

# Clinical pearls for the management of duloxetine patients with medical comorbidities

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## Abstract

The effective use of duloxetine can be complicated by acute kidney injury, acute and/or chronic hepatic dysfunction, dysphagia, enteral nutrition, and common pharmacokinetic interactions. This article aimed to review the pharmacological properties of duloxetine pertinent to its use and to discuss the management of duloxetine in patients with common acute and chronic medical comorbidities. Management strategies based on clinical data and expert opinion are reviewed in 3 patient cases.

**Keywords:** duloxetine, comorbidities, pharmacokinetics, nutrition status, renal function, hepatic function, drug interactions

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## Introduction

Duloxetine is a potent inhibitor of serotonin and norepinephrine transporters with a negligible effect on dopamine transporters.<sup>1-4</sup> It is FDA approved to treat MDD, diabetic peripheral

neuropathic pain, and chronic musculoskeletal pain in adults; generalized anxiety disorder and fibromyalgia in both adults and pediatrics. Doses generally range from 30 to 120 mg daily, depending on the indication.<sup>1,2</sup> Additionally, data support the off-label use of duloxetine for indications such as chemotherapy-induced peripheral neuropathy and stress urinary incontinence.<sup>4-6</sup>

The effective use of duloxetine in the acute inpatient setting may be complicated by acute kidney injury (AKI), hepatic dysfunction, dysphagia, and interactions with medications.<sup>1-4</sup> These factors may increase risk of duloxetine adverse effects (eg, anxiety, headache, nausea, somnolence) or toxicity (eg, hypertension, myoclonus, tachycardia, seizure). The objective of this article was to discuss the pertinent pharmacological properties of duloxetine and approaches to its management in patients with medical comorbidities, using 3 illustrative cases.

## Pharmacokinetics

Understanding the absorption, distribution, metabolism, and excretion of duloxetine in healthy patients is essential



### Take Home Points:

1. Duloxetine pharmacokinetics can be impacted by common changes to a patient's clinical status during an acute medical hospitalization or chronic treatment. Knowledge of its pharmacologic properties can assist with the rational management of antidepressant therapy in these situations.
2. Duloxetine may be used cautiously in patients with renal impairment if alternative treatments are unavailable, but it should be avoided in patients with any degree of hepatic dysfunction. Duloxetine should also be considered as a potential contributing factor in acute onset hepatic or renal injury.
3. Potential interactions and clinical consequences should be considered when initiating or discontinuing duloxetine or other medications (especially inducers or inhibitors of cytochrome P450 (CYP)1A2 or CYP2D6 substrates) in patients taking duloxetine.

to determine how they may be impacted by complications common among hospitalized patients.

### Absorption

Duloxetine is acid-labile and prepared as a capsule containing enteric-coated pellets. The enteric coating prevents degradation in the acidic environment of the stomach, where pH ranges from 1.5 to 3.5 while allowing dissolution in the remainder of the gastrointestinal tract, where pH typically ranges from 5.7 to 7.4.<sup>3,7</sup>

Duloxetine absorption may be slightly altered in hospitalized patients with inconsistent nutritional intake or timing of medications. Administration of duloxetine with food delays  $t_{\max}$  by approximately 4 hours (due to decreased gastrointestinal motility) and decreases duloxetine area under the plasma concentration-time curve (AUC) by 11% and  $t_{1/2}$  by 18%. Administration with food has not demonstrated any impact on maximum plasma concentration ( $C_{\max}$ ). Decreased gastrointestinal motility at bedtime also delays  $t_{\max}$  and decreases AUC and  $C_{\max}$  by 18% and 29%, respectively, with no effect on  $t_{1/2}$ .<sup>3,8</sup> Despite these changes, empiric dose adjustments are not necessary based on the timing of administration or food intake.

### Distribution

Duloxetine is more than 90% protein bound to albumin and  $\alpha_1$ -acid glycoprotein and readily crosses the blood-brain barrier.<sup>3</sup> Despite being highly protein bound, there are no published cases to date that protein-binding interactions occur or that serum albumin concentrations impact the effects of duloxetine.

