Drug–drug interactions involving antidepressants: focus on desvenlafaxine

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Abstract: Psychiatric and physical conditions often coexist, and there is robust evidence that associates the frequency of depression with single and multiple physical conditions. More than half of patients with depression may have at least one chronic physical condition. Therefore, antidepressants are often used in cotherapy with other medications for the management of both psychiatric and chronic physical illnesses. The risk of drug–drug interactions (DDIs) is augmented by complex polypharmacy regimens and extended periods of treatment required, of which possible outcomes range from tolerability issues to lack of efficacy and serious adverse events. Optimal patient outcomes may be achieved through drug selection with minimal potential for DDIs. Desvenlafaxine is a serotonin–norepinephrine reuptake inhibitor approved for the treatment of adults with major depressive disorder. Pharmacokinetic studies of desvenlafaxine have shown a simple metabolic profile unique among antidepressants. This review examines the DDI profiles of antidepressants, particularly desvenlafaxine, in relation to drugs of different therapeutic areas. The summary and comparison of information available is meant to help clinicians in making informed decisions when using desvenlafaxine in patients with depression and comorbid chronic conditions.

Keywords: desvenlafaxine, polypharmacy, comorbidities, depression, pharmacokinetics

Chronic conditions and association with depression

Major depressive disorder (MDD) is a functionally disabling condition characterized by depressed mood or loss of interest in the usual activities of daily life.[1] Depression is the leading cause of disability and a major contributor to the overall global burden of disease, affecting more than 300 million people worldwide.[2] There is robust evidence showing that depression is more frequent in patients with single and multiple physical disorders than in people who are in good physical health.[3,4] According to the National Institute for Health and Care Excellence (NICE) guidelines, about 20% of patients with a chronic physical condition are also suffering from depression.[4] Conversely, World Health Organization World Mental Health surveys have reported that about 72% of patients with MDD have a comorbid chronic physical condition.[5] The percentage prevalence of depression in patients with different chronic physical conditions is depicted in Figure 1.

Polypharmacy and drug–drug interactions

Patients with multiple comorbidities often take many medications, and are exposed to the risk of drug–drug interactions (DDIs).[6] These are frequently caused by pharmacodynamic (PD) or pharmacokinetic (PK) interactions between different agents.[7] In PD interactions, one drug may alter the pharmacological actions of another drug through new, additive, synergistic, or antagonistic effects.[7] In PK interactions,

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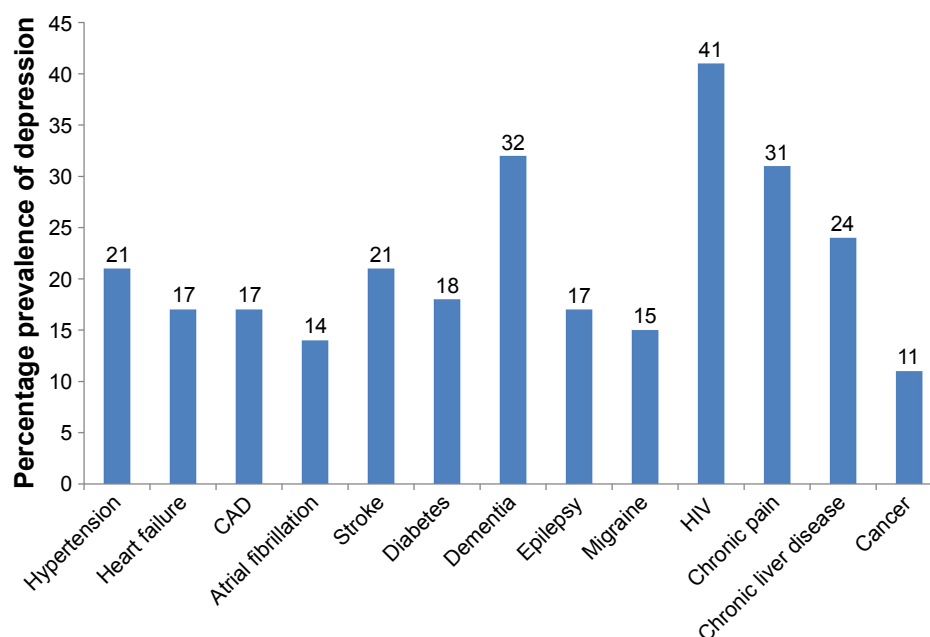Email sajita.setia@pfizer.com

Figure 1 Prevalence of depression in patients with chronic physical conditions.
Notes: Data from: Dumbreck et al 2015[35] (diabetes, heart failure), Guthrie et al 2012[49] (atrial fibrillation, chronic pain, CAD, dementia, hypertension, stroke), Kalaydjian and Merikangas[59] (migraine), Ng et al[107] (cancer), Tao et al[75] (HIV), Tellez-Zenteno et al[54] (epilepsy), and Weinstein et al[100] (chronic liver disease).
Abbreviation: CAD, coronary artery disease.

one drug affects the absorption, distribution, metabolism, or excretion of another concomitant drug.[7] Most DDIs involve PK interactions through impairment of drug elimination by interfering with hepatic metabolism, renal excretion, or transcellular transport.[8] Hepatic cytochrome P450 (CYP) enzymes are essential for metabolism of most medications, including many antidepressants.[9,10] Although there are more than 50 isoenzymes in the CYP superfamily, six of them metabolize 90% of drugs, with the two most significant being CYP2D6 and CYP3A4.[10] Nearly 50% of psychiatric and geriatric patients have been found to use at least one drug metabolized by CYP2D6, and 62% of these drugs were either antidepressants or antipsychotics.[11]

The genes for some CYP enzymes exhibit polymorphism, producing interindividual variability in metabolic capacity.[12] For instance, extensive (normal), intermediate, poor, and ultrarapid metabolizer phenotypes have been identified for CYP2D6.[12] Poor metabolizers have no functional CYP2D6 alleles, and may experience drug-induced adverse events or suboptimal clinical response.[12] In many ways, the clinical effect of drug metabolism in poor CYP2D6 metabolizers may be similar to DDIs related to CYP2D6 inhibition.[12] Furthermore, polypharmacy including CYP2D6 substrates/inhibitors may induce CYP2D6 phenoconversion.[13] As such, the predictability of the pharmacologic effect of a drug may remain uncertain in these scenarios.

