Duloxetine: Drug information

(For additional information see "Duloxetine: Patient drug information" and see "Duloxetine: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Suicidal thoughts and behavior:

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors.

Brand Names: US

Cymbalta; Drizalma Sprinkle

Brand Names: Canada

AG-Duloxetine; APO-Duloxetine; Auro-Duloxetine; Cymbalta; JAMP-Duloxetine; M-Duloxetine; Mar-Duloxetine; MINT-Duloxetine; MYLAN-Duloxetine [DSC]; NRA-Duloxetine; PMS-Duloxetine; PRIVA-Duloxetine; RAN-Duloxetine; RIVA-Duloxetine; SANDOZ Duloxetine; TEVA-Duloxetine

Pharmacologic Category

Antidepressant, Serotonin/Norepinephrine Reuptake Inhibitor

Dosing: Adult

Chemotherapy-induced peripheral neuropathy (off-label use): Oral: Initial: 30 mg once daily for 1 week, then 60 mg once daily (Smith 2013).

Fibromyalgia (delayed-release particles capsule only): Oral: Initial: 30 mg once daily for 1 week, then increase to 60 mg once daily as tolerated. Alternatively, slower titrations have

been evaluated: 20 mg once daily, then increase by 20 mg every week up to 60 mg once daily as tolerated (Murakami 2017). Maximum dose: 60 mg/day; doses up to 120 mg/day were studied in clinical trials but did not confer any additional benefit.

Generalized anxiety disorder: Oral: Initial: 60 mg once daily; for some patients, it may be desirable to start at 30 mg once daily for 1 week before increasing to 60 mg once daily. Maintenance: 60 mg once daily. Although doses >60 mg/day did not confer additional benefit in clinical trials, some experts consider it reasonable to escalate the dose in individuals who do not respond satisfactorily to 60 mg/day (Bystritsky 2018; Simon 2010). If dose is escalated, increase by 30 mg increments at intervals of ≥1 week as needed and tolerated (Bystritsky 2018). Maximum: 120 mg/day.

Major depressive disorder (unipolar): Oral: Initial: 40 to 60 mg/day divided twice daily or given as a single daily dose. For some patients, it may be desirable to start at 30 mg once daily for 1 week before increasing to 60 mg once daily. Maintenance: 60 mg once daily. Although doses >60 mg/day did not confer additional benefit in clinical trials, based upon limited data, individual patients may benefit from dose escalation (Nelson 2020; Shelton 2007). If dose is escalated, increase by 30 mg increments at intervals of ≥1 week as needed and tolerated (Nelson 2020). Maximum: 120 mg/day.

Musculoskeletal pain, chronic:

Low back and nonradicular neck pain, chronic (alternative agent): **Note:** Adjunct for patients with an inadequate response to nonpharmacologic and NSAID therapy (ACP [Qaseem 2017]; Chou 2018; Isaac 2019)**.**

Oral: Initial: 30 mg once daily for 1 to 2 weeks, then increase to 60 mg once daily as tolerated; maximum dose: 60 mg/day (Isaac 2019; manufacturer's labeling).

Osteoarthritis of the knee (alternative agent): **Note:** For patients with moderate to severe symptoms and an inadequate response to nonpharmacologic interventions and oral NSAIDs or oral NSAIDs are contraindicated (Deveza 2018; OARSI [McAlindon 2014]).

Oral: Initial: 30 mg once daily for 1 week, then 60 mg once daily. Maximum dose (manufacturer's labeling): 60 mg/day. Doses up to 120 mg/day may provide some additional benefit (Chappell 2009); however, adverse effects may be increased (Micca 2013).

Neuropathic pain associated with diabetes mellitus: Oral: Initial: 60 mg once daily; lower initial doses may be considered in patients when tolerability is a concern; maximum dose:

60 mg/day; doses up to 120 mg/day were studied in clinical trials but did not confer any additional benefit (Ormseth 2011).

Stress urinary incontinence (women and men) (off-label use): Note: For patients who are unresponsive to nonpharmacologic interventions or have comorbid depression (ACP [Qaseem 2014]; Fink 2008; NICE 2013).

Oral: 40 mg twice daily (Filocamo 2007; Li 2013). Lower initial doses have been used in women to reduce adverse effects: 20 mg twice daily for 2 weeks then 40 mg twice daily (Castro-Diaz 2007; Schagen van Leeuwen 2008).