### Metabolism

Duloxetine is primarily metabolized via cytochrome (CYP) 1A2 with minor contribution from CYP2D6.<sup>1,3</sup> Duloxetine is a moderate inhibitor of CYP2D6.<sup>1</sup>

### Excretion

Duloxetine is excreted in urine (72%) and feces (19%), with only 1% to 3% excreted unchanged.<sup>3,9</sup> FDA labeling states duloxetine use be avoided in all patients with a glomerular filtration rate (GFR) less than 30 mL/min and is not removed by dialysis.<sup>1,2</sup> Outside of the United States, including Canada and Europe, the guidance allows the use of duloxetine at lower doses in patients with impaired renal function or end-stage kidney disease (ESKD).<sup>10-13</sup> Duloxetine clearance decreases with increasing doses, suggesting saturable metabolism.<sup>14</sup> Clearance also decreases with advancing age, possibly because of decreased renal function, reduced blood flow to the liver, and declining hepatic enzyme activity.<sup>14-16</sup>

### Case 1: Managing Duloxetine in Patients With Dysphagia

A 68-year-old patient presents to the emergency department with new-onset aphasia and gait abnormalities. Neurologic workup is positive for acute ischemic stroke, and the patient is admitted for treatment. Their past medical history is significant for depression, type 2 diabetes mellitus, hypertension, and diabetic neuropathy. Current medications include duloxetine 90 mg daily, gabapentin 400 mg 3 times daily, insulin glargine 20 units at bedtime, and losartan 50 mg daily. The patient's chronic conditions have been stable on these medications for years.

Upon admission, a nasogastric (NG) tube (12 French) is ordered for nutrition and medication administration due to stroke-related dysphagia, with a plan to reassess after 1 week.

### Methods for Duloxetine Administration in Dysphagia

The simplest way to convert medications from oral to enteral administration is to use equivalent oral liquid doses. If an oral liquid is unavailable, immediate-release tablets can often be crushed and mixed with water to be administered via tube. Immediate-release capsules can also be opened, and the contents mixed and administered likewise. However, most capsules were not designed to be administered in this fashion, and doing so may lead to clogged tubing. In addition, with limited exceptions, extended-release tablets and capsules should not be crushed or opened and administered in this way because of resulting changes in expected pharmacokinetics. Intravenous (IV) administration of some chronic

medications may be warranted for a brief time when available; however, quick return to enteral administration is best practice and tied to improved outcomes such as reduced infections, shorter length of stay, reduced costs, and improved patient comfort.<sup>17</sup>

In patient case 1, gabapentin is available in a 250 mg/5 mL oral solution and losartan tablets can be crushed. While the dose of subcutaneous insulin may need to be adjusted for changes in nutritional status, administration is not affected by the need for an NG tube. Duloxetine, however, presents a problem because it is an extended-release capsule without an available oral liquid or IV product.

## Duloxetine Formulation Differences

Duloxetine is available in 2 delayed-release pellet capsule formulations. Cymbalta and its multiple generic equivalent products (duloxetine) and Drizalma Sprinkle capsules (DSp), which do not have a generic equivalent to date.<sup>2</sup> Primary differences between the 2 formulations are the ingredients “starch” and polyethylene glycol, which are only in DSp, and the utilization of different coating agents for the capsule pellets. While no published literature is available regarding why different ingredients were used in the DSp formulation, there are data with simvastatin demonstrating that polyethylene glycol increases dissolution rate, resulting in increased bioavailability.<sup>18</sup> This, theoretically, may allow for improved bioavailability of DSp.

According to the labeling, DSp can be opened and sprinkled on acidic foods such as applesauce.<sup>2</sup> Duloxetine itself is acid labile and will degrade in an acidic environment with pH below 5.5. Duloxetine capsule pellets have an enteric coating that dissolves in a higher pH. Therefore, the pellets cannot be crushed as the medication will degrade in the stomach before being absorbed.<sup>19</sup> DSp may also be administered via 12 French or a larger NG tube when combined with 50 mL of water in an all-plastic catheter-tip syringe and gently mixed for 10 seconds before enteral tube administration. An additional 15 mL of water should be flushed to ensure no pellets are left in the syringe.<sup>2</sup>

While generic duloxetine is labeled to be given as an intact capsule, it has been demonstrated that the contents remain stable at room temperature for up to 2 hours when sprinkled on acidic foods, such as applesauce, but not chocolate pudding.<sup>19</sup> As there are no data available to guide the administration of duloxetine via an NG tube, doing so should be considered only as a short-term option. If duloxetine administration via an NG tube is attempted, the same method detailed in DSp labeling should be used, and all pellets should remain intact before medication delivery. Holding duloxetine in these cases may result in discontinuation symptoms and significant patient discomfort.

