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CLINICALLY SIGNIFICANT PSYCHOTROPIC DRUG-DRUG INTERACTIONS IN THE PRIMARY CARE SETTING

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Abstract

In recent years, the growing numbers of patients seeking care for a wide range of psychiatric illnesses in the primary care setting has resulted in an increase in the number of psychotropic medications prescribed. Along with the increased utilization of psychotropic medications, considerable variability is noted in the prescribing patterns of primary care providers and psychiatrists. Because psychiatric patients also suffer from a number of additional medical comorbidities, the increased utilization of psychotropic medications presents an elevated risk of clinically significant drug interactions in these patients. While life-threatening drug interactions are rare, clinically significant drug interactions impacting drug response or appearance of serious adverse drug reactions have been documented and can impact long-term outcomes. Additionally, the impact of genetic variability on the psychotropic drug's pharmacodynamics and/or pharmacokinetics may further complicate drug therapy. Increased awareness of clinically relevant psychotropic drug interactions can aid clinicians to achieve optimal therapeutic outcomes in patients in the primary care setting.

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INTRODUCTION

Clinicians within the primary care setting are increasingly providing pharmacotherapy management of patients with psychiatric illnesses, with over 25% of primary care patients seeking care for major depression and 14% for schizophrenia [1, 2]. Within the primary care setting, prescriptions for psychotropic medications have increased by 48%, with primary care providers (PCPs) writing 65% and 80% of all anxiolytic and antidepressant prescriptions respectively [3]. Additionally, recent surveys have shown that office-based physicians routinely prescribe medications off-label for which evidence based guidelines or FDA-approval status is lacking, especially for psychotropics [4]. Studies have also demonstrated difference in prescribing practices of psychotropic medications based upon professional and consumer advertising, socioeconomic status and ethnicity [5–8]. However, despite the precipitous increase in psychotropic medications prescribed for patients within the primary care setting, studies reporting on the utilization of psychotropics in managing patients with mental illness by PCPs vary considerably from that of psychiatrists, demonstrating an increased need in clarifying the use of psychotropics in primary care patients [9, 10].

In addition to the myriad of mental illnesses encountered by PCPs, patients with psychiatric disorders also exhibit a high prevalence of comorbid medical illnesses including obesity, diabetes, hypertension and dyslipidemia [11, 12]. The pharmacologic management of these medical comorbidities is complicated by the use of psychotropics, which often exhibit significant metabolic liabilities and increase the risk for serious drug-drug interactions (DDIs).

Clinically significant drug-drug interactions are defined as events in which the pharmacodynamic or pharmacokinetic characteristics of a drug are modified by the addition of a second drug to the patient's medication regimen, which can often result in an increase of serious adverse reactions or attenuation of efficacy [13, 14]. The two major types of DDIs include pharmacokinetic interactions and pharmacodynamic interactions [15, 16]. Pharmacodyamic interactions occur when concomitantly administered medications share similar target sites of actions (i.e. receptor) producing either additive or antagonistic effects that can enhance or weaken the physiologic effect of the primary drug respectively [17, 18]. Clinically significant pharmacodynamic DDIs can produce extrapyramidal symptoms (EPS), central nervous system (CNS) depression, seizures, serotonin syndrome and QT-interval prolongation [18, 19].

Pharmacokinetic DDIs involve modification of drug absorption, distribution, metabolism and elimination by the addition of a second drug resulting in a change (increase or decrease) of the primary drug's serum concentration and are often difficult to predict [20]. DDIs involving changes in drug absorption are often the result of changes in the physiochemical

properties of the primary drug (i.e. changes in gastric pH) leading to decreased absorption [19, 21]. Additionally, transport of a large number of drugs across the intestinal wall are regulated by transporter proteins, principally among these is P-glycoprotein (P-gp), which may play a significant role in determining blood concentrations and bioavailability of many drugs [19, 22]. Inhibition of P-gp by drugs such as verapamil result in decreased translocation of drug back into the intestinal lumen and a subsequent increase in systemic exposure of drug leading to a potential increase risk in adverse effects or enhanced efficacy [23].

DDIs involving changes in drug distribution pose a theoretical risk due to differences in protein affinity and displacement from plasma drug binding proteins (i.e. albumin) [17]. While drug interactions involving plasma binding protein displacement can result in elevation in plasma concentrations of the displaced drug, the clinical significance of these interactions is limited since displacement from binding proteins results in an increase in unbound plasma concentrations, facilitating increased metabolism and clearance of the displaced drug [24].

The majority of pharmacokinetic DDIs involve alterations in phase I metabolism by inhibition or induction of a family of cytochrome P-450 hepatic enzymes (CYP450). CYP450 enzymes consist of a superfamily of heme-containing proteins localized within the endoplasmic reticulum of the liver as well as in the brain and periphery, and are responsible for the metabolism of endogenous substances and xenobiotics [25, 26]. While approximately 40 different CYP450 enzymes have been identified, six enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) are responsible for mediating ≈90% of all CYP450 activity mediating phase I metabolism of drugs [27]. Therefore, drugs that inhibit or induce the metabolic activity of the CYP450 enzymes have the potential to affect the metabolism of concomitantly administered drugs increasing the risk of adverse effects or changes in efficacy (Table 1). Potentially clinically significant DDIs involving psychotropic medications and management considerations are listed in Tables 2 and 3. In addition to drugs that inhibit or induce CYP450s, a number of these hepatic isoenzymes exhibit single nucleotide polymorphisms (SNPs) that are single base differences in the DNA sequence that can impact the metabolic capacity or expression of the enzyme (Table 2) [28]. A polymorphism is traditionally defined as a least occurring allele in 1% or more of the population. These genotypic variants can occur in the coding or regulatory regions of the gene responsible for transcribing the CYP450. These SNPs can produce variable phenotypes in CYP450 activity such as rapid metabolism of debresoquine by ultra-rapid metabolizers of CYP2D6 or increased isoniazid toxicity in slow acetylators of N-acetyl transferase 2 (NAT2) [29].