Discontinuation of therapy: When discontinuing antidepressant treatment that has lasted for >3 weeks, gradually taper the dose (eg, over 2 to 4 weeks) to minimize withdrawal symptoms and detect reemerging symptoms (APA 2010; WFSBP [Bauer 2015]). Reasons for a slower taper (eg, over 4 weeks) include use of a drug with a half-life <24 hours (eg, paroxetine, venlafaxine), prior history of antidepressant withdrawal symptoms, or high doses of antidepressants (APA 2010; Hirsch 2019). If intolerable withdrawal symptoms occur, resume the previously prescribed dose and/or decrease dose at a more gradual rate (Shelton 2001). Select patients (eg, those with a history of discontinuation syndrome) on long-term treatment (>6 months) may benefit from tapering over >3 months (WFSBP [Bauer 2015]). Evidence supporting ideal taper rates is limited (Shelton 2001; WFSBP [Bauer 2015]).

Switching antidepressants: Evidence for ideal antidepressant switching strategies is limited; strategies include cross-titration (gradually discontinuing the first antidepressant while at the same time gradually increasing the new antidepressant) and direct switch (abruptly discontinuing the first antidepressant and then starting the new antidepressant at an equivalent dose or lower dose and increasing it gradually). Cross-titration (eg, over 1 to 4 weeks depending upon sensitivity to discontinuation symptoms and adverse effects) is standard for most switches, but is contraindicated when switching to or from an MAOI. A direct switch may be an appropriate approach when switching to another agent in the same or similar class (eg, when switching between two SSRIs), when the antidepressant to be discontinued has been used for <1 week, or when the discontinuation is for adverse effects. When choosing the switch strategy, consider the risk of discontinuation symptoms, potential for drug interactions, other antidepressant properties (eg, half-life, adverse effects, and pharmacodynamics), and the degree of symptom control desired (Hirsch 2018; Ogle 2013; WFSBP [Bauer 2013]).

Switching to or from an MAOI:

Allow 14 days to elapse between discontinuing an MAOI and initiation of duloxetine.

Allow ≥5 days to elapse between discontinuing duloxetine and initiation of an MAOI according to manufacturer labeling; however, some experts recommend a 14-day washout period (APA 2010).

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Renal Impairment: Adult

The renal dosing recommendations are based upon the best available evidence and clinical expertise. Senior Editorial Team: Bruce Mueller, PharmD, FCCP, FASN, FNKF; Jason Roberts, PhD, BPharm (Hons), B App Sc, FSHP, FISAC; Michael Heung, MD, MS.

CrCl ≥30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling; however, pharmacokinetic studies suggest that mild to moderate renal impairment (CrCl 30 to 80 mL/minute) has no significant effect on duloxetine clearance.

CrCl <30 mL/minute: The manufacturer's labeling recommends to avoid use; duloxetine and inactive metabolites AUC expected to increase significantly (Lobo 2010). When necessary, some experts recommend cautious use of lower initial doses (eg, 30 mg daily); titrate slowly, not to exceed 60 mg once daily; monitor closely for adverse effects (Davison 2014; Lobo 2010; Nagler 2012; Nguyen 2019).

Hemodialysis: Not dialyzable: The manufacturer's labeling recommends to avoid use; duloxetine AUC approximately doubled and inactive metabolites AUC increased 7- and 9-fold (Lobo 2010). When necessary, some experts recommend cautious use of lower initial doses (eg, 30 mg daily); titrate slowly, not to exceed 60 mg once daily; monitor closely for adverse effects (Davison 2014; Lobo 2010; Nagler 2012; Nguyen 2019).

Peritoneal dialysis: Unlikely to be dialyzable (expert opinion): The manufacturer's labeling recommends to avoid use; duloxetine and inactive metabolites AUC expected to increase significantly (Lobo 2010). When necessary, some experts recommend cautious use of lower initial doses (eg, 30 mg daily); titrate slowly, not to exceed 60 mg once daily; monitor closely for adverse effects (Davison 2014; Lobo 2010; Nagler 2012; Nguyen 2019).

CRRT: Unlikely to be significantly removed by CRRT. Dose as for CrCl <30 mL/minute (expert opinion).

PIRRT (eg, sustained, low-efficiency diafiltration): Unlikely to be significantly removed by PIRRT. Dose as for CrCl <30 mL/minute (expert opinion).

Dosing: Hepatic Impairment: Adult

Avoid use in hepatic impairment.

Dosing: Pediatric

(For additional information see "Duloxetine: Pediatric drug information")

Note: Duloxetine is available as 2 different capsule formulations: A delayed-release particles capsule (eg, Cymbalta) which is intended to be swallowed whole and delayed-release sprinkle capsule (eg, Drizalma Sprinkle) which is intended to be opened; both have similar dosing; approved indications for formulations in pediatric patients may vary (see "Use").