In patient case 1, using the DSp formulation would be the best choice, assuming the product is available on the hospital’s formulary. If unavailable, it may be reasonable to open generic duloxetine capsules and administer them according to the same procedure for a short period of time. However, if difficulties arise with tube patency or the patient’s prognosis is such that they will need prolonged enteral medication administration, alternative antidepressant medication options should be discussed with the patient, caregivers, and outpatient providers. The choice can be made based on the history of response to other antidepressants, concurrent disease states and medications, and patient preference. Given the high rate of depression in the post-stroke setting and the positive outcomes associated with antidepressant treatment for post-stroke depression, discontinuation of treatment altogether is not recommended.<sup>20</sup>

## Case 2: Managing Changes in Renal Function

A 75-year-old patient is admitted to the hospital with altered mental status, nausea, and dehydration. They are found to have an AKI with calculated creatinine clearance (CrCl) of 16 mL/min (baseline = 55 mL/min). The patient’s caregiver reports a fever and night sweats for the past 2 days. Past medical history includes generalized anxiety disorder, and the only prior-to-admission medication is duloxetine 60 mg by mouth every evening. The patient has been taking this medication with good effects and no adverse effects for 2 years and is initially resistant to changing medications or holding doses because “duloxetine saved my life.” Fluid replacement and home duloxetine dose are ordered. Over several days of treatment, the patient’s CrCl improves slightly to 28 mL/min, but they remain mildly confused and are now reporting that it feels like their limbs are twitching. They report feeling sweaty overnight with return of their nausea, and vitals reflect new low-grade fever. Nephrology is consulted and determines this may represent a new baseline in terms of renal function. After infectious and other causes are ruled out, duloxetine toxicity is considered a likely cause of symptoms. The patient and caregiver agree to initiate a cross titration from duloxetine 60 mg daily to sertraline 25 mg daily. Sertraline is ultimately titrated to 75 mg daily without worsening anxiety. Confusion, nausea, and twitching resolve, and vital signs return to normal.

## Impact of Impaired Renal Function on Duloxetine

The effects of renal impairment on the pharmacokinetics of duloxetine have been analyzed in a single-dose, phase I study and in pooled steady-state data from Phase II/III trials.<sup>21</sup> In the phase I study, 12 patients with ESKD and 12 patients with a CrCl greater than 75 mL/min were given a

single 60 mg dose of duloxetine immediately after dialysis or after a 3-hour fast, respectively. In patients with ESKD, duloxetine exposure, measured by  $C_{max}$  and AUC, was approximately double that of healthy patients, while clearance was approximately half.<sup>21</sup> Patients with ESKD reported more nausea, diarrhea, and vomiting than healthy subjects.<sup>2</sup> Based on these results, it may be reasonable to reduce the dose of duloxetine by 50% in patients with ESKD, though the evidence is limited to this single small trial.

In pooled data from four phase II/III trials, 176 patients with normal renal function ( $CrCl > 90$  mL/min), 223 patients with mild renal impairment ( $CrCl$  61-90 mL/min), and 64 patients with moderate renal impairment ( $CrCl$  31-60 mL/min) were given duloxetine 20 to 120 mg daily to model duloxetine clearance.<sup>21</sup> There was no significant difference in duloxetine clearance between patients with normal renal function or mild or moderate renal impairment.<sup>21</sup> Based on these data, dose reductions are not empirically necessary in patients with  $CrCl$  greater than 30 mL/min or with fluctuating renal function due to AKI. However, the duloxetine dose should be reduced if adverse effects occur. Despite the lack of guidance in the product labeling, in patients whose  $CrCl$  declines to less than 30 mL/min, duloxetine may be reasonably continued in certain cases with close monitoring for signs and symptoms of toxicity.

