Interakcije benzodiazepina i njihove kliničke implikacije

/ Benzodiazepine Interactions and Their Clinical Implications

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Anksiozni poremećaji se ubrajaju među najčešće psihijatrijske poremećaje te je broj oboljelih osoba posljednjih nekoliko desetljeća u značajnom porastu. Takve promjene su rezultirale povećanom upotrebom anksiolitika, a posebno benzodiazepina. S obzirom na to da mnogi pacijenti koriste benzodiazepine zajedno s drugim terapijama, važno je uzeti u obzir moguće interakcije do kojih može doći. Cilj ovog preglednog rada je pružiti uvid u farmakokinetičke i farmakodinamske interakcije benzodiazepina s različitim lijekovima, s posebnim naglaskom na ulogu enzima citokroma P450 i GABA-A receptora. Evaluacija specifičnih kombinacija lijekova, njihovih učinaka na metabolizam i djelovanje benzodiazepina kao i mogućih kliničkih posljedica može pomoći u donošenju informiranih kliničkih odluka te smanjenju rizika od nuspojava lijekova.

/ Anxiety disorders are among the most common mental health conditions, with a notable rise in the affected population in the past few decades. Such changes have led to an increased prescription of anxiolytics, particularly benzodiazepines. Given that many patients use benzodiazepines alongside other medications, it is crucial to consider the potential interactions that may occur. The aim of this review article is to provide insight into the pharmacokinetic and pharmacodynamic interactions of benzodiazepines with various other drugs, with special emphasis on the role of cytochrome P450 enzymes and the GABA-A receptors. An evaluation of specific drug combinations, their effects on the metabolism and benzodiazepine action, as well as potential clinical implications, can provide valuable insights when it comes to making informed clinical decisions and minimizing the risk of adverse drug reactions.

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UVOD

Anksiozni poremećaji su među najraširenijim mentalnim poremećajima, osobito u zemljama s visokim prihodima. Broj oboljelih značajno je porastao, sa 194,9 milijuna 1990. godine na 301,4 milijuna 2019. godine (1). U Europi su mentalni poremećaji glavni uzroci godina života s nesposobnošću (YLD) pri čemu anksiozni poremećaji čine 4 % ukupnog tereta invaliditeta. Najčešće propisivani lijekovi za liječenje ovih stanja su anksiolitici i hipnotici čija je primjena doživjela značajan porast (2). Anksiolitici su namijenjeni za smanjenje anksioznosti i poboljšanje sna tako što djeluju na središnji živčani sustav (SŽS). Benzodiazepini su najčešće korištena skupina zbog svog brzog djelovanja i relativno velike terapijske širine (3). Povijest anksiolitika seže u drevna vremena; alkohol i opijum bili su najraniji poznati sedativi i ostali su stoljećima glavni izbor za sedaciju. Sinteza barbiturne kiseline bila je veliki napredak početkom 20. stoljeća te je dovela do stvaranja barbiturata. Međutim, ovi su lijekovi imali značajne nedostatke. Benzodiazepini su slučajno otkriveni 1955. godine i brzo su stekli popularnost zbog poboljšanog sigurnosnog profila (4). Mnogi pacijenti, osobito oni stariji, obično uzimaju više lijekova istovremeno s navedenim psihotropnim lijekovima. To može dovesti do interakcija koje uključuju i farmakokinetičke i farmakodinamske procese što potencijalno ima neželjene posljedice liječenja i dobrobiti pacijenta (2,5).

Cilj ovog preglednog rada jest sveobuhvatno prikazati najčešće farmakokinetičke i farmakodinamske interakcije benzodiazepina kako bi se osigurala njihova sigurna primjena u kliničkoj praksi.

METODE

Proveden je opsežan pregled literature korištenjem baza podataka PubMed i Google Scholar. Korišteni su sljedeći pojmovi za pretraživanje: *"anxiety disorders", "anxiolytics", "benzodiazepi-*

INTRODUCTION

Anxiety disorders are among the most prevalent mental disorders, especially in high-income countries. The number of patients has significantly increased, from 194.9 million in 1990 to 301.4 million in 2019 (1). Mental disorders are the primary contributors to years lived with disability (YLD) in Europe, while anxiety disorders account for 4% of the overall disability burden. The most frequently prescribed medications for the treatment of these conditions are anxiolytics and hypnotics, therefore their use has increased significantly (2). Anxiolytics are designed to reduce anxiety and improve sleep by affecting the central nervous system (CNS). Benzodiazepines are the most commonly used group due to their rapid onset of action and relatively high therapeutic range (3). The history of anxiolytics dates back to ancient times; alcohol and opium were the earliest known sedatives and for centuries remained the primary option for sedation. Barbituric acid synthesis represented a major breakthrough in the early 1900s, leading to the creation of barbiturates. However, these drugs had significant drawbacks. Benzodiazepines were discovered by accident in 1955, and quickly gained popularity due to their improved safety profile (4). Many patients, particularly older individuals, tend to take multiple medications along with the aforementioned psychotropic drugs. This can lead to drug-drug interactions involving both pharmacokinetic and pharmacodynamic processes, which may potentially lead to undesirable consequences for the patient's treatment and well-being (2, 5).

The aim of this review article is to provide a comprehensive presentation of the most common pharmacokinetic and pharmacodynamic interactions of benzodiazepines in order to optimize their safe use in clinical practice.

METHODS

A comprehensive literature review was conducted using the PubMed and Google Scholar databases. The following search terms were utilized: "anxiety

nes", "benzodiazepine pharmacokinetics", "benzodiazepine pharmacodynamics," "benzodiazepine drug-drug interactions", "benzodiazepines and cytochrome P450", "GABA-A receptor system", "benzodiazepine metabolism", "clinical implications of benzodiazepines", "benzodiazepine adverse effects", "benzodiazepine and antidepressants", "benzodiazepine and SSRI", "benzodiazepine and SNRI", "benzodiazepine and antibiotics", "benzodiazepine and tuberculosis", "benzodiazepine and antimycotics", "benzodiazepine and azoles", "benzodiazepine and oral contraceptives", "benzodiazepine and antisecretory drugs", "benzodiazepine and PPIs", "benzodiazepine and antiepileptics", "benzodiazepine and ethanol", "benzodiazepine and opioids", "benzodiazepines and propofol" i "benzodiazepine and anaesthetics". Istraživanja koja nisu bila objavljena na engleskom ili hrvatskom jeziku nisu pružala relevantne podatke o interakcijama benzodiazepina ili su bila objavljena kao sažetci konferencija bez dostupnog punog teksta nisu uzeta u obzir. Podatci su sintetizirani kako bi se pružio sveobuhvatan pregled farmakokinetičkih i farmakodinamičkih interakcija benzodiazepina.