Fibromyalgia, juvenile: Adolescents ≥13 years: Oral: Delayed-release particles capsule (eg, Cymbalta): Initial: 30 mg once daily; after 1 week, may increase to 60 mg once daily based on tolerability and response. In a multicenter double-blind placebo-controlled trial (n=91 duloxetine, n=93 placebo, 13 weeks duration) and the open-label extension phase that followed (n=106, 26 weeks duration), the endpoint of change in 24-hour average pain severity score (Brief Pain Inventory [BPI]) from baseline to end of the blinded phase of the trial (13 weeks) was not statistically significantly different in duloxetine vs placebo patients; however, significantly more duloxetine-treated patients experienced ≥30% and ≥50% reductions in pain severity (measured by BPI) (Upadhyaya 2019).

Generalized anxiety disorder (GAD): Children ≥7 years and Adolescents ≤17 years: Oral: Delayed-release particles and sprinkle capsules (eg, Cymbalta, Drizalma Sprinkle): Initial: 30 mg once daily; after 2 weeks, may increase based on response and tolerability to 60 mg once daily; recommended daily dose range: 30 to 60 mg once daily; if further dose increases are necessary, titrate doses in increments of 30 mg once daily; maximum daily dose: 120 mg/**day** (Strawn 2015).

Major depressive disorder (MDD): Limited data available, efficacy not established: Children ≥7 years and Adolescents ≤17 years: Oral: Initial: 30 mg once daily; may increase based on response and tolerability by 30 mg/dose increments every 2 weeks; maximum daily dose: 120 mg/**day**. Dosing based on 2 double-blind, placebo-controlled studies (n=800, ages 7 to 17 years) comparing duloxetine (n=341) to fluoxetine (n=234) or placebo (n=225) for the treatment of MDD; treatment with duloxetine or fluoxetine was not shown

to improve Children's Depression Rating Scale-Revised (CDRS-R) any better than placebo in either trial; trials were conducted with delayed-released particle capsule formulation (Atkinson 2014; Emslie 2014).

Discontinuation of therapy: Consider planning antidepressant discontinuation for lower-stress times, recognizing non-illness-related factors could cause stress or anxiety and be misattributed to antidepressant discontinuation (Hathaway 2018). Upon discontinuation of antidepressant therapy, gradually taper the dose to minimize the incidence of discontinuation syndromes (withdrawal) and allow for the detection of reemerging disease state symptoms (eg, relapse). Evidence supporting ideal taper rates after illness remission is limited. APA and NICE guidelines suggest tapering therapy over at least several weeks with consideration to the half-life of the antidepressant; antidepressants with a shorter half-life may need to be tapered more conservatively. After long-term (years) antidepressant treatment, WFSBP guidelines recommend tapering over 4 to 6 months, with close monitoring during and for 6 months after discontinuation. If intolerable discontinuation symptoms occur following a dose reduction, consider resuming the previously prescribed dose and/or decrease dose at a more gradual rate (APA 2010; Bauer 2002; Fenske 2009; Haddad 2001; NCCMH 2010; Schatzberg 2006; Shelton 2001; Warner 2006).

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

MAO inhibitor recommendations:

Switching to or from a MAO inhibitor intended to treat psychiatric disorders:

Allow at least 14 days to elapse between discontinuing a MAO inhibitor intended to treat psychiatric disorders and initiation of duloxetine.

Allow at least 5 days to elapse between discontinuing duloxetine and initiation of a MAO inhibitor intended to treat psychiatric disorders.

Dosing: Renal Impairment: Pediatric

Children ≥7 years and Adolescents:

GFR ≥30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling; however, pharmacokinetic studies suggest that mild to moderate renal impairment (CrCl 30 to 80 mL/minute) has no significant effect on duloxetine clearance.

GFR <30 mL/minute: Avoid use.

End-stage renal disease (ESRD): Avoid use; increased concentrations of duloxetine and metabolites may occur.

Dosing: Hepatic Impairment: Pediatric

Children ≥7 years and Adolescents: Avoid use in hepatic impairment; patients with moderate hepatic impairment have shown decreased hepatic metabolism and elimination.

Dosing: Geriatric

Generalized anxiety disorder: Oral: Initial: 30 mg once daily; after 2 weeks, may increase to 60 mg once daily; titrate doses >60 mg once daily in increments of 30 mg once daily; maximum dose: 120 mg/day.

Major depressive disorder (unipolar): Based on pharmacokinetic studies, manufacturer labeling suggests dosage adjustment is not necessary; however, lower initial starting doses (eg, 20 mg/day) and lower maintenance doses (eg, 30 to 60 mg/day) have been recommended by some experts for elderly patients with comorbid conditions (Kennedy 2005). Refer to adult dosing.

Other indications: Refer to adult dosing.

Discontinuation of therapy: Refer to adult dosing.