In patient case 2, given the signs and symptoms of duloxetine toxicity that the patient was exhibiting (sweating, fever, twitching, nausea, and confusion), the choice was made to switch medications altogether rather than reduce the dose of duloxetine. This case represents the importance of considering the entire clinical picture when choosing the best course of action. For example, if the patient had reported a difficult history with anxiety treatments such as numerous adequate trials of other antidepressant medications without benefit or poor tolerability with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, it may have been possible to reduce the dose of duloxetine by 50% and monitor for symptomatic improvement instead. Given possible changes in clearance and half-life, it may take up to 2 weeks to achieve a new steady state level.<sup>21</sup> Or if the patient had experienced an AKI without changes to their baseline renal function and symptoms of toxicity, it may have been reasonable to continue duloxetine at the previous dose, with close monitoring for adverse effects.

### Impact of Duloxetine on Renal Function

Medication-related AKI has been reported with duloxetine in a single case report, but retrospective evidence is mixed.<sup>22-24</sup> In the published case report, a 63-year-old woman presented with anuria and serum creatinine (SCr) of 6.3 mg/dL approximately 1 month after initiating duloxetine. Additional home medications were amlodipine 5 mg daily and levothyroxine

125 mcg daily. Upon discontinuation of duloxetine, the SCr decreased to 2.5 mg/dL within 2 days and 1.0 mg/dL within 8 days of discontinuation.<sup>22</sup> The timing of symptom onset and resolution suggests that duloxetine may have contributed to AKI in this patient.

Tully and colleagues<sup>23</sup> compared outcomes between 105 SSRI and SNRI users versus 4031 nonusers after coronary artery bypass graft (CABG) surgery. The SNRI group included duloxetine and venlafaxine. Within the hospital, renal dysfunction requiring dialysis after CABG had an adjusted odds ratio of 2.18 (95% confidence interval [CI], 1.06-4.45,  $P = .03$ ) in patients on an SSRI/SNRI versus those who were not.<sup>23</sup> The study did not report the breakdown of patients by individual agent. Thus, it is unclear from these data how duloxetine compares to other SSRIs and SNRIs regarding AKI risk. While these data are specific to CABG recipients, they suggest that markers of renal function should be monitored in patients taking duloxetine after a surgical procedure.

The risk of AKI with SNRIs versus SSRIs was explored further in a retrospective cohort study assessing data from eight Canadian Network of Observational Drug Effect Studies databases. Five of these studies directly compared duloxetine and SSRIs. A total of 38 974 cases of AKI were matched to 384 034 controls. After adjusting for confounders, no significant difference in AKI rate ratio (RR) was found between duloxetine and SSRI groups in the pooled data (RR 1.02, 95% CI 0.95-1.10).<sup>24</sup> There was, however, a significant difference in RR of AKI associated with duloxetine users compared with SSRI users in 2 of 5 individual databases included in the pooled analysis.<sup>24</sup> While the pooled data suggest that duloxetine is unlikely to present a higher risk of AKI than SSRIs, the heterogeneity of the findings suggests that more research should be done in this area. In patients presenting with AKI, recent initiation of duloxetine should be considered as a potential contributing factor, but routine monitoring of renal function with duloxetine initiation or maintenance treatment is not warranted based on available data.

In practice, it is reasonable to monitor renal function at least annually to observe any changes in renal function associated with age or chronic medical conditions such as diabetes. Unexplained or new-onset adverse effects despite long-term use of duloxetine should also warrant a screen for changing renal clearance. Ultimately, the choice to continue treatment with duloxetine or switch medications in these settings should be weighed against the risk of adverse effects or treatment failure should the alternative prove less effective.