PREGLED LITERATURE

Vrste interakcija između lijekova

Interakcije između lijekova mogu se svrstati u dvije glavne kategorije: farmakokinetičke i farmakodinamske. Farmakokinetičke interakcije nastaju djelovanjem jednog lijeka na koncentraciju drugog u krvi. To može biti posljedica promjena u metabolizmu, apsorpciji, izlučivanju ili distribuciji lijeka i teško je predvidivo (6). Važan mehanizam farmakokinetičkih interakcija je biotransformacija, proces kojim se strane tvari modificiraju i eliminiraju. Najčešće se odvija u dvije faze:

1. Faza I: Enzimi citokroma P450 (CYP) uvode funkcionalne skupine u molekulu lijeka čime strane tvari postaju topljive u vodi i podložnije daljnjem metabolizmu.

disorders," "anxiolytics," "benzodiazepines", "benzodiazepine pharmacokinetics", "benzodiazepine pharmacodynamics", "benzodiazepine drug-drug interactions", "benzodiazepines and cytochrome P450", "GABA-A receptor system", "benzodiazepine metabolism", "clinical implications of benzodiazepines", "benzodiazepine adverse effects", "benzodiazepine and antidepressants", "benzodiazepine and SSRI", "benzodiazepine and SNRI", "benzodiazepine and antibiotics", "benzodiazepine and tuberculosis", "benzodiazepine and antimycotics", "benzodiazepine and azoles", "benzodiazepine and oral contraceptives", "benzodiazepine and antisecretory drugs", "benzodiazepine and PPIs", "benzodiazepine and antiepileptics", "benzodiazepine and ethanol", "benzodiazepine and opioids", "benzodiazepines and propofol" and "benzodiazepine and anaesthetics". Studies which were not published in English or Croatian languages, which did not provide relevant data on benzodiazepine interactions, or which were published as conference abstracts without full text available, were not taken into consideration. The data obtained were synthesized in order to provide a comprehensive overview of the pharmacokinetic and pharmacodynamic interactions of benzodiazepines.

LITERATURE REVIEW

Types of drug interactions

Drug-drug interactions primarily fall into two main categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions occur when one drug alters the blood concentration of another. This can happen through changes in the metabolism, absorption, excretion or distribution of a drug, and is hard to anticipate (6). An important mechanism in pharmacokinetic interactions is biotransformation, a process through which foreign substances are modified and eliminated. It typically occurs in two phases:

1. Phase I: Cytochrome P450 (CYP) enzymes introduce functional groups to the drug

2. Faza II: Reakcije konjugacije povezuju metabolite iz faze I s endogenim molekulama poput glukuronske kiseline, sulfata ili aminokiselina kako bi se poboljšala stabilnost i olakšalo izlučivanje (7,8).

Glavne izoforme CYP enzima važne za metabolizam psihotropnih lijekova, uključujući anksiolitike, su: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 i CYP3A4, pa je razumijevanje njihove funkcije i mogućih interakcija ključno za uspješno izbjegavanje štetnih učinaka lijekova (8,9).

Farmakodinamika, s druge strane, proučava kako lijekovi utječu na tijelo i na koji način uzrokuju svoje terapijske učinke. Fokusira se na mehanizme djelovanja, kinetiku vezivanja za receptore i signalne kaskade, što pruža uvid u selektivnost lijeka i moguće nuspojave (8,10).

Farmakokinetičke interakcije benzodiazepina

Benzodiazepini se brzo apsorbiraju oralnim putem zbog svoje lipofilnosti i podliježu jetrenom metabolizmu dvama glavnim putovima: oksidacijom CYP450 enzimima (posebno CYP3A4) i glukuronidacijom. Mnogi benzodiazepini proizvode farmakološki aktivne metabolite od kojih neki imaju dugi poluvijek eliminacije. Vrijeme eliminacije značajno varira među različitim benzodiazepinima što određuje trajanje učinaka te mogućnost akumulacije (4,8).

Antidepresivi

Anksiozni i depresivni poremećaji često se javljaju istovremeno. Glavna farmakološka terapija za ove poremećaje uključuju selektivne inhibitore ponovnog unosa serotonina (SIPPS), selektivne inhibitore ponovnog unosa serotonina i noradrenalina (SNRI) i benzodiazepine. Iako korisna, ovakva kombinirana terapija povećava mogućnost klinički važnih interakcija (11) (tablica 1). Među antidepresivima, SIPPS se posebno ističu po svojim farmakokinetičkim

molecule, making the foreign substances water-soluble and more susceptible to further metabolism.

2. Phase II: Conjugation reactions bind Phase I metabolites to endogenous molecules such as glucuronic acid, sulfate, or amino acids to enhance stability and facilitate excretion (7, 8).

The main CYP enzyme isoforms important for the metabolism of psychotropic drugs, including anxiolytics, are: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, therefore understanding their function and potential interactions is crucial for successfully avoiding adverse drug reactions (8, 9).

Pharmacodynamics, on the other hand, studies how drugs affect the body and in which way they produce their therapeutic effects. It focuses on mechanisms of action, receptor binding kinetics, and (downstream) signaling cascades, thus providing insight into drug selectivity and possible side effects (8, 10).

Pharmacokinetic interactions of benzodiazepines

Benzodiazepines are rapidly absorbed orally due to their high lipophilic profile, and undergo hepatic metabolism through two main pathways: oxidation via CYP450 enzymes (especially CYP3A4), and glucuronidation. Many benzodiazepines produce pharmacologically active metabolites, some with long elimination half-lives. Their elimination time varies considerably among different types of benzodiazepines, which determines the duration of effects and possibility of accumulation (4, 8).

Antidepressants

Anxiety and depressive disorders often occur together. The most well-established pharmacological treatments for these disorders include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines. This combination therapy, while beneficial, raises the potential of clinically significant interactions (11) (Table 1).