Nevertheless, knowledge of pharmacogenomics based on patient genotype can be used to predict drug metabolism and hence individualize drug therapy.[14] However, the clinical and economic advantages of pharmacogenetic testing remain unclear.[15] Therefore, currently there are no formal recommendations to conduct this testing prior to initiating antidepressant treatment.[15]

The DDIs that result in complicated outcomes, such as an increase of serious adverse reactions, lack of efficacy, or tolerability issues, may be clinically significant.[16,17] This however is also influenced by several factors, such as a compromised metabolic pathway due to renal disease, liver disease, or poor/intermediate CYP-metabolizing status or therapeutic index of medicine.[16] The clinical relevance of many DDIs is easily underestimated, as detection is challenging and possible outcomes may vary widely.[17] Therefore, it is critical to avoid DDIs where possible through selection of appropriate medications with the least potential for DDIs.

Desvenlafaxine
Efficacy and tolerability
Desvenlafaxine succinate is a serotonin–norepinephrine reuptake inhibitor (SNRI) approved for the treatment of MDD in adults at a recommended dose of 50 mg/day.[18] Analysis from nine fixed-dose, short-term, placebo-controlled studies

in adult outpatients with MDD showed statistically significant improvements with desvenlafaxine 50 and 100 mg/day versus placebo for all efficacy end points.[19] A few head-to-head studies have also shown comparable efficacy and safety of desvenlafaxine versus escitalopram.[20–22]

Desvenlafaxine is recommended with level 1 evidence by the American Psychiatric Association 2010 guidelines.[23] Canadian Network for Mood and Anxiety Treatments 2009 and 2016 guidelines also recommended it as one of the first-line antidepressants for MDD.[24,25] Australian and New Zealand College of Psychiatrists 2015 practice guidelines recommended desvenlafaxine over other antidepressants, which are metabolized by the liver for patients with hepatic impairments.[26]

Metabolism and elimination

Desvenlafaxine (or *O*-desmethylvenlafaxine) is the major active metabolite of the SNRI venlafaxine after metabolism by CYP2D6. This metabolite has antidepressant activity, and its salt, desvenlafaxine succinate, is an approved drug.[27] Renal excretion is an important route of desvenlafaxine elimination, with around 45% eliminated unchanged in the urine.[18,28] Its metabolism primarily involves the non-CYP enzymes UGTs to form its glucuronide metabolite, which is also renally excreted.[18,28] The UGTs are a family of enzymes involved in detoxification and inactivation of compounds, and their activity is generally spared in liver disease.[29,30] The minor hepatic metabolic pathway involves CYP3A4 ($<$5%).[18,31] This hepatic metabolism has been shown to play a limited role in desvenlafaxine elimination, indicating a relatively uncomplicated metabolism.[31] On the other hand, with the concern that desvenlafaxine is predominantly renally excreted, prescribing information states that desvenlafaxine doses above the 50 mg/day recommended therapeutic dose should not be used in patients with moderate–severe renal impairment or end-stage renal disease.[18,31] Results from PK studies have demonstrated decreasing systemic clearance of single oral 100 mg desvenlafaxine with severity of renal impairment.[32] However, urinary recovery of total desvenlafaxine and its metabolites are similar in renal impaired versus healthy patients.[32]

Desvenlafaxine may have a low risk of variability in pharmacologic effect resulting from CYP2D6 polymorphisms or DDIs when coadministered with CYP2D6 substrates or inhibitors.[12,14] Table 1 depicts the relationship between other antidepressants and CYP enzymes, in addition to desvenlafaxine.[23,33,34]

Potential DDIs with antidepressants

Dumbreck et al conducted a systematic examination of the NICE guidelines for potentially serious DDIs between drugs recommended for depression and eleven other common conditions.[35] Among recommended antidepressants, 89 potentially serious DDI pairs were identified, with bleeding risk as the most common, particularly with selective serotonin-reuptake inhibitors (SSRIs). Other potential DDIs included lithium toxicity with SSRIs, ventricular arrhythmias with tricyclic antidepressants (TCAs), and central nervous system toxicity with TCAs and monoamine oxidase inhibitors (MAOIs).

Current evidence-based guidelines for both physical diseases and psychiatric disorders have been criticized for their lack of applicability to patients with comorbid conditions.[36] However, insufficient evidence is available to formulate guidelines for many diverse combinations of comorbidities.[17,37] The following section highlights potential DDIs when antidepressants are administered concomitantly in patients with comorbid chronic physical conditions. We have prioritized the chronic conditions based on Figure 1 (conditions with relatively higher prevalence rates of depression). Table 2 summarizes the potential DDIs between desvenlafaxine and drugs in each therapeutic class for treating the chronic conditions discussed.