### Case 3: Duloxetine Drug Interactions and Hepatic Considerations

A 49-year-old patient with a history of alcohol use disorder and chronic back pain presents to the clinic requesting

medication for back pain and neuropathy. The baseline complete metabolic panel (CMP) from a 1-month-prior visit is within normal limits. Duloxetine 60 mg daily and tramadol 50 mg 3 times daily as needed for pain are initiated. One month later, the patient returns to the clinic endorsing continued back pain, asking for “something stronger,” and reports insomnia, nausea, and vomiting. They endorse drinking 1 to 2 beers per night to help with sleep. Repeat CMP results with AST = 205 U/L, ALT = 175 U/L, and normal bilirubin. After holding medications for 1 week, CMP returns to normal. The patient resumed tramadol, and duloxetine was switched to nortriptyline 25 mg at bedtime for neuropathy with a plan to titrate.

## Impact of Duloxetine on Hepatic Function

Drug-induced liver injury (DILI) and hepatic failure associated with duloxetine use have been reported.<sup>1</sup> A retrospective cohort study compared individuals treated with duloxetine (n = 30 844) to individuals treated with venlafaxine (n = 21 000), SSRIs (n = 28 479) or nonpharmacological treatments (n = 22 714) and found no statistically significant difference in risk of hepatic dysfunction.<sup>25</sup> However, labeling indicates transaminase elevations more than 3 times the upper limit of normal occurred in 1.25% of patients taking duloxetine compared with 0.45% of patients taking placebo in clinical trials. The median time to detection of transaminitis was 2 months, and the degree elevation appeared to be dose related.<sup>1</sup> Additionally, labeling includes reports of fatal hepatic failure, hepatocellular injury, cholestatic jaundice, hepatomegaly, and transaminase levels more than 20 times the upper limit of normal in patients taking duloxetine. While DILI is rare, duloxetine may be a contributing factor to its occurrence. Regular monitoring of liver function tests is not recommended on the product label. However, in practice, it is reasonable to assess baseline liver function in patients with risk factors for liver disease and to follow up 1 to 3 months after initiation. This practice is intended to aid in the determination of the role of duloxetine in the new onset of liver injury. If a patient on duloxetine develops jaundice, abdominal pain, or other evidence of liver dysfunction, DILI should be considered, and the medication should be stopped unless another clear and reversible cause can be established.

While duloxetine does not interact directly with ethanol according to pharmacokinetic studies, package labeling cautions against the use of duloxetine in patients with “substantial alcohol use” and that use concomitant “with heavy alcohol intake may be associated with severe liver injury.”<sup>1</sup> The labeling does not define “substantial alcohol use” nor indicate whether this risk was established from clinical trial data (where alcohol use disorder is generally excluded) or postmarketing data. Based on the potential risk and confounding of

cause if liver injury does occur, it is wise to avoid duloxetine use in patients with alcohol use disorder.

## Impact of Hepatic Dysfunction on Duloxetine

An open-label study included in duloxetine prescribing information compared duloxetine pharmacokinetics in 6 patients with moderate cirrhosis (Child-Pugh class B) with 6 healthy subjects following a single 20-mg dose. The researchers found patients with cirrhosis had a 5-fold and 3-fold increase in AUC and  $t_{1/2}$ , respectively, compared with healthy controls.<sup>1,26</sup> In patients with chronic liver disease who are clinically stable on duloxetine, it is reasonable to continue the medication in the absence of adverse effects if switching to an alternative treatment is unacceptable. Patients should be monitored for signs of duloxetine toxicity, including nausea, headache, jitteriness, and muscle twitching. Empiric dose reductions may be considered, especially for patients taking more than 60 mg daily.

In patient case 3, a recent CMP was available for baseline comparison, so new labs were not necessary. The elevations of AST and ALT after starting duloxetine were consistent with medication-induced transaminitis. Alcohol may have contributed but was not likely the sole factor with reported intake. With no changes in bilirubin, albumin, or other signs of hepatocellular injury, it is not likely that duloxetine metabolism changed in this case because of liver dysfunction.

## Pharmacokinetic Interactions

Clinically relevant pharmacokinetic interactions primarily involve duloxetine as a CYP1A2 substrate or a CYP2D6 inhibitor.