TABLICA 1. Klinički značajne farmakokinetičke interakcije benzodiazepina s lijekovima
TABLE 1. Clinically significant pharmacokinetic interactions of benzodiazepines with drugs

LIJEK / DRUG	Učinak na CYP enzime / Effect on CYP enzymes	Učinak na koncentraciju benzodiazepina i kliničko značenje / Effect on benzodiazepine concentration and clinical significance
Fluoksetin / Fluoxetine	inhibicija CYP3A4 / inhibition of CYP3A4	alprazolam: ↑ konc.; psihomotorno oštećenje / alprazolam: ↑ concentration; psychomotor impairment
Fluvoksamin / Fluvoxamine	inhibicija CYP3A4, CYP2C, CYP1A2 / inhibition of CYP3A4, CYP2C, CYP1A2	alprazolam: ↑↑ konc.; psihomotorno oštećenje i oštećenje pamćenja / alprazolam: ↑↑ concentration; psychomotor impairment and memory impairment
Eritromicin / Erythromycin	inhibicija CYP3A4 / inhibition of CYP3A4	midazolam: ↑↑↑ konc.; dulji sedativni učinak – smanjiti dozu 50-75 % / midazolam: ↑↑↑ concentration; prolonged sedative effect – lower the dose by 50-75%
Klaritromicin / Clarithromycin	inhibicija CYP3A4 / inhibition of CYP3A4	midazolam: ↓ klirens; povećanje vremena spavanja / midazolam: ↓ clearance; increased sleep time
Itrakonazol / Itraconazole	inhibicija CYP3A4 / inhibition of CYP3A4	midazolam: ↑ konc.; / midazolam: ↑ concentration; triazolam: ↑ konc.; / triazolam: ↑ concentration
Cimetidin / Cimetidine	inhibicija više CYP enzima / inhibition of multiple CYP enzymes	diazepam: ↑ poluvijek eliminacije; pojačan sedativni učinak / diazepam: ↑ elimination half-life; enhanced sedative effect
Karbamazepin/fenitoin / Carbamazepine/Phenytoin	indukcija CYP3A4 / induction of CYP3A4	midazolam: ↓↓ konc.; potrebne veće doze midazolama za postizanje terapijskog učinka / midazolam: ↓↓ concentration; higher doses of midazolam required to achieve therapeutic effect
Valproat / Valproic acid	inhibicija glukuronidacije / inhibition of glucuronidation	lorazepam: ↓ glukuronidacija; pospanost i vrtoglavica – pratiti pacijenta / lorazepam: ↓ glucuronidation; drowsiness and dizziness – monitor patient

učincima zbog utjecaja na jetrene CYP enzime. Tri SIPPS-a se izdvajaju kao snažni inhibitori CYP enzima: fluoksetin, fluvoksamin i paroksetin (12,13). Među benzodiazepinima koji se metaboliziraju putem faze I preko CYP enzima su alprazolam, diazepam, klonazepam, midazolam i triazolam. CYP3A4 je primarni enzim koji metabolizira većinu benzodiazepina, dok su CYP2C19 i CYP2D6 također često uključeni, što može dovesti do promjena koncentracija ako se uzimaju zajedno s prethodno navedenim antidepresivima (14). Kada se alprazolam primjenjuje s fluoksetinom, dolazi do povećanja koncentracije alprazolama u plazmi za približno 30 %, što je povezano s većim psihomotornim oštećenjem, evidentnim u lošijim rezultatima psihomotornih testova (15). Fluoksetin također povećava koncentracije i diazepama smanjujući klirens i produžujući poluvijek eliminacije. Međutim, ta interakcija nije dovela do klinički vidljivih oštećenja (16). Triazolam i midazolam se intenzivno metaboliziraju putem enzima CYP3A4 (14). Međutim, istraživanja nisu pronašla značajne promjene u njihovim koncen-

Among antidepressants, SSRIs particularly stand out due to their pharmacokinetic effects caused by their influence on hepatic CYP enzymes. Three SSRIs emerge as potent CYP enzyme inhibitors: fluoxetine, fluvoxamine, and paroxetine (12, 13). Among benzodiazepines metabolized through Phase I reactions that involve CYP enzymes are alprazolam, diazepam, clonazepam, midazolam, and triazolam. CYP3A4 is the primary enzyme metabolizing most benzodiazepines, while CYP2C19 and CYP2D6 are also often involved, which can lead to potential concentration changes if they are co-administered with aforementioned antidepressants (14). When alprazolam is administered with fluoxetine, the concentration of alprazolam in the plasma increases by approximately 30%, which is associated with greater psychomotor impairment, evident in lower results in psychomotor tests (15). Fluoxetine also increases the concentrations of diazepam by decreasing clearance and prolonging elimination half-life. However, this interaction did not cause observable clinical impairments (16). Triazolam and midazolam are extensively metabolized by the CYP3A4 enzyme (14). However, studies have found no significant

tracijama kada se ti lijekovi uzimaju s fluoksetinom (17,18). Kao inhibitor CYP2C i CYP1A2, fluvoksamin može povećati koncentracije diazepama i alprazolama (19,20). Perucca i sur. (19) su primijetili da istovremena primjena diazepama s fluvoksaminom može dovesti do povećanja vršnih koncentracija diazepama u plazmi, smanjenja klirensa i produljenja poluvijeka eliminacije pa je preporučljivo da pacijenti koji koriste fluvoksamin ne uzimaju istovremeno i benzodiazepine koji se primarno metaboliziraju oksidacijom (19). Fleishaker i sur. (20) su pokazali da fluvoksamin može značajno smanjiti klirens alprazolama što rezultira približno udvostručenim koncentracijama tog lijeka u plazmi, te dovodi do većeg oštećenja psihomotoričkih sposobnosti i pamćenja u usporedbi sa svakim lijekom posebno (20). Farmakokinetičke interakcije sertralina i paroksetina s diazepamom također su proučavane no nisu pronađene klinički relevantne promjene (21,22). Sertralin pri 200 mg/dan je uzrokovao smanjenje klirensa diazepama za 13 % u usporedbi s placebom, ali ta promjena se ne smatra značajnom (21).