Cardiovascular conditions

Cardiovascular (CV) conditions and depression frequently coexist.[38] Prevalence rates of MDD in the different CV/metabolic conditions are illustrated in Figure 1. β-Blockers like propranolol, timolol, metoprolol, and carvedilol are metabolized extensively by CYP enzymes, including CYP2D6.[39] Antidepressants that are potent CYP2D6 inhibitors, eg, paroxetine, fluoxetine, duloxetine, and bupropion, have been found to cause additional reductions in heart rate when administered with propranolol.[39] Clinically significant bradycardia has been reported with coadministration of paroxetine/fluoxetine and metoprolol.[40] Other antihypertensives, such as calcium-channel blockers are substrates and inhibitors of CYP3A4.[39] When calcium-channel blockers are coadministered with CYP3A4 inhibitors, there is a risk of hypotension and bradycardia.[10] Similar PK mechanisms are involved in DDIs in hypercholesterolemia treatment. The risk of myopathy is greater when metabolism of statins is repressed by CYP3A4 inhibitors.[10] Also, most antiarrhythmic agents, which have narrow therapeutic indices, are metabolized via CYP enzymes and prone to interactions with

Table 1 Antidepressants and CYP enzymes

Antidepressants	Major elimination pathway	Other elimination pathways	Inhibitory effect on CYP isoenzyme
SSRI			
Citalopram	CYP2C19	CYP3A4, CYP2D6	CYP1A2, CYP2B6, CYP2C19, CYP2D6
Escitalopram	CYP2C19	CYP3A4, CYP2D6	CYP2D6, CYP2C9
Fluoxetine (active metabolite norfluoxetine)	CYP2D6	CYP2C9, CYP2C19, CYP3A4	CYP2D6,** CYP2C9,* CYP2C19,* CYP3A4,* CYP1A2
Fluvoxamine	CYP1A2, CYP2D6		CYP1A2,** CYP2C19,** CYP2C9,* CYP3A4,* CYP2D6
Paroxetine	CYP2D6	CYP3A4	CYP2D6,** CYP1A2, CYP2C9, CYP2C19, CYP3A4
Sertraline	CYP2B6	CYP2C19, CYP2C9, CYP3A4, CYP2D6	CYP2D6,* CYP1A2, CYP2C9, CYP2C19, CYP3A4
SNRI			
Desvenlafaxine	Renal	UGT, CYP3A4	None
Duloxetine	CYP1A2	CYP2D6	CYP2D6*
Levomilnacipran	Renal	CYP3A4, CYP2C8, CYP2C19, CYP2D6, CYP2J2, UGT	None
Milnacipran	Renal	UGT, CYP3A4	CYP3A4
Venlafaxine (active metabolite desvenlafaxine)	CYP2D6	CYP3A4	CYP2D6, CYP3A4
Others			
Agomelatine	CYP1A2	CYP2C9, CYP2C19	None
Bupropion (active metabolite hydroxybupropion)	CYP2B6		CYP2D6*
Mirtazapine	CYP2D6, CYP3A4	CYP1A2, UGT	None
Reboxetine	CYP3A4		None
Vilazodone	CYP3A4	CYP2C19, CYP2D6, carboxylesterase	CYP2C8?
Vortioxetine	CYP2D6	CYP3A4, CYP2C19, CYP2C9, CYP2A6, CYP2C8, CYP2B6	None

Notes: **Potent; *moderate; ?undetermined; no symbol, weak. Data from Flockhart,[33] Gelenberg et al,[23] and Spina et al.[34]
Abbreviations: CYP, cytochrome P450; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor; UGT, uridine diphosphate glucuronosyltransferases.

CYP inhibitors.[41] There are consistent reports of DDIs with warfarin and multiple agents, including SSRIs.[10] Warfarin is a substrate of CYP3A4, CYP1A2, and CYP2C9 and can upregulate CYP3A4 and 2C9.[42] A recent study investigating the effect of CYP2C9-mediated warfarin–SSRI interaction, however, revealed comparable clinical outcomes, showing that SSRIs with CYP2C9 inhibition (eg, fluvoxamine and fluoxetine) may not affect warfarin-treatment outcomes if patients are closely monitored.[43] Of the newer oral thrombin inhibitors, rivaroxaban and apixaban are contraindicated in combination with drugs that inhibit CYP3A4.[44] These include antidepressants like fluvoxamine (Table 1).

Although desvenlafaxine may be helpful in avoiding most PK interactions, there are some PD interactions with CV medications (Table 2). First, caution is advised in patients with CV or lipid-metabolism disorders, as elevation in blood pressure, heart rate, and cholesterol levels has been observed in clinical studies with desvenlafaxine.[18] Second, due to anti-platelet effects of the serotonergic mechanism, there is a need to exercise caution with regard to abnormal bleeding risks

with concomitant desvenlafaxine and aspirin, antiplatelets, or other drugs that affect coagulation.[4,18] Abnormal bleeding risk is also associated with concomitant SSRIs and antiplatelet agents, and likewise caution is advised.[4]

Diabetes mellitus

Depression is a common morbidity in diabetes mellitus, being twice as common in patients with diabetes mellitus than in the general population.[45,46] Depression in diabetic patients is often treated with antidepressants.[45] However, there have been some reports of hypoglycemia associated with antidepressants (eg, SSRIs and MAOIs).[4,45]

One postulated mechanism is related to CYP2C9 inhibition. Sulfonylureas and nateglinide are substrates of CYP2C9, while several SSRIs are inhibitors of this enzyme (Table 1).[14] A decrease in total clearance of tolbutamide has been found during treatment with fluvoxamine.[47] Increased PD effects of sulfonylureas and increased risk of hypoglycemia have also been reported when glibenclamide, glimepiride, or glipizide was coadministered with other CYP2C9 inhibitors.[48]