Switching antidepressants: Refer to adult dosing.

Dosage Forms: US

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule Delayed Release Particles, Oral:

Cymbalta: 20 mg, 30 mg, 60 mg [contains fd&c blue #2 (indigotine)]

Generic: 20 mg, 30 mg, 40 mg, 60 mg

Capsule Delayed Release Sprinkle, Oral:

Drizalma Sprinkle: 20 mg [contains brilliant blue fcf (fd&c blue #1), fd&c red #40, fd&c yellow #10 (quinoline yellow)]

Drizalma Sprinkle: 30 mg [contains brilliant blue fcf (fd&c blue #1), fd&c red #40]

Drizalma Sprinkle: 40 mg

Drizalma Sprinkle: 60 mg [contains brilliant blue fcf (fd&c blue #1), fd&c red #40, fd&c yellow #10 (quinoline yellow)]

Generic Equivalent Available: US

May be product dependent

Dosage Forms: Canada

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule Delayed Release Particles, Oral:

Cymbalta: 30 mg, 60 mg [contains fd&c blue #2 (indigotine)]

Generic: 30 mg, 60 mg

Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication:

Cymbalta: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021427s052lbl.pdf#page=38

Drizalma Sprinkle: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212516s001lbl.pdf#page=49

Administration: Adult

Oral: Administer without regard to meals. Swallow capsule whole; do not crush or chew.

Delayed-release particles capsule: Although the manufacturer does not recommend opening the capsule to facilitate administration, duloxetine has been found to be stable for up to 2 hours after sprinkling the contents of capsule on applesauce or in apple juice (not chocolate pudding) taking care not to crush the pellets and damage the enteric coating (Wells 2008). Tolerability studies of this administration technique have not been conducted. Adverse effects have been reported to the FDA when patients opened the capsules, however, reports do not detail if pellets were crushed (FDA 2007).

Delayed-release sprinkle capsule: Capsule can be opened and contents sprinkled over small amount of applesauce; instruct patient to swallow drug/food mixture immediately after mixing. Contents of capsule can also be added to a plastic catheter tip syringe with 50 mL of water and shaken for 10 seconds before administering through a 12 French or larger nasogastric tube.

Administration: Pediatric

Oral: Administer without regard to meals.

Delayed-release particles capsule (eg, Cymbalta): Swallow capsule whole; do not crush or chew. Although the manufacturer does not recommend opening the capsule to facilitate administration, duloxetine has been found to be stable for up to 2 hours after sprinkling the contents of capsule on applesauce or in apple juice (not chocolate pudding) taking care not to crush the pellets and damage the enteric coating (Wells 2008). Tolerability studies of this administration technique have not been conducted. Adverse effects have been reported to the FDA when patients opened the capsules; however, reports do not detail if pellets were crushed (FDA 2007).

Delayed-release sprinkle capsule (eg, Drizalma Sprinkle):

Oral: Swallow capsule whole; do not crush or chew. For patients with difficulty swallowing, capsules may be opened and contents sprinkled over small amount of applesauce; instruct patient to swallow drug/food mixture immediately after mixing.

Nasogastric tube: Contents of capsule can be added to a plastic catheter tip syringe with 50 mL of water and gently shaken for 10 seconds before administering through a 12 French or larger nasogastric tube. Ensure no pellets are left in the syringe; if present, rinse syringe with an additional 15 mL of water.

Use: Labeled Indications

Fibromyalgia (delayed-release particles capsule only): Management of fibromyalgia in adult and pediatric patients ≥13 years of age.

Generalized anxiety disorder: Treatment of generalized anxiety disorder in adult and pediatric patients ≥7 years of age.

Major depressive disorder (unipolar): Treatment of unipolar major depressive disorder in adults.

Musculoskeletal pain, chronic: Management of chronic musculoskeletal pain including osteoarthritis of the knee and low back pain in adults.

Neuropathic pain associated with diabetes mellitus: Management of pain associated with diabetic peripheral neuropathy in adults.

Use: Off-Label: Adult

Chemotherapy-induced peripheral neuropathy; Stress urinary incontinence (men); Stress urinary incontinence (women)

Medication Safety Issues

Sound-alike/look-alike issues:

Cymbalta may be confused with Symbyax.

Drizalma may be confused with Drisdol, Drisdan.

DULoxetine may be confused with Dexilant, FLUoxetine, PARoxetine, vortioxetine.

Geriatric Patients: High-Risk Medication:

Beers Criteria: Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) are identified in the Beers Criteria as potentially inappropriate medications to be used with caution in patients 65 years and older due to its potential to cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia; monitor sodium concentration closely when initiating or adjusting the dose in older adults (Beers Criteria [AGS 2019]).