Antibiotici i antimikotici

Poznato je da antibiotici imaju potencijal za interakcije s lijekovima putem inhibicije ili indukcije CYP enzima. Među različitim skupinama antibiotika, makrolidi, rifamicini i fluorokinoloni su pokazali najznačajnije učinke na metabolizam drugih lijekova uključujući i benzodiazepine (23) (tablica 1). Istraživanje Luurile i sur. (24) pokazalo je da eritromicin, inhibitor CYP3A4, umjereno utječe na farmakokinetiku diazepama i flunitrazepama. Zabilježeno je povećanje koncentracije diazepama u plazmi za 63 % i produljenje poluvijeka eliminacije za 70 % te dvostruko produljenje poluvijeka eliminacije flunitrazepama prilikom uzimanja navedenih lijekova s eritromicinom. Međutim, ove interakcije bile su od male kliničke važnosti, bez značajnih promjena u psihomotornim učincima (24). Benzodiazepin koji je pokazao značajnu interakciju s eritromicinom je midazolam. Studija Olkkole i sur. (25) pokazala je

changes in their concentrations when these drugs are taken with fluoxetine (17, 18). As an inhibitor of CYP2C and CYP1A2, fluvoxamine can increase the concentrations of diazepam and alprazolam (19, 20). Perucca et. al (19) found that concurrent administration of diazepam with fluvoxamine can lead to increased peak plasma diazepam concentrations, reduced clearance and prolonged elimination half-life, therefore it is recommended that patients using fluvoxamine should not combine it with benzodiazepines that are primarily metabolized by oxidation (19). Fleishaker et al. (20) demonstrated that fluvoxamine can significantly reduce the clearance of alprazolam, resulting in approximately doubled plasma concentrations of this drug, which leads to greater impairment of psychomotor skills and memory compared to each drug alone (20). Pharmacokinetic interactions of sertraline and paroxetine with diazepam were also studied, however, no clinically relevant changes were found (21, 22). A dose of 200 mg/day of sertraline caused a 13% decrease in diazepam clearance compared to the placebo, however this change is not considered meaningful (21).

Antibiotics and antimycotics

It is well-known that antibiotics have a potential for drug-drug interactions due to inhibition or induction of CYP enzymes. Among various classes of antibiotics, macrolides, rifamycins, and fluoroquinolones have shown the most significant effects on the metabolism of other drugs, including benzodiazepines (23) (Table 1). It was observed in the study conducted by Luurila et al. (24) that erythromycin, a CYP3A4 inhibitor, moderately affects diazepam and flunitrazepam pharmacokinetics. It was noted that the diazepam plasma concentration increased by 63% and the elimination half-life was prolonged by 70%, while the elimination half-life of flunitrazepam was doubled when these drugs were taken together with erythromycin. However, these interactions were of minor clinical importance, and caused no significant changes in psychomotor effects (24). A benzodiazepine that showed significant interaction when administered together with erythromycin

da eritromicin gotovo trostruko povećava maksimalnu koncentraciju midazolama u plazmi, produljuje poluvijek eliminacije s 2,4 na 5,7 sati te povećava oralnu bioraspoloživost s 33 % na 82 %. Posljedica navedenih promjena su snažniji i dulji sedativni učinci s psihomotornim oštećenjima koja traju i do 6 sati, stoga se preporučuje smanjiti doze midazolama za 50-75 %. ako se koristi u kombinaciji s eritromicinom. Klaritromicin je još jedan antibiotik koji značajno utječe na kinetiku midazolama, najvjerojatnije inhibicijom CYP3A. Ova interakcija je dovela do smanjenja klirensa midazolama, povećanja njegove biodostupnosti u jetri te dvostrukog povećanja vremena spavanja (interval između trenutka kada blagi zvučni podražaji više ne mogu probuditi pacijente i trenutka kada su još uvijek budni i svjesni takvih podražaja) (26). Antituberkulotici također mogu djelovati na metabolizam drugih lijekova putem farmakokinetičkih mehanizama, prvenstveno uključujući CYP1A2, CYP2C9/10, CYP2C19, CYP2E1 i CYP3A3/4. Rifampicin, koji djeluje kao induktor, i izoniazid, koji je inhibitor, su tuberkulotici s najznačajnijim mogućnostima interakcija (27). Studija Ochs i sur. (28) pokazala je da izoniazid može značajno produljiti poluvijek eliminacije diazepama s 34 na 45 sati i smanjiti njegov klirens. Nasuprot tome, pacijenti na kombiniranoj terapiji koja uključuje rifampicin pokazali su skraćeni poluvijek eliminacije diazepama s 58 na 14 sati te povećan klirens (28). Antimikotici, posebno azoli, također mogu imati značajan utjecaj na CYP enzime (29). Pacijenti kod kojih je itrakonazol primjenjivan istovremeno s midazolamom ili triazolamom pokazali su povećane teškoće na testovima psihomotorike, sugerirajući moguću izraženiju sedaciju, pospanost te oštećenu koordinaciju kao posljedicu kombinacije navedenih lijekova. Budući da je itrakonazol potentan inhibitor CYP3A4 koji značajno povećava koncentracije midazolama i triazolama u plazmi te produžuje njihov poluvijek eliminacije čak i pri niskim dozama (100 mg), istovremenu primjenu ovih lijekova treba izbjegavati (30). Učinak itrakonazola na konis midazolam. A study conducted by Olkkola et al. (25) found that erythromycin increased the maximum midazolam plasma concentration (Cmax) by almost three times, prolonged the elimination half-life from 2.4 to 5.7 hours, and increased its oral bioavailability from 33% to 82%. This led to stronger and longer-lasting sedative effects, with psychomotor impairment lasting up to six hours, therefore it was recommended to reduce midazolam doses by 50-75% if they are administered together with erythromycin. Clarithromycin is another antibiotic that has a significant effect on midazolam kinetics, most likely due to CYP3A inhibition. This interaction led to reduced midazolam clearance, its increased hepatic bioavailability, and a doubled sleep time (the interval between the moment when mild auditory stimuli can no longer wake the patient and the moment when they are still awake and aware of such stimuli.) (26). Antituberculotic drugs can affect the metabolism of other medications as well, through pharmacokinetic mechanisms primarily involving CYP1A2, CYP2C9/10, CYP2C19, CYP2E1, and CYP3A3/4. Rifampicin, which acts as an inducer, and isoniazid, an inhibitor, are antituberculotics with the most significant drug-drug interactions (27). A study by Ochs et al. (28) found that isoniazid can significantly prolong the elimination half-life of diazepam from 34 to 45 hours, and can reduce its clearance. In contrast, patients on a combination therapy which includes rifampicin showed a shortened diazepam elimination half-life from 58 to 14 hours, and increased clearance (28). Antimycotics, particularly azoles, can also significantly interact with CYP enzymes (29). Patients who were administered itraconazole together with midazolam or triazolam showed increased difficulty in their psychomotor tests, suggesting a more pronounced sedation, drowsiness, and impaired coordination as a consequence of combining these drugs. Since itraconazole is a potent CYP3A4 inhibitor that markedly increases plasma concentrations of midazolam and triazolam, and prolongs their elimination half-life even at low doses (100 mg), this drug combination should be avoided (30). The effect of itraconazole

centracije diazepama također je proučavan te su primijećene neznatne farmakokinetičke interakcije bez kliničke važnosti, pa se, za razliku od midazolama i triazolama, diazepam može koristiti u normalnim dozama prilikom kombiniranja s itrakonazolom (31). Isavukonazol je noviji antimikotik širokog spektra te je posebno istraživana njegova mogućnost interakcije s drugim lijekovima. Njegov učinak inhibicije CYP3A4 prikazan je kroz interakcije s raznim supstratima CYP3A4, među kojima je i midazolam. Kada se midazolam primjenjuje zajedno s isavukonazolom, koncentracija midazolama u krvi značajno se povećava, pri čemu se njegov Cmax povećava i za 72 % (32).