Table 2 Summary of potential DDIs with desvenlafaxine

Therapeutic class/drugs	Pharmacologic profile of polypharmacy agents	Potential DDI with desvenlafaxine
Cardiovascular conditions		
β-blockers (eg, propranolol, timolol, metoprolol, carvedilol)	Substrate of CYP2D6[39]	No interaction expected,[a] but caution is still advised, as elevation in blood pressure, heart rate, and cholesterol levels was observed in clinical studies[18]
CCBs, statins (eg, lovastatin, simvastatin, atorvastatin), rivaroxaban, apixaban	Substrate of CYP3A4[10,39,44]	No interaction expected,[a] but caution is still advised, as elevation in blood pressure, heart rate, and cholesterol levels was observed in clinical studies[18]
Antiarrhythmic agents (eg, quinidine, disopyramide, lignocaine, mexiletine, flecainide, amiodarone, dronedarone)	Substrate, inducer, or inhibitor of various CYP enzymes[41]	Potent CYP3A4 inhibitors may result in higher levels of desvenlafaxine[18] Effect of CYP3A4 induction is unknown[b]
Warfarin	Substrate of CYP3A4, CYP1A2 and CYP2C9; induction of CYP3A4 and CYP2C9[42]	Risk of abnormal bleeding, caution with concomitant aspirin, antiplatelet drugs, or other drugs that affect coagulation[10,18] Effect of CYP3A4 induction is unknown, but may decrease levels of desvenlafaxine[b]
Diabetes mellitus		
Sulfonylureas (eg, tolbutamide, glipizide), nateglinide	Substrate of CYP2C9[14]	No interaction expected,[a] but caution is still advised, as hypoglycemic events reported with other antidepressants[45]
Neurological conditions		
Dementia		
Donepezil, galantamine	Substrate of CYP2D6 and CYP3A4[51]	No interaction expected[a]
Memantine	Renally excreted by tubular secretion[52]	Effect on tubular secretion is unknown[b]
Epilepsy		
Carbamazepine, phenobarbital, phenytoin, primidone	Induction of CYP enzymes (eg, CYP1A2, CYP3A4) and UGTs (eg, UGT1A1, UGT2B7, and UGT2B15)[34]	Interaction not studied, but unlikely to be relevant according to CYP involvement in metabolism[34] Effect of UGT induction is unknown, but may decrease levels of desvenlafaxine[b]
Valproic acid	Inhibition of CYPs (eg, CYP2C9, CYP2C19 and CYP3A4), some UGTs (eg, UGT1A4 and UGT2B7)[34]	Potent CYP3A4 inhibitors may result in higher levels of desvenlafaxine[18,b]
Carbamazepine, phenytoin, phenobarbital, primidone	Substrate of CYP3A4 or CYP2C9[34]	No interaction expected[a]
Lamotrigine, topiramate	Induction of UGTs and/or CYP3A4[34]	Effect of CYP3A4 and UGT induction is unknown, but may decrease levels of desvenlafaxine[b]
Bupropion, TCAs	Strong proconvulsive properties[53,57]	Possibility of seizures, caution in patients with seizure disorder[18]
Migraine		
Triptans	Affinity for 5HT$_1$ receptor (serotonergic property)[66]	Possibility of serotonin syndrome, caution when coadministered with serotonergic agents[18,67]
Sumatriptan, zolmitriptan	Substrate of MAOA[61]	No interaction expected[a]
Frovatriptan, eletriptan	Substrate of CYP1A2 or CYP3A4[61,62]	No interaction expected[a]
Schizophrenia		
FGAs (eg, phenothiazines), asenapine (SGA)	Inhibition of CYP2D6[69,72]	No interaction expected, [a]but caution for serotonin syndrome when coadministered with antidopaminergic agents[18]
SGAs, apart from amisulpride	Substrate of various CYP enzymes (eg, CYP2D6, CYP3A4) and UGTs[69]	No PK DDI was shown between desvenlafaxine and aripiprazole[18]
Clozapine	Associated with hypertension[69]	Increased risk for tachycardia and/or hypertension when administered with desvenlafaxine[69,b]
HIV		
Protease inhibitors (eg, ritonavir)	Inhibition of CYP3A4 and/or CYP2D6[77,78]	Potent CYP3A4 inhibitors may result in higher levels of desvenlafaxine[18,b]
Efavirenz	Inhibition of CYP2C19; induction of CYP3A4 and CYP2D6[77]	No interaction expected[a]
Nevirapine	Substrate and inducer of CYP3A4 and CYP2B6[82]	Effect of CYP3A4 induction is unknown, but may decrease levels of desvenlafaxine[b]
Indinavir	Substrate and inhibitor of CYP3A4[80]	No PK DDI was shown between desvenlafaxine and indinavir[81]

(*Continued*)

Table 2 (*Continued*)