Patient case

A 57-year old man with a history of atrial fibrillation and melancholic major depression has been on a stable regimen of warfarin 5 mg/day (most recent international normalized ratio (INR) of 2.0) and desipramine 200 mg/day. The patient is also a 2–3 pack/day smoker and was subsequently prescribed bupropion titrated to 150 mg/day for smoking cessation. After being on a stable bupropion dose for 14 days, the patient reported frequent palpitations,

dizziness and confusion. His family care physician ordered an ECG that showed a sinus tachycardia at 130 beats/min and a widened QRS interval to 150 msec. The patient was admitted for cardiac monitoring and laboratory work up. The patient's laboratory work revealed a normal INR/PT, however his serum desipramine level came back at 595 ng/mL (normal range = 50–300 ng/mL). The patient had his desipramine discontinued and his sinus tachycardia and CNS symptoms were fully resolved in 1 week. In this patient's case, the addition of a moderately potent CYP2D6 inhibitor, bupropion, led to an increase in serum concentrations of desipramine producing the cardiovascular and CNS adverse effects seen in this patient.

PSYCHOTROPIC DRUG INTERACTIONS

Antipsychotics

Antipsychotics are used as both monotherapy or augmentation therapy in a number of psychiatric disorders. As a result, concomitant therapy with antipsychotics may result in pharmacokinetic interactions producing adverse reactions. Due to their large volume of distribution, lipophilicity and extensive protein binding, the metabolic clearance of most antipsychotics is remarkably slow [30].

First generation antipsychotics (FGAs) such as phenothiazines undergo biotransformation primarily by CYP2D6 with minor contributions from CYPs 1A2 and 3A4 [31]. Significant increases in antipsychotic concentration can occur if a potent CYP2D6 inhibitor is administered, i.e., paroxetine [32]. In addition to being substrates of CYP2D6, several phenothiazines also exhibit dose-dependent inhibition of CYP2D6 activity [31].

The butyrophenone, haloperidol, undergoes metabolism via CYP3A4 and UDP glucuronidation (one of many Phase II metabolism enzymes, where a water soluble molecule is added onto the drug or metabolite) and is a moderate inhibitor of CYP2D6 [33–35]. The clinical significance of DDIs involving haloperidol are limited as many studies involving CYP3A4 inhibitors have only led to small increases in haloperidol plasma concentrations resulting in no adverse effects [35]. However concomitant administration of haloperidol with inducers of CYP3A4 have been shown to significantly reduce haloperidol levels resulting in untoward clinical outcomes, i.e., exacerbation of symptoms or relapse [35].

Induction of CYP1A2 by polycyclic aromatic hydrocarbons associated with cigarette smoke can increase the clearance of several FGAs including chlorpromazine, fluphenazine and haloperidol [36–38]. Smoking cessation in patients taking FGAs has been associated with emergence of EPS-related symptoms due to a decreased clearance of the drug [39]. In smokers receiving antipsychotics, the prevalence of antipsychotic-associated EPS is significantly less than non-smokers, however the dose of antipsychotic may need to be increased due to the increased clearance associated by CYP1A2 induction [39]

Several phenothiazines and haloperidol have been identified inhibitors of P-gp, although the clinical significance of haloperidol P-gp interactions has not been fully studied [40]. Concomitant administration of these FGAs with drugs like verapamil or rifampin, which are

known inhibitors and inducers of P-gp respectively may alter the pharmacokinetic properties of these medications.

Most DDIs involving second generation antipsychotics (SGAs) occur at the metabolic level involving alterations in biotransformation by CYP450s [41]. Unlike FGAs such as phenothiazines that are known inhibitors of CYP2D6, in vitro studies of SGAs have not demonstrated alterations in CYP biotransformation of substrate medications [42]. Clozapine and its active metabolite, nor-clozapine, are primarily metabolized by CYP1A2, although other CYPs have been implicated in its biotransformation [43]. Clinically significant DDIs have been reported in patients taking fluoroquinolones or fluvoxamine, potent inhibitors of CYP1A2 [44, 45]. Conversely, drug or chemical-mediated induction of CYP1A2, has also been reported to significantly lower clozapine serum levels. Drugs such as omeprazole, carbapazepine or rifampin and aryl-hydrocarbons in cigarette smoke can significantly lower clozapine and olanzapine levels, while discontinuation of these substances may result in rebounding clozapine levels leading to toxicity [30, 46]. Aripiprazole and risperidone metabolism primarily occurs by CYP2D6 and 3A4 with increased antipsychotic levels observed in patients that demonstrate CYP2D6 poor metabolism characteristics, i.e., polymorphisms [30]. Clinically significant DDIs with inhibitors of CYP2D6 and 3A4 have been reported with risperidone, while administration of the CYP34 inhibitor, itraconazole failed to result in significant adverse reactions [47, 48].