Oralni kontraceptivi

Žene su sklonije doživljavanju anksioznosti u odnosu na muškarce zbog čega često koriste psihotropne lijekove. Mnoge žene koriste oralne kontraceptive (OK) koji mogu inhibirati enzime CYP1A2, CYP3A4, CYP2C19 i CYP2D6 odgovorne za metabolizam mnogih psihotropnih lijekova, uključujući benzodiazepine (33) (tablica 1.). Iako su provođena istraživanja o interakcijama između oralnih kontraceptiva i benzodiazepina, pokazalo su da većina interakcija nije klinički značajna (34-37). Međutim, primijećeno je da OK mogu usporiti eliminaciju alprazolama i triazolama smanjujući njihov klirens (34,35), te ubrzati eliminaciju temazepama i lorazepama (35). OK mogu i povećati glukuronidaciju lorazepama i oksazepama, što dovodi do brže eliminacije i povećanog klirensa tih lijekova. To može značiti da će žene koje koriste OK potencijalno trebati veće doze lorazepama i oksazepama kako bi postigle terapijske razine (36). Ipak, potrebna su dodatna istraživanja kako bi se u potpunosti razjasnila klinička važnost ovih farmakokinetičkih interakcija (34-37).

Antisekretorni lijekovi

Antisekretorni lijekovi, kao što su inhibitori protonske pumpe (IPP) i antagonisti histaminskih receptora, često se koriste za liječenje

on diazepam concentrations was also studied and minor pharmacokinetic interactions with no clinical significance were observed, therefore, unlike midazolam and triazolam, diazepam can be used in normal doses if combined with itraconazole (31). Isavuconazole is a novel broad-spectrum antifungal agent, and its drug-drug interactions were especially studied. Its CYP3A4 inhibitory effect was demonstrated through interactions with various CYP3A4 substrates, among which was midazolam. When midazolam is co-administered with isavuconazole, midazolam concentrations in blood increase substantially, and its Cmax increases by as much as 72 % (32).

Oral contraceptives

Women are more likely than men to experience anxiety, which is why they often use psychotropic medications. Many women use oral contraceptives (OCs) which can inhibit CYP1A2, CYP3A4, CYP2C19 and CYP2D6 enzymes responsible for the metabolism of many psychotropic drugs, including benzodiazepines (33) (Table 1). Although studies have been conducted on the interactions between oral contraceptives and benzodiazepines, most have shown no clinically relevant interactions (34-37). It was observed, however, that OCs can impair the elimination of alprazolam and triazolam by lowering their clearance (34, 35), and can accelerate the elimination of temazepam and lorazepam (35). OCs can also increase the glucuronidation of lorazepam and oxazepam, resulting in faster elimination and increased clearance of these drugs. This may suggest that women taking OCs could potentially require higher doses of lorazepam and oxazepam in order to achieve therapeutic levels (36). However, additional research is needed in order to fully elucidate the clinical significance of these pharmacokinetic interactions (34-37).

Antisecretory drugs

Antisecretory drugs, such as proton pump inhibitors (PPIs) and histamine receptor antagonists, are commonly used to treat conditions involving

pretjerane sekrecije želučane kiseline. Poznato je da mogu utjecati na koncentracije drugih lijekova, prvenstveno zbog svog učinka na pH želučane kiseline te metabolizma putem jetrenih CYP enzima (38). U istraživanju Locniskara i sur. (39) ispitanici su dobivali 10 mg intravenskog diazepama istovremeno s cimetidinom četiri puta dnevno. Pokazalo se da cimetidin povećava poluvijek eliminacije diazepama s 55 na 72 sata, smanjuje ukupni klirens diazepama te povećava površinu ispod krivulje (AUC) za desmetildiazepam (aktivni metabolit diazepama), što može rezultirati pojačanim i produljenim sedativnim učinkom (39) (tablica 1.). Učinak cimetidina na oksazepam i lorazepam također je proučavan. Utvrđeno je da kombinacija ovih lijekova nema značajan učinak na farmakokinetičke parametre, stoga se oksazepam i lorazepam mogu sigurno koristiti s cimetidinom (40). Omeprazol pokazuje slične interakcije s diazepamom kao i cimetidin te dovodi do smanjenja klirensa diazepama i produljenja poluvijeka eliminacije (41). Intenzitet ove interakcije ovisi o brzini kojom osoba metabolizira omeprazol: kod brzih metabolizatora omeprazola, klirens diazepama može se smanjiti za oko 26 %, a poluvijek eliminacije diazepama može se povećati za oko 20 %, Nasuprot tome, spori metabolizatori pokazuju malo ili nimalo interakcija, pa mogu sigurno koristiti kombinacije prethodno navedenih lijekova (42).