Therapeutic class/drugs	Pharmacologic profile of polypharmacy agents	Potential DDI with desvenlafaxine
Chronic pain		
Opioids		
Codeine, fentanyl, methadone, morphine, oxycodone, pethidine, tramadol	Substrate of CYP3A4 and/or CYP2D6[86,87]	No interaction expected[a]
Fentanyl, methadone, pethidine, tramadol	Inhibition of serotonin reuptake (serotonergic property)[63]	Possibility of serotonin syndrome, caution when coadministered with serotonergic agents[18,63]
NSAIDs		
Ibuprofen, naproxen, diclofenac, celecoxib, etoricoxib	Substrate of several CYP enzymes including CYP3A4, CYP2C9, or CYP2D6[91–96]	No interaction expected[a]
Ibuprofen, indomethacin, diclofenac, meloxicam, celecoxib	Inhibition of CYP2C9 or CYP2C8/2D6[91]	No interaction expected[a]
Ibuprofen, diclofenac	Inhibition of UGT[91]	Effect of UGT inhibition unknown, but may increase levels of desvenlafaxine[b]
All NSAIDs	Risk of gastrointestinal bleeding[91]	Caution for abnormal bleeding with concomitant aspirin, antiplatelet drugs, or other drugs that affect coagulation[18]
Chronic liver disease		
IFNα	Inhibition of CYP1A2[103]	No interaction expected[a]
Direct-acting antivirals, such as ritonavir, boceprevir, simeprevir	Inhibition of CYP3A4[104,105]	Potent CYP3A4 inhibitors may result in higher levels of desvenlafaxine[18,b]
Simeprevir, asunaprevir	Substrate of CYP3A4/5[128,129]	No interaction expected[a]
Ombitasvir, dasabuvir, paritaprevir	Inhibition of UGTs[104]	May increase desvenlafaxine levels (clinical significance unknown); monitor and titrate dose according to clinical response[106]
Cancer		
Antiemetic agents		
5HT$_3$-receptor antagonists (ondansetron, tropisetron, dolasetron, palonosetron)	Substrate of CYP2D6[111]	No interaction expected[a]
Granisetron, corticosteroids (dexamethasone, methylprednisolone, prednisolone, prednisone)	Substrate of CYP3A4[109,111]	No interaction expected[a]
Dexamethasone, prednisone	Induction of CYP3A4[109]	Effect of CYP3A4 induction is unknown, but may decrease levels of desvenlafaxine[b]
Anticancer agents		
Vinca alkaloids (eg, vincristine, vinblastine, vinorelbine), taxanes (eg, docetaxel, paclitaxel), tyrosine-kinase inhibitors (eg, erlotinib, gefitinib, imatinib), irinotecan	Substrate of CYP3A4[111,112,115,116,126]	No interaction expected[a]
Erlotinib	Substrate of CYP1A2[115]	No interaction expected[a]
Cyclophosphamide, ifosfamide	Substrate of CYP3A4 and CYP2B6[119]	No interaction expected[a]
Doxorubicin	Substrate of CYP3A4 and CYP2D6[120]	No interaction expected[a]
Tamoxifen	Substrate of CYP2D6[121]	No interaction documented; desvenlafaxine may represent a safe and effective treatment unlikely to alter the efficacy of tamoxifen[125]
Imatinib, gefitinib, irinotecan	Inhibition of CYP3A4/5, CYP2D6, and/or CYP2C9[111,116,117,126]	Potent CYP3A4 inhibitors may result in higher levels of desvenlafaxine[18,b]

Notes: This table is not exhaustive, and serves only as a guide to potential DDIs with desvenlafaxine. [a]No interaction expected, based on known PK characteristics of desvenlafaxine;[18] [b]no documented evidence in current literature.
Abbreviations: 5HT, 5-hydroxytryptamine; AE, adverse event; CCB, calcium-channel blocker; CYP, cytochrome P450; DDI, drug–drug interaction; FGA, first-generation antipsychotic; MAOA, monoamine oxidase A; NSAID, nonsteroidal anti-inflammatory drug; PK, pharmacokinetic; SGA, second-generation antipsychotic; TCA, tricyclic antidepressant; UGT, uridine diphosphate glucuronosyltransferases.

Therefore, it is suggested that concomitant use of CYP2C9 inhibitors (eg, sertraline, fluoxetine, and fluvoxamine) and sulfonylureas or nateglinide be avoided, due to the potential risk of hypoglycemia.[14]

Other postulated mechanisms include possible increase in insulin sensitivity after long-term use of antidepressants with high affinity for the serotonin-reuptake transporter or depression itself predisposing to impairment of glucose control.[45] Although no association has been shown between antidepressant use in diabetic patients and an increased risk of hypoglycemia requiring hospitalization, a trend for higher risk of hypoglycemia was identified in antidepressants with high affinity for the serotonin-reuptake transporter.[45] Other than the regular blood-glucose monitoring to prevent hypoglycemia,[45] SNRIs, mirtazapine, and reboxetine have been identified as alternative antidepressants for management of depression in diabetes.[4]

Neurological conditions
Dementia
The comorbid prevalence of depression in dementia patients has been reported as 32%.[49] In a study at a dementia-management center, DDIs involving antidepressants were responsible for 6.1% of adverse events.[50] Donepezil and galantamine are metabolized through CYP2D6 and 3A4, and may be affected by specific inhibitors of those enzymes.[51] Coadministration of paroxetine (potent CYP2D6 inhibitor) has been found increase to galantamine exposure by 40%.[51] Memantine is excreted unchanged in urine, but may have decreased clearance when coadministered with medications that interfere with tubular secretion.[52]