Olanzapine undergoes metabolism via CYP1A2 and UGT with minimal contributions by CYP2D6 [41]. There are few clinically significant DDIs with olanzapine with potent inhibitors or inducers of CYP1A2 such as with medications like fluvoxamine and carbamazepine respectively [30]. However potentially significant interactions with ciprofloxacin have been reported to increase serum olanzapine levels and lead to prolonged QT-intervals [49, 50]. Some have reported DDIs with olanzapine and valproic acid, however the clinical significance of this interaction still requires thorough evaluation [51, 52]. Additionally, polycyclic aromatic hydrocarbons from smoking are potent inducers of CYP1A2 and have been shown to significantly increase olanzapine clearance by 98%, reducing serum concentrations [53]. Olanzapine-related parkinsonian symptoms have also been reported in a patient after smoking cessation [54].

Asenapine is primarily cleared by CYP1A2 and UGT and studies examining the impact of co-administration of several CYP inhibitors and inducers found that fluvoxamine and carbamazepine produced a 29% increase and 16% decrease in plasma concentrations of asenapine respectively, while the UGT inhibitor, valproate had no effect [55, 56]. The new SGA, iloperidone is primarily cleared by CYP2D6, with minor 3A4 activity and DDI studies have demonstrated that inhibitors of CYP2D6 significantly reduce the clearance of iloperidone and its metabolite posing potentially significant risks of QTc prolongation [57].

Lurasidone is a metabolized via CYP3A4 with 2 active metabolites, and highly significant interactions occurring with both enzyme inducers and inhibitors. Ketoconazole and other potent CYP3A4 inhibitors are contraindicated due to an almost 10x increase in AUC [58]. Moderate inhibitors of 3A4 (i.e. diltiazem) may be used with caution provided the dose of

lurasidone is no more than 40 mg per day [59]. Potent inducers such as rifampin can dramatically increase clearance of lurasidone [58].

Both ziprasidone and paliperidone have the least potential for drug-drug interactions via the CYP450 system. Ziprasidone metabolism is largely mediated by a non-CYP mechanism involving the aldehyde oxidase system, while the minor pathway involves CYP3A4, accounting for about 33% of its metabolism. Paliperidone, the 9-hydroxy metabolite of risperidone is largely devoid of Phase I metabolism, undergoing primarily Phase II conjugation reactions, which accounts for >60% of its metabolism.

Many SGA are also substrates for P-gp and administration of SGAs with P-gp inhibitors may produce increased adverse reactions by decreasing efflux of the drug from the CNS. Additionally, SGA such as olanzapine, quetiapine, clozapine, risperidone and paliperidone have been shown to be inhibitors of P-gp [60, 61]. In a rodent study comparing the behavioral effects of risperidone given concomitantly with the P-gp inhibitor PSC 833, rats given the combination exhibited significantly increased catalepsy compared to risperidone-vehicle treated group [62]. Because of substrate similarities between CYP3A4 and P-gp, co-administration of quetiapine with known inhibitors of CYP3A4 like HIV protease inhibitors and azole antifungals are contraindicated [40, 63].

Antidepressants

Tricyclic antidepressants (TCAs) undergo biotransformation by 4 major CYP450 (1A2, 2C9/19, 2D6 and 3A4), however they are often less problematic with respect to CYP450 inhibition than the selective serotonin reuptake inhibitors (SSRIs), although clinically significant DDIs involving inhibition of CYP2C19 have been reported [64, 65]. Secondary TCAs (desipramine and nortriptyline) are weak inhibitors of CYP2D6 and have limited DDIs, while the tertiary TCAs (amitriptyline and imipramine) are potent inhibitors of CYP2C19 [65]. Clinically significant DDIs involving TCAs are often the result of concomitant administration with other medications that inhibit CYP450 (i.e. paroxetine) resulting in decreased TCA clearance. Severe adverse reactions, including fatality have been associated with TCA and SSRI combination [66]. However, concomitant use of TCAs and SSRIs can be safely used provided that the doses of TCAs are titrated accordingly [19].

The majority of second generation antidepressants (i.e. SSRIs) undergo extensive hepatic oxidative metabolism mediated by CYP450 isoenzymes, however unlike the TCAs, newer antidepressants have a relatively wide therapeutic index, limiting the severity of adverse effects when concomitantly administered with enzyme inhibitors or inducers [67, 68]. However, a number of second generation antidepressants, especially the SSRIs and the mixed-serotonin antagonist, nefazodone have been shown to significantly inhibit CYP450 isoenzymes resulting in clinically significant DDIs [13, 69]. SSRIs such as fluoxetine and paroxetine are potent inhibitors of CYP2D6, while fluvoxamine is a potent inhibitor of CYP1A2 and 2C19 and are therefore particularly likely to cause DDIs [69]. SSRIs such as sertraline, citalopram and escitalopram at usual therapeutic dosages are generally far less likely to cause significant alterations of CYP450 status.

The selective serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine exhibit weak to moderate inhibitory actions on CYP2D6 producing limited DDI potential [70]. Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), undergoes metabolism via CYP2B6 with moderate inhibitory actions at CYP2D6, although case reports of nortriptyline and metoprolol toxicity have occurred [70–72]. The addition of bupropion to venlafaxine, significantly shifts the ratio of venlafaxine to desmethylvenlafaxine (a CYP2D6 metabolite) [73].

Other newer antidepressants such as mirtazapine and reboxetine (European) have not been reported to result in clinically significant DDIs [70, 74]. The mixed serotonin antagonist, nefazodone undergoes metabolism via CYP3A4, but is also a potent inhibitor of the enzyme [75]. DDI studies examining the PK and PD effects of nefazodone demonstrated over 400% increase in the midazolam AUC along with significant impairment in subject's cognitive function [76]. Other studies have shown that concomitant administration of nefazodone with terfenadine and loratadine produced significant prolongation of the QT-interval, nephrotoxicity when administered with tacrolimus or cyclosporine and myopathy with simvastatin [77–79]. In part due to these DDI considerations, nefazodone has been withdrawn from clinical use. Among the potentially most significant DDIs with SSRIs that inhibit CYP2D6, are the reductions in the analgesic potential of several opioid therapies [80, 81].