Antiepileptici

Antiepileptici (AED) se primarno koriste za liječenje epilepsije, često u kombinaciji s drugim lijekovima. Većina se metabolizira u jetri uz pomoć enzima CYP2C9, CYP2C19 i CYP3A4, te uridin difosfat glukuronosiltransferaze. AED mogu djelovati kao induktori ili inhibitori navedenih enzima što može utjecati na njihov vlastiti metabolizam i metabolizam drugih lijekova koji se koriste istovremeno (43). Fenitoin i fenobarbital su poznati induktori više skupina CYP enzima te se pokazalo da mogu značajno utjecati na farmakokinetiku klonazepama. Fenitoin može sma-

excessive gastric acid secretion. They are known to interact with the concentrations of other medications, primarily due to their effect on gastric pH and metabolism due to hepatic CYP enzymes (38). In a study conducted by Locniskar et al. (39), the subjects received 10 mg of intravenous diazepam concurrently with cimetidine four times a day. It was observed that cimetidine increases diazepam elimination half-life from 55 to 72 hours, reduces total diazepam clearance, and increases the area under the curve (AUC) for desmethyldiazepam (the active metabolite of diazepam), which could all result in enhanced and prolonged sedative effects (39) (Table 1). Cimetidine interactions with oxazepam and lorazepam were also studied. It was observed that this drug combination has no significant effect on any pharmacokinetic parameters, therefore oxazepam and lorazepam can safely be used with cimetidine (40). Omeprazole was shown to have similar interactions with diazepam as cimetidine, and leads to reduced diazepam clearance, and increased elimination half-life (41). The intensity of this interaction depends on how quickly a person metabolizes omeprazole: in rapid metabolizers of omeprazole, diazepam clearance can decrease by about 26%, and diazepam elimination half-life can increase by about 20%. In contrast, slow metabolizers show little to no interactions at all, therefore they can safely use combinations of the aforementioned drugs (42).

Antiepileptics

Antiepileptic drugs (AEDs) are primarily used in the treatment of epilepsy, often in combination with other medications. They are mostly metabolized in the liver by the CYP2C9, CYP2C19 and CYP3A4 enzymes, and by the uridine diphosphate glucuronosyltransferase. AEDs have the potential to act as inducers or inhibitors of these enzymes, which can affect their own metabolism and the metabolism of other concurrently administered drugs (43). Phenytoin and phenobarbital are known inducers of several types of CYP enzymes, and have been shown

njiti poluvijek eliminacije klonazepama za 31 %, povećati klirens za 46-58 % te smanjiti koncentraciju u plazmi za 28 %. Fenobarbital ima blaže učinke, smanjujući poluvijek eliminacije za 10 %, povećavajući klirens za 19-24 % i smanjujući koncentracije u plazmi za 11 %. Međutim, kliničko značenje ovih promjena još uvijek nije u potpunosti razjašnjeno (44). Tang i sur. (45) su u svom istraživanju pokazali da je 8 od 30 pacijenata imalo nuspojave poput pospanosti i vrtoglavice za vrijeme istovremenog uzimanja lorazepama i valproata. Smatra se kako su ovi simptomi rezultat inhibicije glukuronidacije lorazepama, vjerojatno zbog izravnog djelovanja valproata na glukuronidacijske enzime. Stoga se preporučuje primjena najniže učinkovite doze lorazepama uz praćenje pacijenata kada se koristi u kombinaciji s valproatom (45) (tablica 1.). Backman i sur. (46) su usporedili farmakokinetiku oralnog midazolama kod 6 pacijenata s epilepsijom koji su uzimali karbamazepin ili fenitoin sa 7 zdravih ljudi u kontrolnoj skupini. Utvrđeno je da je kod pacijenata s epilepsijom površina ispod krivulje (engl. *area under the curve*, AUC) koncentracije midazolama u plazmi bila tek 5,7 % od vrijednosti kod kontrolnih osoba, vršna koncentracija midazolama samo 7,4 % vrijednosti u kontrolnoj skupini, a poluvijek eliminacije je bio značajno kraći. Takvi rezultati su posljedica indukcije CYP3A enzima antiepilepticima, što ukazuje da su potrebne veće doze midazolama za postizanje željenih hipnotičkih učinaka ako se primjenjuje zajedno s karbamazepinom ili fenitoinom (46).

Farmakodinamske interakcije benzodiazepina

Benzodiazepini djeluju modulirajući aktivnost GABA-A receptora, unutar glavnog inhibicijskog sustava u SŽS-u. Vežući se za specifična mjesta na GABA-A receptorima, povećavaju učestalost otvaranja kloridnih kanala, čime pojačavaju inhibiciju i smanjuju neuronsku ekscitaciju. To ima za posljedicu sedativne, anksiolitičke i antikonvulzivne učinke (3,4). Kada se benzodiazepini

to affect the pharmacokinetics of clonazepam. Phenytoin can decrease the elimination half-life of clonazepam by 31%, increase clearance by 46-58 %, and lower plasma concentrations by 28%. Phenobarbital has milder effects, decreasing the elimination half-life by 10%, increasing clearance by 19-24 %, and lowering the plasma concentrations by 11%. However, the direct clinical impact of these changes has still not been fully clarified (44). In their study, Tang et al. (45) found that 8 out of 30 patients experienced side effects such as drowsiness and dizziness when taking lorazepam and valproic acid at the same time. These symptoms are considered to be the result of inhibition of lorazepam glucuronidation, presumably due to the direct effects of valproic acid on glucuronidation enzymes. It is, therefore, recommended to use the lowest effective doses of lorazepam when combined with valproic acid, with close patient monitoring (45) (Table 1). Backman et al. (46) compared the pharmacokinetics of oral midazolam in six epilepsy patients taking carbamazepine or phenytoin to seven healthy control subjects. It was determined that the area under the curve (AUC) of midazolam plasma concentration in the epilepsy patients amounted to only 5.7% of the control subjects' value, the peak midazolam concentration amounted to only 7.4% of the control subjects' value, while the elimination half-life was significantly shorter. These results were likely caused by the induction of CYP3A enzymes due to the antiepileptics, which indicates that higher doses of midazolam are required in order to produce the desired hypnotic effects if it is administered together with carbamazepine or phenytoin (46).

Pharmacodynamic interactions of benzodiazepines

Benzodiazepines act by modulating the activity of GABA-A receptors, within the main inhibitory system in the CNS. By binding to specific sites on GABA-A receptors, they increase the frequency of chloride channel openings, thus enhancing

zepini koriste s drugim depresorima središnjeg živčanog sustava,mogu imati ozbiljne posljedice poput pojačane sedacije i respiratorne depresije, čime se povećava rizik od smrti (47).