Epilepsy
In patients with epilepsy, MDD is the most common psychiatric illness, at a lifetime prevalence rate of 17.4%.[53,54] Apart from managing seizures, antiepileptic drugs are also increasingly prescribed for nonepileptic conditions, such as neuropathic pain and migraine.[34] In general, PK interactions with antiepileptic drugs are well documented and recognized. Phenytoin, carbamazepine, and barbiturates are potent inducers of CYP enzymes and UGTs, potentially decreasing the exposure of some antidepressants (Table 1).[34,53] Valproic acid is a broad-spectrum inhibitor of various enzymes, including CYPs and some UGTs.[34] On the other hand, many antidepressants also inhibit CYP metabolism to varying degrees (Table 1) and can elevate antiepileptic-drug levels.[53] Among the newer antiepileptic drugs, only lamotrigine and topiramate have inductive effects on CYP enzymes.[55,56] As such,

in the polypharmacy of antidepressants and antiepileptic drugs, selection of antidepressants with minimal potential for PK interactions is highly recommended.[53,57] There have been no reports that SNRIs, including desvenlafaxine, affect the PK of antiepileptic drugs.[34]

However, some antidepressants may potentially have a PD interaction with antiepileptic agents, lowering seizure thresholds and exacerbating seizure attacks.[53] Studies have shown that seizure risk varies by dose and drug, and hence antidepressants with the strongest proconvulsive properties (eg, bupropion and TCAs) should be avoided in epileptic patients.[53,57] Desvenlafaxine has not been systematically evaluated in patients with seizure disorders, and should be prescribed with care in these patients.[18]

Migraine
Several studies have shown strong associations between migraine and MDD.[58] Depression has been found to be nearly three times more common in patients with severe headaches/migraine.[59] Sumatriptan and zolmitriptan are metabolized by monoamine oxidase A (MAOA), and thus coadministration with MAOIs can potentiate the side effects of triptans.[60,61] Frovatriptan is eliminated mainly by CYP1A2.[61] Eletriptan is primarily metabolized by CYP3A4, and CYP3A4 inhibitors (Table 1) have been labeled as contraindicated.[62]

The frequency of triptan–SSRI coprescription was about 20% in a study examining triptan prescriptions.[62] However, there are debatable concerns regarding the safety and PD interactions of this coprescription.[63–65] Pharmacologically, triptans demonstrate only weak affinity for 5-hydroxytryptamine 1 ($5HT_1$) receptors and no activity at $5HT_2$ receptors,[66] which are believed to be mechanistically implicated in the development of serotonin syndrome.[65] However in 2010, the US Food and Drug Administration recommended that patients treated concomitantly with a triptan and SSRI/SNRI be informed of the possibility of serotonin syndrome.[67] In the same year, the American Headache Society position paper stated that inadequate data were available to determine the risk of serotonin syndrome with concomitant triptan and SSRIs/SNRIs.[64] Given the severity of serotonin syndrome, clinicians are still advised to be vigilant of symptoms of the toxicity.[64] For desvenlafaxine, serotonin syndrome is a precaution when coadministered with serotonergic agents, such as triptans.[18]

Schizophrenia
Second-generation antipsychotics (SGAs) and newer antidepressants are often prescribed together in patients with

concomitant psychotic and depressive symptoms, such as those with schizoaffective disorder or psychotic depression.[68] Apart from amisulpride, SGAs are extensively metabolized through CYP enzymes, and some also by glucuronidation.[69] This makes SGAs prone to PK interactions with CYP inhibitors (Table 1). For example, there have been reports of akathisia and parkinsonian symptoms during coadministration of fluoxetine and risperidone, presumably due to inhibition of CYP2D6 by fluoxetine.[70] Also, PK studies and case reports have demonstrated increases in clozapine plasma levels attributed to CYP1A2 and CYP3A4 inhibition by fluvoxamine.[69] Another study showed that citalopram administration had no effect on plasma levels of clozapine or risperidone.[71] Desvenlafaxine 100 mg daily does not affect the PK of a single 5 mg dose of aripiprazole (substrate of CYP2D6 and 3A4).[70]

Except for asenapine (mild CYP2D6 inhibitor), SGAs appear to affect the activity of CYP enzymes insignificantly.[72,73] First-generation antipsychotics (FGAs), such as phenothiazines, however, are potent CYP2D6 inhibitors, and may interact with concomitant antidepressants, such as paroxetine or venlafaxine.[69] Additionally, there is a PD interaction of concern. Among all SGAs, only clozapine is associated with hypertension (usually <5%).[68] Caution is advised to monitor the risk for tachycardia and/or hypertension during coadministration of clozapine and SNRIs, including desvenlafaxine.[68]

Human immunodeficiency virus

HIV has now transitioned into a nonfatal chronic condition, due to improved access to highly active antiretroviral therapy (HAART).[74] However, comorbidity with incommunicable diseases, including mental disorders in HIV, has become increasingly common.[74] The pooled prevalence of HIV and comorbid depression has been found to be up to 41%.[75]

There have been several case reports of serotonin syndrome with coadministration of fluoxetine and various HAARTs.[76] Based on PK mechanisms, protease inhibitors are known CYP3A4 inhibitors, and ritonavir also inhibits CYP2D6.[77,78] As such, ritonavir is expected to produce large increases in the exposure of drugs metabolized by CYP.[78] A PK study of escitalopram showed statistically significant changes in some PK parameters after coadministration of single-dose ritonavir, although overall results concluded no clinical relevance.[79] In another study, single-dose indinavir (substrate and inhibitor of CYP3A4) before and after 10 days of desvenlafaxine 50 mg daily showed no PK interaction between the two agents.[80,81]

Reverse-transcriptase inhibitors like efavirenz have been shown to inhibit CYP2C19 and induce CYP3A4 and CYP2D6, potentially affecting levels of sertraline, citalopram, and bupropion.[77] Interactions of nevirapine (substrate and inducer of CYP3A4 and 2B6) have also been studied.[82] There was a clinically significant reduction in clearance of nevirapine when administered with fluvoxamine, and significantly decreased concentrations of fluoxetine when coadministered with nevirapine. Unlike other antidepressants with significant CYP activity, desvenlafaxine has low potential for interactions through PK mechanisms with HAART.