In addition to pharmacokinetic interactions, antidepressants have also been reported to be involved in clinically significant pharmacodynamic interactions. Pharmacodynamic effects associated with elevated TCA concentrations include enhancement of their off-target pharmacology (i.e. confusion, delirium, dry mouth, sedation, tachycardia), however serious cardiac effects have been reported with concomitant use of TCAs with CYP-inhibiting SSRIs [66, 82, 83]. Concurrent use of SSRIs with coumarin anticoagulants have also been associated with increased hospitalization due to non-GI bleeding events [84]. Another potentially life threatening PD interaction, serotonin syndrome may occur with concomitant use of serotonin-enhancing medications such as TCAs, SSRIs monoamine oxidase inhibitors (MAOIs) and mirtazapine, but has also been associated with other non-psychotropics such as linezolid, meperidine, non-subcutaneous sumatriptan and tramadol [19, 85]. The FDA even issued an alert indicating the potentially life-threatening risk of SSRIs and SNRIs used concomitantly with triptan medications [86]. Many DDIs involving MAOIs are related to PD interactions involving other medications or diet. Non-selective MAOIs (i.e. phenylzine) inhibit both MAO isoforms and can produce clinically-significant hypertension when ingestion of tyramine containing food or beverage products are consumed [87]. Selective inhibitors of MAO-B (i.e. selegiline) have not been reported to produce hypertensive-crisis associated with ingestion of dietary amines [88].

Anxiolytics

Benzodiazepines (BZDs) vary markedly with respect to their pharmacodynamic and pharmacokinetic properties. Common DDIs involving BZDs often result in an increase in pharmacologic effects of the BZD due to either enhanced pharmacodynamic effects (i.e. synergism with other GABA acting agents) or pharmacokinetic interactions (i.e. Inhibition

of CYP450 metabolism) producing elevated serum BZD concentrations. The CYP3A4 system is primarily responsible for the metabolism of the majority of BZDs, followed by CYP2C19 [89]. The 3-hydroxybenzodiazepines such as lorazepam, oxazepam and temazepam undergo Phase II conjugation reactions and are therefore devoid of CYP450 interactions [90]. Many BZDs are given concomitantly with antidepressants during the treatment of depression or anxiety disorders, however many of these medications inhibit CYP3A4, and can increase serum concentrations of the BZDs. Fluoxetine, fluvoxamine and paroxetine are potent inhibitors of CYP3A4 and 2C19 and have been shown to impact the metabolism of several benzodiazepines, increasing their serum concentrations by 30–100% [91–93]. Within the intensive care setting, reduced clearance of midazolam by routinely used concomitant medications such as fentanyl and propofol, both inhibitors of CYP3A4, has been reported [94, 95]. The increase in midazolam serum concentration with CYP3A4 inhibitors has been shown to decrease cognitive performance on symbol-digit tasks and could be associated with increased risk of ICU-related delirium [76, 96]. SSRIs such as sertraline, citalopram and escitalopram have limited impact on BZD pharmacokinetics. Other antidepressants such as nefazodone have also been shown to significantly alter BZD pharmacokinetics, often requiring dose reduction of the BZD [97, 98]. Other antidepressants such as venlafaxine, mirtazapine, duloxetine and reboxetine have limited DDI potential with BZDs [99].

Other common DDIs via CYP450 inhibition include drugs such as cimetidine, omeprazole, azole antifungals, macrolide antibiotics and antiretrovials, therefore primary care providers should exercise caution when administering these medications concomitantly with BZDs. Less common DDIs with BZDs involve alterations in UGT by valproic acid, which decreases the Phase II conjugation reactions involved in lorazepam and oxazepam metabolism [100].

Inducers of CYP3A4 or 2C19 can also impact the pharmacokinetics of BZDs by increasing metabolism and reducing elimination half-life. Drugs such as rifampin, phenytoin and hypercium (St. John’s Wort) can increase expression of CYP isoenzymes resulting in reduced serum concentrations of BZDs [89].

Compared with the classical BZDs, reports of clinically significant DDIs with non-benzodiazepine hypnotics drugs like zolpidem, zaleplon and zopiclone have been infrequently reported in the literature [101]. Zolpidem is largely dependent upon CYP3A4 for metabolism and DDIs involving azole antifungals and rifampin have been reported in the literature [102, 103]. Zopiclone is also metabolized by CYP3A4 and reports of clinically significant DDIs with rifampin and itraconazole have been reported in the literature [104]. In contrast, few clinically relevant DDIs have been reported with zaleplon [101].