Adverse Reactions (Significant): Considerations

Activation of mania or hypomania

Antidepressants (when used as monotherapy) may precipitate a mixed/manic episode in patients with bipolar disorder. Treatment-emergent **mania** or **hypomania** in patients with unipolar major depressive disorder (MDD) has been reported, as many cases of bipolar disorder present in episodes of MDD (Baldessarini 2013, Dunner 2005, Peritogiannis 2008).

Mechanism: Non-dose-related; idiosyncratic. Unclear to what extent mood switches represent an uncovering of unrecognized bipolar disorder or a more direct pharmacologic effect independent of diagnosis (Baldessarini 2013, Patel 2015, Tondo 2010).

Onset: Varied; a systematic review observed that the risk of switching increased significantly within the initial 2 years of antidepressant treatment in patients with unipolar MDD receiving an antidepressant as monotherapy, but not thereafter (up to 4.6 years) (Baldessarini 2013).

Risk factors:

- Family history of bipolar disorder (Patel 2015)
- Depressive episode with psychotic symptoms (Patel 2015)
- Younger age at onset of depression (Martin 2004, Patel 2015)
- Antidepressant resistance (Patel 2015)

Bleeding risk

Serotonergic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), may increase the risk of bleeding, particularly if used concomitantly with antiplatelets and/or anticoagulants. Multiple observational studies have found an association with SSRI use and a variety of bleeding complications (Bixby 2019, Douros 2018), although prospective studies have not determined if the cause of the increased risk of bleeding is due to SSRI use alone. For SNRIs, less data exists compared to SSRIs and data supporting an association with bleeding are conflicting (Carvalho 2016, Cheng 2015, Li 2014, Tully 2012, Young 2016). However, there are case reports of **gingival hemorrhage** associated with duloxetine and some observational studies have observed an increased risk for **postpartum hemorrhage** (exposure during late gestation), stroke (**cerebrovascular accident**), and **gastrointestinal hemorrhage** in patients receiving SNRIs, predominately with studies using venlafaxine (Balhara 2007, Coupland 2011, Gicquel 2017, Hanley 2016, Huybrechts 2020, Jiang 2016, Leong 2017, Mawardi 2019, Schafer 2019).

Mechanism: Possibly via inhibition of serotonin-mediated platelet activation (inhibition of the serotonin reuptake transporter) and subsequent platelet dysfunction. SNRIs may also increase gastric acidity, which may increase the risk of GI bleeding (Bixby 2019).

*Onset:*Varied; based on data evaluating SSRIs, it has been suggested that the onset of risk is variable but likely delayed for several weeks until SNRI-induced platelet serotonin depletion becomes clinically significant (Andrade 2010), although the onset of bleeding may be more unpredictable if patients are taking concomitant antiplatelets, anticoagulants, or nonsteroidal anti-inflammatory drugs (NSAIDs).

Risk factors:

• Concomitant use of antiplatelets and/or anticoagulants (Carvalho 2016, de Abajo 2008)

• Preexisting platelet dysfunction or coagulation disorders (eg, von Willebrand factor) (Carvalho 2016, de Abajo 2008, Halperin 2007)

Hepatotoxicity

Liver test abnormalities may occur with use, but ALT elevations are usually self-limiting. However, postmarketing cases of **hepatotoxicity**, including **hepatitis, cholestatic hepatitis, cholestatic jaundice,** acute **hepatic necrosis,** and fulminant hepatic failure/**acute hepatic failure**, have been reported rarely, including fatalities and cases occurring in patients without risk factors. The pattern of hepatic injury associated with duloxetine is often **hepatocellular hepatitis**, but cholestatic and mixed hepatocellular-cholestatic forms have also been described (Bunchorntavakul 2017, Carvalho 2016, Hanje 2006, Kang 2011, LiverTox 2018, McIntyre 2008, Park 2010, Park 2013, Voican 2014, Vuppalanchi 2010).

Mechanism: Unknown by which duloxetine may cause liver injury, but likely due to a metabolic byproduct since metabolism occurs in the liver, primarily by CYP1A2 and 2D6 and is susceptible to drug-drug interactions with agents that alter these microsomal enzymes. Idiosyncratic drug-induced liver injury (DILI) is due to either direct cellular injury (metabolic idiosyncratic DILI) or are immune-mediated (immune-allergic idiosyncratic DILI). Both metabolic and immunoallergic mechanisms have been suggested for duloxetine; however, it has been reported that autoimmune (autoantibodies) and immunoallergic features (rash, fever, eosinophilia), more indicative of an immune-allergic mechanism, have been uncommon features in cases of duloxetine-associated DILI (Bunchorntavakul 2017, Carvalho 2016, LiverTox 2018, Voican 2014).