### CYP1A2 Mediated

Duloxetine is primarily and extensively metabolized by CYP1A2. Coadministration of duloxetine with fluvoxamine 100 mg, a strong inhibitor of CYP1A2 and moderate inhibitor of CYP2D6, increases duloxetine AUC by 460% and  $C_{max}$  by 141%, with a 2-fold increase in oral bioavailability.<sup>1</sup> Coadministration of duloxetine with CYP1A2 inhibitors should be avoided whenever possible. The FDA-recognized strong, moderate, and weak inhibitors of CYP1A2 are included in Table 1.<sup>27</sup>

Cigarette smoke induces CYP1A2 and decreases duloxetine AUC by approximately 33%.<sup>1</sup> A retrospective cohort study assessed steady state duloxetine levels in 89 nonsmoking versus 36 smoking duloxetine users.<sup>28</sup> Despite higher duloxetine doses (median dose 90 mg vs 60 mg,  $P = .001$ ), duloxetine users who smoked had lower median serum duloxetine concentrations (29 vs 48 ng/mL,  $P < .001$ ) and dose-adjusted serum concentrations were 53.6% lower in

**TABLE 1: CYP1A2-mediated interacting agents<sup>27</sup>**

CYP1A2 Inhibitors	
Strong <sup>a</sup>	Moderate <sup>a</sup>
Ciprofloxacin	Methoxsalen
Fluvoxamine	Mexiletine
	Oral Contraceptives
	Vemurafenib
CYP1A2 Inducers	
Moderate <sup>b</sup>	
	Phenytoin
	Rifampin
	Teriflunomide
	Smoking

<sup>a</sup>Strong and moderate inhibitors increase the area under the curve (AUC) of sensitive substrates agents by  $\geq 5$ -fold, and  $\geq 2$  to  $< 5$ -fold, respectively.

<sup>b</sup>Moderate inducers increase the AUC of sensitive substrate agents by  $\geq 50\%$  to  $< 80\%$ .

smoking versus nonsmoking duloxetine users.<sup>28</sup> Nonsmoking users were older than the smoking users (median 63 vs 47 years,  $P < .001$ ), which would theoretically put them at higher risk of medication accumulation due to age-associated decreases in hepatic enzyme activity; however, that alone is unlikely to account for the significantly higher serum duloxetine concentrations. Additionally, a small, prospective cohort study measuring steady-state duloxetine serum concentrations in 8 smoking versus 15 nonsmoking duloxetine users found the mean serum concentration was  $24.3 + 18.8$  ng/mL in smoking users versus  $67.8 + 87.5$  ng/mL in nonsmoking users (mean dose 84 mg/d versus 90.5 mg/d, respectively).<sup>29</sup>

Transcription may return to baseline within 18 hours of inducer discontinuation and a reduction in CYP1A2 activity by 28.2% can be seen within 4 days of smoking cessation, so patients may display signs and symptoms of duloxetine toxicity within days of stopping smoking.<sup>13,30</sup> Because the hydrocarbons in cigarette smoke mediate this interaction, nicotine replacement will not prevent duloxetine levels from increasing with smoking cessation. This interaction should also be considered in patients initiating or discontinuing other CYP1A2 inducers (Table 1). Patients should be counseled regarding the need for dose reduction in the future if they decide to stop smoking.

## CYP2D6 Mediated

Duloxetine is a moderately potent inhibitor of CYP2D6, which may result in a 2- to 3-fold increase in substrate concentrations.<sup>31</sup> Cytochrome 2D6 is responsible for the metabolism of commonly prescribed medication classes, including antipsychotics, opioids, and beta-blockers.<sup>32</sup> When duloxetine is administered with active substrates of CYP2D6, patients should be monitored for adverse effects associated with toxicity of the interacting agent. For example, 1 retrospective study compared outcomes between antidepressants when coadministered with beta-blockers. The authors found

**TABLE 2: CYP2D6-mediated interacting agents<sup>27</sup>**

CYP2D6 Substrates	
Sensitive <sup>a</sup>	Moderately Sensitive <sup>a</sup>
Atomoxetine	Encainide
Desipramine	Imipramine
Dextromethorphan	Metoprolol
Eliglustat	Propafenone
Nebivolol	Propranolol
Nortriptyline	Tramadol
Perphenazine	Trimipramine
Tolterodine	S-venlafaxine
R-venlafaxine	
CYP2D6 Inhibitors	
Strong <sup>b</sup>	Moderate <sup>b</sup>
Bupropion	Abiraterone
Fluoxetine	Cinacalcet
Paroxetine	Duloxetine
Quinidine	Lorcaserin
Terbinafine	Mirabegron

<sup>a</sup>Sensitive and moderately sensitive substrates demonstrate an increased area under the curve (AUC) of  $\geq 5$ -fold and  $\geq 2$  to  $< 5$ -fold, respectively, when administered with strong index inhibitors.