Etanol

Benzodiazepini i alkohol u kombinaciji djeluju aditivno zbog svojih zajedničkih učinaka na GABA sustav, pojačavajući sedaciju, kognitivne smetnje i psihomotornu depresiju (tablica 2.). Ova kombinacija pokazala je povećan rizik od nuspojava i predoziranja (48). Morland i sur. (49) usporedili su kombinirane učinke diazepama i etanola s učincima svake tvari pojedinačno te su primijetili da ispitanici doživljavaju pojačane subjektivne smetnje smanjene koncentracije, motivacije i pažnje, kao i lošije rezultate na testovima složene koordinacije (49). Triazolam je također pokazao aditivne farmakodinamske učinke s etanolom koji su se očitovali u povećanoj posturalnoj nestabilnosti te oštećenju vizualno-motoričke koordinacije i pamćenja (50). Triazolam, kao i temazepam, može dovesti do značajnih kliničkih oštećenja čak i ako se kombiniraju samo s umjerenim dozama etanola (51). Linnoila i sur. (52) pokazali su da je verbalno procesuiranje informacija posebno osjetljivo na kombinirane učinke alprazolama i alkohola. Njihova istraživanja pokazala su izraženo oštećenje u navedenom kognitivnom području prilikom primjene alprazolama u kombinaciji s alkoholom ističući time specifičnu interakciju koja nije uočena s drugim benzodiazepinima (52). U svakom slučaju, zbog značajnog povećanja rizika od ozbiljnih nuspojava i oštećenja, izuzetno je važno izbjegavati konzumaciju alkohola istovremeno s uzimanjem benzodiazepina.

Opioidi i anestetici

Istraživanja su pokazale da opioidi mogu modulirati GABA-ergičku aktivnost i obratno. Povećano provođenje kloridnih iona zbog djelovanja benzodiazepina i smanjeno otpuštanje ekscitatornih neurotransmitera zbog djelovanja opioi-

inhibition and reducing neuronal excitability. This produces sedative, anxiolytic and anticonvulsant effects (3, 4). When used with other central nervous system depressants, benzodiazepines can have serious consequences such as enhanced sedation and respiratory depression, consequently increasing the risk of death (47).

Ethanol

Benzodiazepines and alcohol interact additively due to their shared effects on the GABA system, enhancing sedation, cognitive impairment and psychomotor depression (Table 2). This combination has been shown to increase the risk of side effects and overdose (48). Morland et al. (49) compared the combined effects of diazepam and ethanol to the effects of each substance alone, and observed that subjects experienced increased subjective impairments of reduced concentration, motivation and attention, as well as worse performance on complex coordination tests (49). Triazolam also showed additive pharmacodynamic effects in combination with ethanol, which manifested in increased postural instability, and impaired visual-motor coordination and memory (50). Triazolam, as well as temazepam, could produce significant clinical impairments even when combined with only moderate doses of ethanol (51). Linnoila et al. (52) demonstrated that verbal information processing is particularly vulnerable to the combined effects of alprazolam and alcohol. Their findings revealed a pronounced impairment in this specific cognitive domain when alprazolam was administered in conjunction with alcohol, thus highlighting a unique interaction which was not observed with other benzodiazepines (52). In any case, due to a significant increase in the risk of serious side effects and impairments, it is crucial to avoid consuming alcohol while taking benzodiazepines.

Opioids and anesthetics

Studies have shown that opioids can modulate GABAergic activity and vice versa. An increased conduction of chloride ions due to benzodiaze-

da može rezultirati sinergističkim depresivnim učinkom na SŽS (53). Prilikom primjene pojedinačne doze diazepama kod pacijenata koji se liječe metadonom i buprenorfinom primijećena je intenzivnija sedacija te porast jačine učinaka lijekova za obje skupine pri čemu je skupina korisnika metadona također pokazala povećanu euforiju, a skupina korisnika buprenorfina posebno povećanu sedaciju (54) (tablica 2.). Kombinirano korištenje benzodiazepina povezano je sa slučajevima predoziranja buprenorfinom. Reynaud i sur. (55) zabilježili su značajan broj kliničkih slučajeva respiratorne depresije izazvane buprenorfinom u terapijskim dozama pri čemu su u većini slučajeva bili prisutni i benzodiazepini (55). Bailey i sur. (56) su istražili respiratorne učinke midazolama i fentanila, sintetičkog opioida, u slučajevima kada se koriste samostalno te u kombinaciji. Pokazali su da kombinacija tih dvaju lijekova značajno povećava učestalost hipoksemije i apneje. Budući da se midazolam, kao i drugi benzodiazepini,

pines and reduced excitatory neurotransmitter release due to opioids can result in a synergistic depressant effect on the CNS (53). When single doses of diazepam are administered to patients treated with methadone and buprenorphine, increased sedation and stronger drug effects for both groups were observed. The methadone group also showed increased euphoria and the buprenorphine group showed particularly increased sedation (54) (Table 2). Concomitant use of benzodiazepines is connected with cases of buprenorphine overdose. Reynaud et al. (55) recorded a significant number of clinical cases of respiratory depression caused by buprenorphine at therapeutic doses, wherein the majority of cases involved benzodiazepines as well (55). Bailey et al. (56) investigated the respiratory effects of midazolam and fentanyl, a synthetic opioid, in cases when used alone and in combination. They showed that the combination of the two drugs significantly increases the incidence of hypoxemia and apnea. Since midazolam, as well as other benzodiazepines, can be used during an-

TABLICA 2. Klinički značajne farmakodinamske interakcije benzodiazepina s lijekovima
TABLE 2. Clinically significant pharmacodynamic interactions of benzodiazepines with drugs

LIJEK / DRUG	Mehanizam interakcije / Mechanism of interaction	Benzodiazepini koji ulaze u interakcije i kliničko značenje / Benzodiazepines that interact and clinical significance
Etanol / Ethanol	intenziviranje učinaka GABA-ergičkog sustava / intensification of GABAergic system effects	• diazepam: subjektivne smetnje smanjene koncentracije, motivacije i pažnje / diazepam: subjective disturbances such as reduced concentration, motivation and attention • triazolam: posturalna nestabilnost / triazolam: postural instability • temazepam: klinička oštećenja čak i pri umjerenim dozama etanola • / temazepam: clinical impairments even at moderate doses of ethanol • alprazolam: oštećenje verbalnog procesuiranja informacija • / alprazolam: impairment of verbal information processing
Metadon / Methadone Buprenorfin / Buprenorphine	modulacija GABA-ergičkog sustava / modulation of GABAergic system	diazepam: intenzivnija sedacija; rizik od respiratorne depresije / diazepam: intensified sedation; risk of respiratory depression
Fentanil / Fentanyl	modulacija GABA-ergičkog sustava / modulation of GABAergic system	midazolam: povećanje učestalosti hipoksemije i apneje / midazolam: increased incidence of hypoxemia and apnea
Naltrekson / Naltrexone	antagonist opioidnih receptora – modifikacija učinaka benzodiazepina / opioid receptor antagonist – benzodiazepine effects modification	diazepam: ↑ negativnih emocionalnih stanja ↓ pozitivnih emocionalnih stanja / diazepam: ↑ negative emotional states ↓ positive emotional states
Barbiturati / Barbiturates	povećanje provodljivosti kloridnih iona GABA receptora / increased chloride ion conductivity of GABA receptors	većina benzodiazepina: pojačano vezanje benzodiazepina na receptore – sinergističke interakcije / most benzodiazepines: increased binding of benzodiazepines to receptors – synergistic interactions
Propofol / Propofol	pojačan učinak GABA-ergičkog sustava / enhanced GABAergic system effect	midazolam: sinergističko djelovanje u postizanju hipnotičkog učinka / midazolam: synergistic action in achieving hypnotic effect