Onset: Varied; DILI associated with antidepressant use usually occurs within several days to 6 months after initiation. In a case series of DILI associated with duloxetine, a median time to onset of 50 days was observed (Carvalho 2016, LiverTox 2018, Voican 2014).

Risk factors:

• Polypharmacy, particularly with concomitant administration of multiple agents metabolized by the same CYP450 isoenzymes (Carvalho 2016, Voican 2014)

• Higher doses (potential risk factor) (Hanje 2006, Kang 2011, Vupppalanchi 2010)

Hyponatremia

Duloxetine is associated with syndrome of inappropriate antidiuretic hormone secretion (**SIADH**) and/or **hyponatremia** (including severe cases), predominantly in the elderly. Data evaluating a risk of hyponatremia with serotonin norepinephrine reuptake inhibitors (SNRIs) are more limited compared to selective serotonin reuptake inhibitors (SSRIs) (with the possible exception for venlafaxine), but there are several case reports and a few observational studies involving duloxetine suggesting an association (Carvalho 2016, Gandhi 2017, Hu 2018, Kulkarni 2019, Leth-Møeller 2016, Mori 2014, Sun 2019, Takayama 2019, Wang 2018).

Mechanism: May cause SIADH via release of antidiuretic hormone (ADH) via serotonin effects on 5-HT receptors and norepinephrine effects on alpha-1-adrenergic receptors (Viramontes 2016) or may cause nephrogenic SIADH by increasing the sensitivity of the kidney to ADH (Mannesse 2013).

Onset: Intermediate; based on data involving SSRIs, hyponatremia usually develops within the first few weeks of treatment (Jacob 2006).

Risk factors:

Based on data involving SSRIs, risk factors include:

• Older age (Jacob 2006)

• Females (Jacob 2006)

• Concomitant use of diuretics (Jacob 2006)

• Low body weight (Jacob 2006)

• Lower baseline serum sodium concentration (Jacob 2006)

• Volume depletion (Jacob 2006)

• History of hyponatremia (potential risk factors) (Mannesse 2013)

• Symptoms of psychosis (potential risk factors) (Mannesse 2013)

Ocular effects

Serotonin norepinephrine reuptake inhibitors (SNRIs) are associated with **acute angle-closure glaucoma** (AACG) in case reports. AACG may cause symptoms including eye pain, changes in vision, swelling, and redness, which can rapidly lead to permanent blindness if not treated (Kirkham 2017, Mahmut 2017, Shifera 2014, Wiciński 2019). In addition, SNRIs may be associated with an increased risk of **cataract** development (Erie 2014).

Mechanism: AACG: Unclear; hypothesized SNRIs may increase the intraocular pressure via serotonergic and adrenergic effects on ciliary body muscle activation and pupil dilation (Chen 2017, Kirkham 2017, Wiciński 2019). In addition, a pseudo-anticholinergic (although debatable for SNRIs) and a dopaminergic effect on ocular tissue cannot be excluded as potential mechanisms (Wiciński 2019).

Risk factors:

For AACG:

- Females (Costagliola 2008, Wiciński 2019)
- ≥50 years of age (slight increased risk) (Costagliola 2008, Wiciński 2019)
- Hyperopia (slight increased risk) (Costagliola 2008, Wiciński 2019)
- Personal or family history of AACG (Costagliola 2008, Wiciński 2019)
- Inuit or Asian descent (Costagliola 2008, Wiciński 2019)

Serotonin syndrome

Serotonin syndrome has been reported and typically occurs with coadministration of multiple serotonergic drugs but can occur following a single serotonergic agent at high therapeutic doses or supratherapeutic doses (Fisher 2002, Gaffney 2015, Gelener 2011, Guo 2018, Joharchi 2019, Liu 2009, Takata 2019). The diagnosis of serotonin syndrome is made based on the Hunter Serotonin Toxicity Criteria (Dunkley 2003) and may result in a spectrum of symptoms, such as anxiety, agitation, confusion, delirium, hyperreflexia, muscle rigidity, myoclonus, tachycardia, tachypnea, and tremor. Severe cases may cause hyperthermia, significant autonomic instability (ie, rapid and severe changes in blood pressure and pulse), coma, and seizures (Bartlett 2017, Boyer 2005, Sun-Edelstein 2008).

Mechanism: Dose-related; overstimulation of serotonin receptors (5-HT_{2A}) by serotonergic agents (Bartlett 2017).

Onset: Rapid; onset is typically within hours of an exposure (but delays of 24 hours or longer have been reported) (Bartlett 2017).

