	Generic name	Availability	Interaction
Naltrexone			
Opioids	Buprenorphine Codeine Fentanyl Idromorphone Morphine Methadone Nalbuphine Oxycodone Pentazocin Tramadole	Medical prescription	Co-administration decreases the effect of opioid agonists and increases the risk of a withdrawal syndrome. In rare cases, a hypersensitivity reaction to opiate agonist may occur.
Neuroleptics	Thioridazine	Medical prescription	Naltrexone enhances the effects of Thioridazine on the CNS. Two cases of excessive drowsiness and lethargy have been reported.
Alcohol disorders treatment	Acamprosate	Medical prescription	Naltrexone increases the absorption and bioavailability of acamprosate.
Nalmefene			
Opioids	Buprenorphine Codeine Fentanyl Idromorphone Morphine Methadone	Medical prescription	Co-administration decreases the effect of opioid agonists and increases the risk of a withdrawal syndrome.

	Oxycodone
	Tramadole

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.