Mood stabilizers

As with the BZDs drugs, DDIs involving mood stabilizers may either be pharmacodynamic or pharmacokinetic. The most clinically relevant DDIs involving antiepileptic drugs (AEDs) used as mood stabilizers involve either the induction or inhibition of drug metabolism mediated by the CYP450 system and are summarized in Table 1. AEDs such as valproic acid (VPA), carbamazepine (CBZ), lamotrigine (LTG) and topiramate (TOP) are routinely

used as either monotherapy or as augmentation therapy in mood disorders. A number of DDIs involving valproic acid have been reported in the literature [105]. Valproic acid is an inhibitor of CYP2C9 and UGT and can therefore increase the serum concentrations of a number of substrates involving these metabolic pathways [105]. Similarly, a number of drugs also either increase or decrease VPA levels resulting in reduced efficacy or increased side effects (Table 1) [106]. Carbamazepine is a potent inducer of CYP450 and UGT metabolic enzymes and has been demonstrated to produce clinically-significant reductions of a number of drugs possibly necessitating increased doses of affected substrates [105]. Carbamazepine concentrations can also be increased by a number of concomitantly administered drugs such as macrolide antibiotics, verapamil and ketoconazole [106]. Other AEDs used in the treatment of mood disorders such as gabapentin,[107] lamotrigine and topiramate have been reported to have minimal clinically-significant DDIs [105, 108–110]. However a database review of 402 Swedish subjects on lamotrigine and quetiapine, showed that lamotrigine exposure was associated with significantly reduced quetiapine concentrations possibly due to induced glucoronidation via UGT [111].

Drug-drug interactions with AEDs involving Phase II conjugation reactions mediated by the UGT superfamily have also been reported [112]. UGT-mediated drug interactions involving AEDs such as valproic acid, carbamazepine and lamotrigine have been studied in *in vitro* models [113, 114], however the clinical significance of these interactions has not been well characterized [112]. Several AEDs have been reported to either inhibit or induce UGT in *in vitro* assays [89]. Conversely, other drugs such as carbapenems have been associated with reduced VPA levels via induction of UGT-mediated glucoronidation [115]. Psychotropic drugs primarily undergoing Phase II conjugation (ie. oxazepam), may be at greater risk for DDIs involving inhibitors or inducers of UGT and may warrant closer monitoring of therapy [112, 116].

Drug interactions involving lithium involve changes in distribution or elimination of lithium by concomitantly administered drugs. Because lithium is treated like sodium, drugs that inhibit renal reabsorption of sodium at the proximal tubule (i.e. osmotic diuretics) result in reduced lithium concentrations [117]. Other drugs such as theophylline and verapamil have also been shown to increase lithium clearance [105]. Conversely, a number of drugs have been shown to inhibit renal clearance of lithium, increasing the risk of elevated lithium levels and possible neurotoxicity. Drugs such as thiazide diuretics, NSAIDs, ACE inhibitors, furosemide and carbamazepine have been reported to increase lithium serum concentrations [105, 118, 119]. Lithium administered concomitantly with antidepressants and antipsychotics have also been shown to worsen tremor [120].

DRUG TRANSPORTERS

A number of drug transport proteins localized within the small intestine, liver and kidney have been identified in significantly contributing to the pharmacokinetic profile of many drugs (Table 1) [23]. These drug transporters consist of two major families, the solute carrier (SLC) family and the ATP-binding cassette (ABC) transporter family which mediate the majority of efflux and efflux of drugs within cells respectively [121]. A number of psychotropic medications are substrates for P-gp. There is also significant overlap between

substrates, inhibitors and inducers of P-gp and CYP3A4 [122, 123]. Theoretically, inducers of P-gp resulting in increased efflux of drug might limit therapeutically relevant CNS concentrations with standard dosing, possibly resulting in reduced efficacy, whereas inhibitors of P-gp might result in elevated CNS concentrations, producing increased adverse reactions with normal dosing [124, 125]. The significance of inhibition of P-gp on psychotropic medications has been studied in a number of *in vitro* and *in vivo* assays. Two studies examining the effect of P-gp inhibition on intracerebral concentrations of nortriptyline and risperidone, found that significant inhibition of P-gp by cyclosporine-A was required to result in elevated CNS concentrations, indicating a limited effect clinically [126, 127].

Several mood stabilizers and anxiolytic drugs have been identified as substrates of drug transporters (Table 1) [128]. However, there have been few studies examining the role of P-gp inhibition in psychiatric patients taking anticonvulsants as mood stabilizers. The majority of these studies have been conducted in patients with seizure disorders on anticonvulsants and concomitant P-gp inhibitors such as verapamil, diltiazem or nifedipine. Concomitant administration of verapamil or diltiazem has been shown to increase carbamazepine serum concentrations, although it was difficult to determine if this increase was associated with inhibition of P-gp or CYP3A4 [129]. Other studies have linked high expression of brain P-gp from specimens of patients with clinical treatment refractory epilepsy [130, 131], although this link has not been established as a mechanism in treatment refractory bipolar patients.

PHARMACOGENETICS

A number of genetic polymorphisms have been identified in coding and non-coding regions, regulating the expression or function of drug metabolizing enzymes or drug transporters accounting for significant inter-patient and intra-patient pharmacokinetic and pharmacodynamic variability. However, while the field of pharmacogenetics is advancing rapidly, the clinical utility of testing for genetic polymorphisms involved in drug disposition is limited due to costs associated with conducting the genetic tests and the significance of multiple polymorphisms impacting several metabolic pathways simultaneously and its impact on pharmacotherapy [132, 133]. Despite these limitations, polymorphisms identified in CYP2C9, 2C19 and 2D6 have been associated with clinically significant drug effects [134]. Recognizing the importance of pharmacogenetics on drug disposition, the US Food and Drug Administration (US FDA) issued industry guidelines providing a standard for classifying biomarkers and their utility in the clinical use of medications.