Chronic pain

Chronic pain and MDD have been found to have one of the strongest associations of occurrence, with a comorbid prevalence rate of about 31%.[49,83]

Opioids

In a study on DDIs with opioids, concomitant administration with antidepressants showed the highest potential for DDIs.[84] As fentanyl, methadone, and oxycodone are major CYP3A4 substrates, inhibitors of this isoenzyme (Table 1) can cause increased effects of opioids.[85,86] Another study identified increased levels of fentanyl derivatives with CYP3A4 inhibitors.[84] In addition, there could be potential DDIs with CYP2D6 inhibitors (eg, paroxetine), as there are several opioids that are major substrates of CYP2D6 (eg, morphine, codeine).[86,87] Tramadol instead undergoes extensive metabolism via both CYP2D6 and CYP3A4 enzymes.[88] Desvenlafaxine does not seem to interfere in a major way with the CYP-metabolizing pathway of opioids, unlike other antidepressants, thus possibly reducing the risk of PK interactions.[18]

A higher occurrence of serotonin syndrome has been found when opioids, particularly tramadol, are coadministered with an SSRI or SNRI.[63,89] This is because tramadol also has a possible SNRI effect.[90] Consequently, there is a potential for PD interaction, as both desvenlafaxine and tramadol are serotonergic drugs.[18] This interaction could also be conceivable with other serotonergic opioids, such as methadone, pethidine, and fentanyl.[18,63] In contrast, morphine analogs like codeine and oxycodone have not been shown to inhibit the reuptake of serotonin.[63]

Nonsteroidal anti-inflammatory drugs

Many nonsteroidal anti-inflammatory drugs NSAIDs are metabolized by CYP enzymes, and thus their metabolism would be affected by antidepressants inhibiting the same

enzymes (eg, CYP3A4, CYP2C9, CYP2D6).[91–96] Conversely, some NSAIDs modestly inhibit CYP2C9 (eg, ibuprofen, indomethacin, diclofenac, meloxicam), CYP2C8/2D6 (eg, celecoxib), and glucuronidation (eg, ibuprofen, diclofenac), which may increase the concentrations of antidepressants dependent on these pathways for clearance (Table 1).[91] Desvenlafaxine could possibly reduce the risks of such DDIs with NSAIDs related to PK mechanisms.

There are numerous documented DDIs of NSAIDs with antidepressants associated with increased bleeding and PK interactions.[91] NICE and American Psychiatric Association guidelines advise against SSRIs in patients taking NSAIDs because of the potentiated risk of gastrointestinal bleeding.[4,23] A study showed that the risk of abnormal bleeding correlates with increasing degrees of serotonin-reuptake inhibition (eg, intermediate degree – venlafaxine, fluvoxamine, citalopram; high degree – fluoxetine, sertraline, paroxetine).[97] On the other hand, conflicting data regarding the association between SNRIs and potentiated gastrointestinal bleeding risk have been published.[98,99] For desvenlafaxine in particular, although gastrointestinal bleeding is not documented as an adverse reaction, concomitant use of NSAIDs may add to this risk.[18]

Chronic liver disease

The overall prevalence of depression has been found to be 23.6% in patients with chronic liver disease (27.2% in non-alcoholic fatty liver disease, 29.8% in hepatitis C, and 3.7% in hepatitis B).[100] Depression is also a common side effect of IFNα treatment (found in 30%–70% of treated patients).[101] However, the association between chronic hepatitis C and MDD has been shown to be independent of treatment with IFNα.[102]

Studies have shown modest inhibition of CYP1A2 by IFNα.[103] Directly acting antivirals also have inhibitory effects on the activities of CYP enzymes.[104] Boceprevir, simeprevir, and telaprevir are substrates and inhibitors of CYP3A4.[104,105] PK studies on escitalopram (CYP3A4 substrate) have shown no significant DDI with boceprevir, but a 35% decrease in exposure with telaprevir.[106] There is a potential for increased sertraline, mirtazapine, and venlafaxine concentrations, due to CYP inhibition by the antiviral agents.[106] Desvenlafaxine, showing minimal activity on the CYP metabolic pathway, could potentially mitigate such CYP-related PK interactions.

On the other hand, some directly acting antivirals, such as in the combination regimen of paritaprevir, ombitasvir, and dasabuvir, are UGT inhibitors.[104] Interaction studies

between these agents and furosemide (UGT1A1 substrate) have shown increased PK parameters of furosemide.[104] This could imply a potential interaction in the metabolism of desvenlafaxine (Tables 1 and 2).[106] However, no data regarding this are currently available.