može koristiti tijekom anestezije u kombinaciji s opioidima, preporučuje se oprezna primjena i praćenje (56). Naltrekson je antagonist opioida za koji je pokazano da modificira subjektivne i objektivne učinke intoksikacije diazepamom. Naltrekson može povećati negativna emocionalna stanja (sedaciju, umor, anksioznost) i smanjiti pozitivna emocionalna stanja (druželjubivost, energiju, osjećaj euforije), što ukazuje da naltrekson može pomoći u smanjenju zloupotrebe benzodiazepina smanjujući pozitivne učinke povezane s intoksikacijom (57) (tablica 2).

Barbiturati se koriste kao anestetici, hipnotici, anksiolitici te antikonvulzivni lijekovi. Izravno povećavaju provođenje kloridnih iona posredovano GABA-om te mogu pojačati vezanje benzodiazepina na njihove receptore (58) (tablica 2.). Midazolam i tiopental pokazali su sinergističke interakcije prilikom istovremenog korištenja za indukciju anestezije (59). Midazolam je također pokazao, čak i u dozama koje nisu dovoljne za postizanje anestezije samostalno, da pojačava učinkovitost tiopentona uspješno inducirajući hipnozu i anesteziju (60). Propofol je ne-barbituratni anestetik koji se koristi za indukciju i održavanje anestezije. McClune i sur. (61) istraživali su način na koji midazolam i propofol međusobno djeluju u postizanju hipnotičkih učinaka kada se koriste u kombinaciji. Pokazali su da ova dva lijeka ispoljavaju sinergističko djelovanje u postizanju hipnotičkog učinka. Kada se primjenjuju kombinirano, niže doze svakog lijeka mogu postići jednaku razinu anestezije kao i više doze pojedinačnih lijekova. Ovakav pristup omogućuje stabilniju indukciju anestezije uz potencijalno smanjenje nuspojava (61).

ZAKLJUČAK

Benzodiazepini su često korišteni lijekovi za liječenje anksioznosti i drugih psihičkih poremećaja. Iako se općenito smatraju lijekovima s dobrim sigurnosnim profilom, napretkom u razumijevanju njihovih metaboličkih puteva iden-

esthesia in combination with opioids, cautious administration and close monitoring are recommended (56). Naltrexone is an opiate antagonist and it was found to modify the subjective and objective effects of diazepam intoxication. Naltrexone can increase negative emotional states (sedation, fatigue, anxiety) and decrease positive emotional states (friendliness, vigor, sense of euphoria), which indicates that naltrexone may help reduce benzodiazepine abuse by diminishing the positive effects associated with intoxication (57) (Table 2).

Barbiturates are used as anesthetics, hypnotics, anxiolytics, and anticonvulsants. They directly increase GABA-mediated conduction of chloride ions and have the potential to enhance the binding of benzodiazepines to their receptors (58) (Table 2). Midazolam and thiopental were shown to have synergistic interactions when used in combination for anesthesia induction (59). It was also shown that, even at doses not sufficient to produce anesthesia on its own, midazolam enhances the potency of thiopentone by successfully inducing hypnosis and anesthesia (60). Propofol is a non-barbiturate anesthetic used for the induction and maintenance of anesthesia. McClune et al. (61) investigated the manner in which midazolam and propofol interact in achieving hypnotic effects when used in combination. They showed that these two drugs have a synergistic interaction in achieving their hypnotic effects. When administered together, lower doses of each drug can produce the same level of anesthesia as higher doses of either drug alone. This approach could allow for a more stable induction of anesthesia, potentially with fewer side effects (61).

CONCLUSION

Benzodiazepines are medications commonly used for the treatment of anxiety and other mental disorders. While they are generally considered to have a favorable safety profile, numerous drug-drug interactions have been identified

tificirane su brojna uzajamna djelovanja s drugim lijekovima. Ključne interakcije zabilježene su s antidepresivima, antibioticima i antimikoticima, oralnim kontraceptivima, antisekretornim lijekovima, antiepilepticima te depresorima središnjeg živčanog sustava uključujući alkohol, opioide i anestetike. Takve interakcije mogu dovesti do promjena koncentracije benzodiazepina u plazmi, produljenog poluvijeka eliminacije te pojačanih ili umanjenih terapijskih učinaka kao i brojnih neočekivanih nuspojava. Međutim, kliničko značenje mnogih od ovih interakcija još nije u potpunosti utvrđeno pa su potrebna daljnja istraživanja kako bi se razjasnila relevantnost opaženih farmakokinetičkih i farmakodinamičkih promjena. Nužno je poznavati potencijalne farmakološke interakcije, razmotriti alternativne opcije, ako se identificiraju visokorizične kombinacije lijekova, te prilagoditi doze prema potrebi na temelju individualnih odgovora pacijenata, kako bi se optimizirala sigurna i učinkovita uporaba benzodiazepina u kliničkoj praksi.

as an understanding of their metabolic pathways has improved. Key interactions have been observed with antidepressants, antibiotics and antimycotics, oral contraceptives, antisecretory drugs, antiepileptic medications, and central nervous system depressants, including alcohol, opioids and anesthetics. These interactions can lead to altered benzodiazepine plasma concentrations, prolonged elimination half-lives and enhanced or diminished therapeutic effects, as well as many unexpected side effects. However, the clinical significance of many of these interactions has not yet been fully established, so further research is still necessary in order to clarify the relevance of the observed pharmacokinetic and pharmacodynamic changes. Clinicians should know the potential pharmacological interactions, consider alternative options if high-risk drug combinations are identified, and adjust dosages when necessary, based on the individual patient responses, in order to optimize the safe and effective use of benzodiazepines in clinical practice.

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