<sup>b</sup>Strong and moderate inhibitors increase the AUC of sensitive substrates agents by  $\geq 5$ -fold and  $\geq 2$  to  $< 5$ -fold, respectively.

patients receiving beta-blockers (carvedilol, metoprolol, and propranolol) with antidepressants that inhibited 2D6 (fluoxetine, paroxetine, bupropion, and duloxetine) were significantly more likely to require hospitalization for hemodynamic events (hazard ratio [HR] 1.53, 95% CI 1.03-2.81;  $P = .04$ ), while patients who received other antidepressants did not.<sup>33</sup> It is also sensible to consider alternatives or to initiate known substrates of 2D6 at lower than usual doses in conjunction with duloxetine. The FDA-recognized sensitive and moderately sensitive CYP2D6 substrates are included in Table 2.

When duloxetine is coadministered with prodrugs metabolized by CYP2D6, such as tamoxifen, tramadol, or other opioids, it may result in decreased efficacy.<sup>34-36</sup> The interaction between duloxetine and tramadol is commonly overlooked in practice despite having the risk of both toxicity and decreased analgesic effect. Tramadol is a weak mu-opioid receptor agonist that inhibits serotonin and norepinephrine transporters. CYP2D6 mediates the conversion of tramadol to one of the active metabolites, O-desmethyltramadol, which is 200 to 300 times more potent at the mu-opioid receptor than the parent compound. Use of tramadol concurrently with CYP2D6 inhibitors, especially those that also inhibit serotonin reuptake, increases the risk of serotonin syndrome and seizures.<sup>35,36</sup> Additionally, evidence demonstrates use of CYP2D6 inhibitors, like duloxetine, concurrently with tramadol and other opioids that are metabolized to more potent metabolites (codeine, hydrocodone, oxycodone), may lead to inadequate pain control.<sup>35,36</sup>

While duloxetine is metabolized by CYP2D6 and phase II-III trials demonstrated that coadministration of duloxetine

40 mg daily with paroxetine 20 mg daily, a strong CYP2D6 inhibitor, increased duloxetine AUC by 60%, this finding was not statistically significant.<sup>1</sup> In patients taking duloxetine with a concomitant CYP2D6 inhibitor, no empiric dose reductions are recommended. There are no known significant inducers of CYP2D6 that would impact duloxetine metabolism.<sup>37</sup>

In patient case 3, symptoms reported at the first return visit are consistent with SNRI adverse effects, although they have not progressed to serotonin toxicity. This may have been due to duloxetine or the combination of tramadol and duloxetine. In addition, the tramadol was not effective in managing the patient's chronic back pain. Both adverse effects and pain improved upon duloxetine discontinuation. Patients with a history of substance use disorders may have reports of ineffective analgesia misinterpreted. It is essential to assess these patients for potential contributing interactions and advocate for medication changes when warranted.

## Conclusion

Management of duloxetine in patients with medical comorbidities may be complicated by factors such as dysphagia, kidney impairment, hepatic dysfunction, and pharmacokinetic drug interactions. Patients should be monitored for signs and symptoms of toxicity or withdrawal with acute changes in smoking patterns, renal or liver function, or medications, especially during hospitalization and when initiating duloxetine or other potentially interacting medications. In certain cases, evidence suggests it may be reasonable to continue or adjust the use of duloxetine outside of product labeling parameters, such as for patients with short-term kidney impairment or acute dysphagia. However, liver injury or drug interactions associated with duloxetine may necessitate a switch to an alternative treatment. In practice, duloxetine treatment plans must be flexible and individualized to consider each patient's current comorbid condition(s).

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