Risk factors:

• Concomitant use of drugs that increase serotonin synthesis, block serotonin reuptake, and/or impair serotonin metabolism (eg, monoamine oxidase inhibitors [MAOIs]). Of note, concomitant use of some serotonergic agents, such as MAOIs, are contraindicated.

Sexual dysfunction

Serotonin norepinephrine reuptake inhibitors (SNRIs) (data primarily involves venlafaxine) have been associated with **sexual disorder** in both men and women. The following adverse reactions have been associated with duloxetine: **orgasm abnormal**, **erectile dysfunction**, **decreased libido** (Clayton 2007, Delgado 2005, Higgins 2010, Lahon 2011, Nelson 2006, Norman 2008, Seretti 2009, Werneke 2006). **Priapism** has also been reported with duloxetine (Wilkening 2016).

Mechanism: Based on data involving selective serotonin reuptake inhibitors (SSRIs), it has been postulated that increases in serotonin may affect other hormones and neurotransmitters involved in sexual function; in particular, testosterone's effect on sexual arousal and dopamine's role in achieving orgasm (Jing 2016, Stahl 1998).

Suicidal thinking and behavior

Antidepressants are associated with an increased risk of **suicidal ideation** and **suicidal tendencies** in pediatric and young adult patients (18 to 24 years) in short-term studies. In adults >24 years, short-term studies did not show an increased risk of suicidal thinking and behavior; in older adults ≥65 years of age, a decreased risk was observed. Although data have yielded inconsistent results regarding the association of antidepressants and risk of suicide, particularly among adults, collective evidence shows a trend of an elevated risk of suicidality in younger age groups (Friedman 2007, Hammad 2006, Hetrick 2012, Khan 2003, Leon 2007, Parikh 2008, Reeves 2008). Of note, the risk of a suicide attempt is inherent in major depression and may persist until remission occurs.

Mechanism: Not established; one of several postulated mechanisms is that antidepressants may energize suicidal patients to act on impulses; another suggests that antidepressants may produce a worsening of depressive symptoms leading to the emergence of suicidal thoughts and actions (Reeves 2008).

Onset: Varied; increased risk observed in short-term studies (ie, <4 months) in pediatric and young adults; it is unknown whether this risk extends to long-term use (ie, >4 months).

Risk factors:

• Children and adolescents (Friedman 2007, Hammad 2006, Hetrick 2012)

• Depression (risk of suicide is associated with major depression and may persist until remission occurs)

Withdrawal syndrome

Withdrawal syndrome, consisting of both somatic symptoms (eg, dizziness, chills, light-headedness, vertigo, shock-like sensations, paresthesia, fatigue, headache, nausea, tremor, diarrhea, visual disturbances) and psychological symptoms (eg, anxiety, agitation, confusion, insomnia, irritability, mania), have been reported with serotonin norepinephrine reuptake inhibitors (SNRIs), primarily following abrupt discontinuation. One case describes a duloxetine withdrawal seizure (Qadir 2006). Withdrawal symptoms may also occur following gradual tapering (Fava 2015, Gabriel 2017, Hou 2014, Norman 2008, Perahia 2005).

Mechanism: Withdrawal; due to reduced availability of serotonin in the CNS with decreasing levels of the serotonergic agent. Other neurotransmission systems, including increased glutamine and dopamine, may also be affected, as well as the hypothalamic-pituitary-adrenal axis (Jha 2018).

Onset: Rapid; withdrawal symptoms typically occur within a few days of discontinuation (Fava 2018, Hou 2014).

Risk factors:

• Abrupt discontinuation (rather than gradual dosage reduction) of an antidepressant treatment that has lasted for >3 weeks, particularly a drug with a half-life <24 hours (eg, paroxetine, venlafaxine) (APA 2010, Hirsch 2019, WFSBP [Bauer 2015])

• Prior history of antidepressant withdrawal symptoms (Hirsch 2019)

• High dose (Hirsch 2019)

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.

>10%:

Endocrine & metabolic: Weight loss (children and adolescents: 14% to 15%; adults: ≥1%)

Gastrointestinal: Abdominal pain (children and adolescents: 13%; adults: 5%), decreased appetite (6% to 15%; dose related), nausea (18% to 25%; dose related), vomiting (children and adolescents: 9% to 15%; adults: 3% to 4%), xerostomia (adults: 11% to 14%, dose related; children and adolescents: 2%)

Nervous system: Drowsiness (9% to 11%; dose related), fatigue (5% to 11%; dose related), headache (13% to 18%)

1% to 10%:

Cardiovascular: Flushing (3%), increased blood pressure (2%), palpitations (2%)

Dermatologic: Diaphoresis (6%), pruritus (≥1%)