CYP450 enzymes

Several polymorphic variants of the CYP450 isoenzyme system have been found to clinically alter the biotransformation of several psychotropic medications resulting in both minor and serious consequences (Table 2). While known coding SNPs impacting the function of CYP3A4 are rare, a common variant located at the 5′-flanking region (CYP3A4*1B) has been associated with altered drug response [135, 136]. A non-coding SNP found in intron 6 (rs35599367, C>T) was recently found to impact mRNA expression of CYP3A4 and to be associated with differences in statin dose required for lipid control

[136]. Another highly polymorphic CYP450 is the CYP2D6 enzyme which is absent in about 10% Caucasians, and has been attributed to the wide variability of response to antipsychotic therapy [137, 138]. While several studies have pointed to genetic variability of CYP2D6 in determining drug levels of antipsychotics and the relationships to EPS [139], a recent review and meta-analysis failed to detect the clinical validity of pharmacogenetic testing for CYP2D6 SNPs and antipsychotic dosing [137]. The CYP3A family is responsible for over 50% of the hepatic metabolism of medications, and while there is significant inter-individual variability in CYP3A4 expression, this variability has not been attributed to genetic polymorphisms [140]. Polymorphic variation in CYP2D6 and CYP2C19 enzymes has been implicated in mediating the effects of antidepressants. Since most TCAs undergo metabolism by CYP2D6, patients that are poor metabolizers (PMs) receiving TCAs should be given 30–50% of the recommended therapeutic dose, while extensive metabolizers (EMs) should receive 100–130% of the recommended therapeutic dose [27]. Antidepressants that typically do not require dose adjustments due to polymorphic variation in CYP2D6 include bupropion, moclobemide, reboxetine, sertraline, trazodone. S-citalopram metabolism is primarily driven by CYP2C19 [141].

Most typical antipsychotics are metabolized by CYP2D6 and CYP1A2, with several studies showing that PMs of CYP2D6 status was associated with increased tardive dyskinesia (TD) and dystonia risk [142–144]. Studies have also shown that the plasma concentration of many typical antipsychotics is reduced by induction of CYP1A2 associated with smoking [37]. A genetic polymorphism of CYP1A2 has also been associated with increased risk of TD in patients taking antipsychotics [145].

Similarly, clearance of benzodiazepines have also been shown to be impacted by genetic polymorphisms primarily involving CYP3A4 and 2C9/19 isoenzymes [146]. Studies conducted in PMs of CYP2C19 and 3A4 reported reduced clearance and longer half-lives of diazepam and alprazolam respectively [146, 147].

Drug Transporters

Several studies have been conducted examining the role of two more common polymorphic variants of P-gp (MDR1; C2435T and G2667T/A) in patients taking antidepressants. In a study in patients with major depression taking citalopram, patients exhibiting the G2667T polymorphism had significant differences in plasma and CSF levels of citalopram, while wild-type polymorphism was associated with better treatment response [148]. A study examining the MDR1 polymorphisms (C2435T and G2677T/A) indicated that neither genotype was associated with therapeutic response to paroxetine in patients with major depressive disorder [149]. However in a more recent study in elderly depressed patients, MDR1 genotype predicted time to remission in patients treated with paroxetine, but not mirtazapine [150].

The role of polymorphisms of P-gp has also been examined in patients taking first and second generation antipsychotics. In a study of patients receiving clozapine, patients with the C2435T polymorphism exhibited a 1.6-fold increase in mean clozapine concentrations, with no significant differences observed in patients with the G2667G/T polymorphism [151]. In a PK study examining serum concentrations of risperidone and the 9-hydroxy

metabolite performed in P-gp knockout mice, P-gp knock-out mice had 10 times the plasma concentration vs wild-type mice [127]. Risperidone is a substrate for P-gp however genetic variants of P-gp have not been associated with changes in steady-state plasma concentrations of risperidone or its 9-hydroxy metabolite, while CYP2D6 genotypes and age were associated with changes in plasma concentrations [152]. However, a recent study of MDR1 polymorphisms (G2677T/A and C3435T) demonstrated higher scores of extrapyramidal symptoms in heterozygous carriers of both polymorphism in patients treated with acute risperidone [153]. The effects of genetic polymorphisms of P-gp on other SGAs have been conducted and are summarized by Moons T et al. [63].

As with the antidepressants and antipsychotics, most pharmacogenetic studies of drug transporters with mood stabilizers and anxyiolytics have primarily focused on P-gp. While many anticonvulsant medications are MDR1 substrates and has been proposed as a potential mechanism of resistance to therapy, most studies have produced inconclusive results regarding the impact of MDR1 polymorphisms and a recent meta analysis of MDR1 C3435T genotype and resistance to anticonvulsant drugs failed to identify any significant association with resistance and MDR1 genotype [154]. In bipolar patients treated with valproic acid, no difference in serum valproic acid concentration was seen in patients exhibiting the C2335T polymorphism [155].

Pharmacogenetic polymorphisms in P-gp have also been associated with muti-drug resistance in patients with epilepsy [156]. The C3435T polymorphism, which is associated with increased P-gp expression, was found to be associated with drug-resistant epilepsy, however a more recent study failed to find a similar association requiring further investigator of the overall contribution of this polymorphism in drug-resistant epilepsy [156, 157].