Australian and New Zealand College of Psychiatrists 2015 practice guidelines[26] recommended desvenlafaxine over other antidepressants (which are metabolized by the liver) for patients with hepatic impairments. This was based on a PK study that showed that single dose desvenlafaxine 100 mg was well tolerated in both healthy subjects and liver-impaired patients.[31]

Cancer

The pooled prevalence of cancer and comorbid MDD from 31 studies was found to be 10.8% (range 3.7%–49%),[107] with increasing prevalence in cancers with poorer prognoses.[57] Furthermore, more than 21% of patients who use concomitant oral anticancer agents and antidepressants within a three year period are on drug pairs that could potentially cause DDIs.[108] Potential DDIs involving drug transporters and UGTs have not been identified as clinically important between anticancer agents and antidepressants.[109] The following sections focus on DDIs with antiemetic and anticancer agents used in the most commonly diagnosed cancers worldwide, namely lung, breast, and colorectal cancer.[110]

Antiemetic agents

The metabolism of some $5HT_3$ antagonists, such as ondansetron, tropisetron, dolasetron, and palonosetron, involves CYP2D6.[111] Granisetron does not depend on CYP2D6, but is a substrate of CYP3A4.[111] In addition, corticosteroids, including dexamethasone, methylprednisolone, prednisolone, and prednisone, are also metabolized by CYP3A4.[109] Antidepressants with CYP2D6/3A4-inhibitor activity (Table 1) could have DDIs with antiemetic agents. For instance, coadministration of fluoxetine has been shown to reduce the effectiveness of ondansetron.[111] Based on PK profiles, desvenlafaxine could represent a rational choice in avoiding these interactions.

Lung cancer

Antimicrotubule agents, such as vinca alkaloids (eg, vincristine, vinblastine, and vinorelbine) and taxanes (eg, docetaxel and paclitaxel) are extensively metabolized by CYP3A4, potentially interacting with several antidepressants (Table 1).[112] In cancer patients, coadministration of ketoconazole (CYP3A4 inhibitor) leads to decreased

clearance of docetaxel by 49%, resulting in toxicity and risk of febrile neutropenia.[113] Therefore, antidepressants with inhibitory effect on CYP3A4 may have similar interactions with docetaxel. PK studies have shown that desvenlafaxine is not extensively metabolized by CYP3A4, and neither does it measurably alter CYP3A4-mediated metabolism.[114]

Clearance of the tyrosine-kinase inhibitors erlotinib and gefitinib is dependent on CYP3A4, and may be decreased with coadministration of CYP3A4 inhibitors (Table 1). Erlotinib may also be subjected to CYP1A2 inhibition by fluoxetine and fluvoxamine.[115] Gefitinib has inhibitory activities on CYP2C19 and CYP2D6, and can decrease the clearance of CYP2D6 substrates, such as TCAs and venlafaxine.[116,117] Similar but more profound effects have been noticed with another tyrosine-kinase inhibitor: imatinib (used for chronic myelogenous leukemia and gastrointestinal stromal tumors).[118]

Breast cancer

Cyclophosphamide and ifosfamide are both major substrates of CYP3A4 and CYP2B6,[119] while doxorubicin is a major substrate of CYP3A4 and CYP2D6.[120] Clinically significant interactions have been reported with inhibitors of these enzymes (Table 1), resulting in increased concentration and clinical effect of the anticancer agents.[121] Tamoxifen, a commonly prescribed estrogen antagonist for hormone-positive breast cancer patients,[122] relies on CYP2D6 for its biotransformation to the active metabolite.[121] The use of paroxetine (potent CYP2D6 inhibitor) during tamoxifen treatment is associated with an increased risk of death by breast cancer, although venlafaxine does not seem to change this risk significantly.[123] In 2010, the Committee for Medicinal Products for Human Use recommended physicians avoid using potent CYP2D6 inhibitors during tamoxifen treatment whenever possible.[124] It is estimated that 20%–30% of women taking tamoxifen are also treated with antidepressants, magnifying the relevance of this DDI.[121] For desvenlafaxine, studies have shown that it may represent a treatment that is unlikely to alter the metabolism of tamoxifen.[125]

Colorectal cancer

Irinotecan undergoes metabolism by CYP3A4 and also competitively inhibits this isoenzyme and CYP2C9.[126] A case report showed potentially fatal rhabdomyolysis that occurred in a patient who was coadministered with irinotecan and citalopram (CYP3A4 substrate).[127] This speculates a theoretical PK interaction between irinotecan and other CYP3A4 substrates, such as escitalopram and fluoxetine.[117]

Desvenlafaxine is only a minor substrate of CYP3A4, and is not expected to be majorly involved in this interaction.

Conclusion

The coprevalence of chronic physical conditions and depression is very common. The potential for DDIs should be considered when selecting treatment options in patients with multiple comorbidities. This is crucial for achieving optimal patient adherence and outcomes.

The majority of SSRIs undergo extensive hepatic oxidative metabolism mediated by CYP450 isoenzymes. As such, many clinically significant DDIs have been reported, mostly due to inhibition of these enzymes. While SSRIs such as fluoxetine and paroxetine are potent inhibitors of CYP2D6, fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19, and these SSRIs are thus likely to cause DDIs. Other SSRIs, such as sertraline, citalopram, and escitalopram, at usual therapeutic dosages are probably less likely to cause significant alterations in CYP450 status. However, even these interactions may be clinically significant in specific patient populations, eg, in renally and hepatically impaired patients, poor/intermediate CYP metabolizers, or for drugs with a narrow therapeutic range.

The simple metabolic pathway of desvenlafaxine compared to other antidepressants may make it favorable in avoiding CYP-related PK interactions with drugs of many therapeutic classes. However, relevant PD interactions with desvenlafaxine, eg, elevated blood pressure and heart rate, abnormal bleeding, and serotonin syndrome, should be closely monitored in practice.

Author contributions

All authors were involved in conception, design, analysis, interpretation of data, preparation of the manuscript, revising it for important intellectual content, and final approval before submitting it for publication.

Disclosure

SS and GL are employees of Pfizer, manufacturer of desvenlafaxine. YL underwent indirect patient-care pharmacy training for 3 months at Pfizer, Singapore. The authors report no other conflicts of interest in this work.

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