CONCLUSION

Patients suffering from psychiatric disorders are at risk for drug-drug interactions because they are highly likely to receive chronic treatment from multiple medications. Drug interactions from psychotropic medications can result in poor tolerability and/or reduced efficacy impacting the clinical outcomes of patients. Most DDIs involving psychotropic medications are pharmacokinetic (vs. pharmacodynamic), involving the CYP450 isoenzyme family. In preventing DDIs, the most important step PCPs is to eliminate the administration of unnecessary medications, including those over-the-counter (OTC) medications commonly overlooked in outpatient medicine. Careful selection of psychotropic medications, avoiding those with diverse pharmacology (i.e., multiple-targets) and those significantly impacted by concomitant medications that exhibit CYP 2D6 and 3A4 inhibition can also reduce adverse events related to DDIs. Since DDIs often occur within 1–2 weeks after change in existing medications or addition of concomitant medications, it is important to include DDI as part of the differential diagnosis. Certain medications exhibit characteristics which also make them prone to DDIs and include those with narrow therapeutic windows, non-linear pharmacokinetics and long half-lives. Similarly, elderly patients, patients with renal or hepatic impairment or those exhibiting confusion or sedation may be more sensitive to DDIs, therefore new medications added to existing pharmacotherapy regimens should be

initiated a low doses and titrated slowly. Utilization of available tables and DDI software may also be useful to the PCP in determining DDI potential. Lastly, improvements in pharmacogenetic testing may aid the PCP by promoting individualized pharmacotherapy selections and improve patient outcomes. Primary care clinicians can improve patient outcomes by considering the DDI potential of psychotropic medications and monitoring concomitant therapy during the course of treatment (Table 3).

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Table 1

Inhibitors and inducers of hepatic cytochrome P450 (CYP450) enzymes and drug transporters involved in drug metabolism.

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	**Other**	**Psychotropic**	**Other**
1A2	Caffeine Theophyline TCAs Ropinirole Duloxetine Mirtazapine Clozapine Haloperidol Olanzapine Asenapine Tacrine Zolmitriptan	Fluvoxamine+++ Fluoxetine+ Paroxetine+ Sertraline+	Cimetidine+ Omeprazole Fluoroquinolones Ticlopidine	Phenobarbital Secobarbital Carbamazepine Phenytoin	Modafinil Tobacco Charcoal-grilled meat Rifampin
2C9	Warfarin Losartan NSAIDs Glipizide ARBs	Valproic acid+ Fluoxetine++	Fluconazole+++ Miconazole++ Amiodarone++	Secobarbital Carbamazepine	Rifampin
2C19	BZDs PPIs SSRIs (citalopram) Amitriptyline	Fluvoxamine+++ Fluoxetine+	Ketoconazole Cimetidine Omeprazole Lansoprazole	Carbamazepine Valproic acid Phenobarbital Phenytoin	Rifampin
2D6	β-blockers Class 1C antiarrhythmics Codeine Amitriptyline Sertraline Haloperidol TCAs Risperidone Iloperidone Tramadol Venlafaxine Duloxetine Aripiprazole	Bupropion+++ Fluoxetine+++ Paroxetine+++ Duloxetine++ Sertraline+ Citalopram+ Escitalopram+ Haloperidol+ Thioridazine+	Terbinafine++ Quinidine+++ Cimetidine+ Amiodarone+ Mibefradil+ Ritonavir+	None	None

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	**Other**	**Psychotropic**	**Other**
3A4	Acetominophen BZDs Statins Macrolides Quinidine Indinavir, Ritonavir Amlodipine, Felodopine Diltiazem Atorvastatin Buspirone Sertraline Venlafaxine Mirtazapine Haloperidol Iloperidone Trazodone	Fluvoxamine+++ Nefazodone+++	Clarithromycin+++ Erythromycin++ Troleandomycin++ Fluconazole+++ Ketoconazole+++ Itraconazole+++ Indinavir+++ Cimetidine+ Verapamil++ Diltiazem++	Carbamazepine+++ Phenytoin+++ Phenobarbital++ St. John's Wort++ Morphine+ Nicotine+ Topiramate+ Felbamate+	Rifampin+++ Ritonavir++ Indinavir++ Efavirenz Pioglitazone Glucocorticoids
UGT	FGAs SGAs TCAs NSAIDs Carvedilol Furosemide Morphine Tramadol Lorazepam Oxazepam	Diclofenac+++ NSAIDs++ Probenecid++ Valproic acid+		Carbamazepine++ Phenytoin++ Phenobarbital++ Lamotrigine+	Rifampin+ Carbapenems+
OATP1A2	Atenolol Ciprofloxacin Pravastatin		Grapefruit juice Verapamil		
OATP2B1	Statins		Grapefruit juice Cyclosporine		
OAT1	Captopril Furosemide		Indomethacin Olmesartan Probenecid		
OAT3	Furosemide Olmesartan Pravastatin		Gemfibrozil Indomethacin		
OCT2	Amatadine Lamivudine Metformin Ranitidine		Bisoprolol Carvedilol Ranitidine		

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	**Other**	**Psychotropic**	**Other**
MDR1 (P-gp)	Digoxin Fexofenadine Ritonavir TCAs Atypical antipsychotics SSRIs Topiramate Gabapentin Carbamazepine Lamotrigine	Trifluperazine Fluphenazine Haloperidol Amitriptyline Flurazepam	Clarithromycin Cyclosporine Itraconazole Verapamil	Midazolam Phenobarbital Phenytoin Hypericum Morphine Nicotine	Clotrimazole Nifedipine Troglitazone

ARBs, angiotensin receptor blockers; BZD, benzodiazepine; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; FGA, first generation antipsychotics; SGA, second generation antipsychotics; NSAIDs, non-steroidal anti-inflammatory drugs

Relative inhibition: + = (negligible-low); ++ = (moderate); +++ = (high)

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Table 2

Clinically relevant genetic polymorphisms of Phase I (CYP450), Phase II (conjugation) drug metabolism and drug transporters.

Protein (Gene)	Allelic Variant	Phenotype Prevalence (%)			Relevant effects
		CA	AA	AS	
Phase I Enzymes (CYP450)					
CYP1A2	1A2*1C	0.08	0.40	0.24	Association of increased tardive dyskinesia with antipsychotics
CYP2B6	2B6*4 2B6*6	0.04 0.25	0.00 0.3–0.5	0.07 0.17	
CYP2C9	2C9*2 2C9*3	6–8 6–9	ND ND	0 2–3	Reduced substrate specificity
CYP2C19	2C19*2 2C19*3	13 0	13 ND	12–30 6–10	Inactive enzymatic activity
CYP2D6	2D6*2x*N* 2D6*4 2D6*5 2D6*10 2D6*17	2–5 15–20 5–7 2 0	2 2 4 6 34	2 1 6 50 ND	Increased 2D6 activity (EMs) Inactive enzyme (PMs) No 2D6 enzyme Enzyme instability Reduced substrate affinity
CYP3A4	3A4*1B	4	82	1–2	Reduced enzyme expression; increased risk of prostate cancer
Phase II Enzymes					
NAT	NAT2*5B NAT2*6A	50	50	15	Slow acetylation of isoniazid, sulfamethoxazole, caffeine; possible modulation of risk for lung, bladder, breast and colon cancers
GST	GSTM1*A	30–62	23–48	30–60	Decreased GST activity; possible increased TD severity in GSTP1 polymorphism
UGT1A	UGT1A1*28	0.5–10	ND	3	Lamotrigine, irinotecan; decreased clearance of tolbutamide, rifampin, haloperidol Elevations in bilirubin
TPMT	TPMT*3	3.2–10	1–10	4	No TPMT activity; Increased toxicity associated with 6-mercaptopurine
Drug Transporters					
P-glycoprotein, MDR1 (ABCB1)	C3435T G2667T	22–56	20	50–60	
OATP1B1 (SLCO1B1)	V174A	13	2	12	Statins (increased risk of myopathy); rifampin (inhibitor)

CA, Caucasian; AA, African American; AS, Asian

EMs, Extensive metabolizers; PMs, Poor metabolizers

Table 3

Clinical management of commonly encountered psychotropic drug-drug interactions.

Drug (Class)	Concomitant offender (ex.)	Mechanism	Clinical management
BZDs (diazepam, alprazolam, midazolam)	Fluvoxamine Nefazodone Indinavir Clarithromycin Azole-antifungals Grapefruit juice	PK: CYP3A4 inhibition	Decrease dose of BZD by 50%. Monitor for excessive CNS effects
	Thiazolidinediones (Pioglitazone, Troglitazone)	PK: CYP3A4 inducer	Consider increase of BZD dose; monitor for efficacy
TCAs (amitriptyline, desipramine)	Paroxetine Fluoxetine	PK: CYP2D6 inhibition	Reduce dose of TCA; consider obtaining TCA drug levels; monitor for CNS and CV effects.
FGA antipsychotics (phenothiazines, haloperidol)	Fluoxetine Fluvoxamine	PK: CYP2D6 inhibition PK: CYP1A2 inhibition	Increased risk for EPS; consider dose reduction of haloperidol.
	Smoking	PK: CYP1A2 induction	Consider increase antipsychotic dose in smokers; consider obtaining therapeutic drug level to aid in monitoring of ADRs
SGA antipsychotics (clozapine, olanzapine, risperidone, quetiapine)	Fluvoxamine Paroxetine, Fluxoxetine Ketoconazole	PK: CYP1A2 inhibition PK: CYP2D6 inhibition PK: CYP3A4 inhibition	Monitor clozapine concentrations; consider SSRI change. Consider dose reduction of risperidone; monitor for EPS. Monitor for excessive CNS effects.
	Smoking	PK: CYP1A2 inducer	Monitor for clozapine or olanzapine efficacy.
	Oral hypoglycemics and anti-lipidemics	PD: Antipsychotic alterations of glucose and lipids	Patients may require addition or increased doses of medications to manage hyperglycemia and/or hyperlipidemia
SSRIs (paroxetine, sertraline, citalopram) and SNRIs (duloxetine)	MAOIs	PD: Decrease metabolism of serotonin	Monitor for serotonin-syndrome risk; consider 14-day washout prior to starting SSRI.
	Triptans	PD: Enhancement of serotonin	Monitor for serotonin-syndrome risk; consider avoiding combination
	Hydrocodone	PK: CYP2D6 inhibition	Reduction of analgesic effect, due to CYP inhibition. May require increased doses of analgesic or switch to non-CYP2D6 metabolized analgesic
Lithium	ACE inhibitors NSAIDs, thiazides	PK: Inhibition of renal clearance	Monitor for elevated Li+ levels; consider dose reduction
HMG-CoA reductase inhibitors (simvastatin)	Nefazodone Fluvoxamine	PK: CYP3A4 inhibition	Monitor for myopathy; consider removal of offending inhibitor

Drug (Class)	Concomitant offender (ex.)	Mechanism	Clinical management
Warfarin (s-isomer, active)	Carbamazepine	PK: CYP2C9 inducer	Monitor INR
	Fluoxetine, valproic acid	PK: CYP2C9 inhibitor	Monitor INR, PT.
Calcium channel blockers (verapamil, nicardipine, nimodipine)	Nefazodone, fluvoxamine	PK: CYP3A4 inhibitor	Consider decrease of CCB dose by 50%.
COX-2 inhibitors (celecoxib)	Paroxetine	PK: CYP2D6 inhibitor	Monitor therapy
Antihyperglycemic (glimepiride)	Fluvoxamine	PK: CYP1A2 inhibitor	Monitor glycemic status
Clopidogrel	Fluvoxamine Nefazodone	PK: CYP1A2 inhibition PK: CYP3A4 inhibition	May weaken anti-platelet effects of clopidogrel; monitor therapy.