Endocrine & metabolic: Decreased libido (3%), hot flash (≥1%), orgasm abnormal (2%), weight gain (≥1%)

Gastrointestinal: Constipation (9% to 10%; dose related), diarrhea (6% to 9%), dysgeusia (≥1%), dyspepsia (2%), flatulence (≥1%), viral gastroenteritis (adolescents: 5%)

Genitourinary: Ejaculatory disorder (2%), erectile dysfunction (4%), urinary frequency (≥1%)

Hepatic: Increased serum alanine aminotransferase (>3 x ULN: 1%)

Nervous system: Abnormal dreams (≥1%), agitation (3% to 4%), anorgasmia (≥1%), anxiety (3%), chills (≥1%), delayed ejaculation (2%; dose related), dizziness (8% to 9%), hypoesthesia (≥1%), insomnia (7% to 10%), lethargy (≥1%), paresthesia (≥1%), rigors (≥1%), sleep disorder (≥1%), vertigo (≥1%), yawning (2%)

Neuromuscular & skeletal: Musculoskeletal pain (≥1%), tremor (2% to 3%)

Ophthalmic: Blurred vision (3%)

Respiratory: Cough (children and adolescents: 3%), nasopharyngitis (adolescents: 9%), oropharyngeal pain (children and adolescents: 4%; adults: ≥1%), upper respiratory tract infection (adolescents: 7%)

<1%:

Cardiovascular: Acute myocardial infarction, cardiomyopathy (Takotsubo), cold extremity, orthostatic hypotension, tachycardia

Dermatologic: Contact dermatitis, ecchymoses, erythema of skin, night sweats, skin photosensitivity

Endocrine & metabolic: Dehydration, dyslipidemia, hyperlipidemia, hypothyroidism, increased serum cholesterol, increased thirst, menstrual disease

Gastrointestinal: Bruxism, dysphagia, eructation, gastric ulcer, gastritis, gastroenteritis, gastrointestinal hemorrhage, halitosis, stomatitis

Genitourinary: Dysuria, malodorous urine, menopausal symptoms, nocturia, sexual disorder (literature suggests an incidence of 46%) (Lahon 2011), urinary urgency

Hematologic & oncologic: Nonthrombocytopenic purpura

Nervous system: Abnormal gait, apathy, confusion, disorientation, disturbance in attention, dysarthria, falling, feeling abnormal, irritability, malaise, myoclonus, sensation of cold, suicidal tendencies

Neuromuscular & skeletal: Asthenia, dyskinesia, muscle spasm, muscle twitching

Ophthalmic: Diplopia, dry eye syndrome, visual impairment

Otic: Otalgia, tinnitus

Renal: Polyuria

Respiratory: Laryngitis, pharyngeal edema

Frequency not defined:

Endocrine & metabolic: Decreased serum potassium, increased serum bicarbonate, increased serum potassium

Hepatic: Increased serum alkaline phosphatase, increased serum aspartate aminotransferase

Nervous system: Suicidal ideation (Parikh 2008)

Neuromuscular & skeletal: Bone fracture, increased creatinine phosphokinase in blood specimen

Postmarketing:

Cardiovascular: Cerebrovascular accident (Leong 2017), hypersensitivity angiitis, hypertensive crisis, supraventricular cardiac arrhythmia, syncope

Dermatologic: Erythema multiforme, skin rash, Stevens-Johnson syndrome (Strawn 2011), urticaria

Endocrine & metabolic: Galactorrhea not associated with childbirth, hyperglycemia, hyperprolactinemia, hyponatremia (Hu 2018), SIADH (Mori 2014)

Gastrointestinal: Acute pancreatitis, colitis, gingival hemorrhage (rare: <1%) (Balhara 2007; Gicquel 2017)

Genitourinary: Gynecological bleeding, postpartum hemorrhage (Huybrechts 2020), priapism (Wilkening 2016), urinary retention

Hepatic: Acute hepatic failure (rare: <1%) (Hanje 2006), cholestatic hepatitis (rare: <1%) (Vuppalanchi 2010), cholestatic jaundice (rare: <1%) (Park 2010), hepatic necrosis (rare: <1%) (LiverTox 2018), hepatitis (rare: <1%) (LiverTox 2018), hepatocellular hepatitis (rare: <1%) (Vuppalanchi 2010), hepatotoxicity (rare: <1%) (Park 2013), increased serum transaminases (rare: <1%) (Kang 2011)

Hypersensitivity: Anaphylaxis, angioedema, hypersensitivity reaction

Nervous system: Aggressive behavior (particularly early in treatment or after treatment discontinuation), extrapyramidal reaction, hypomania (rare: <1%) (Peritogiannis 2008), mania (rare: <1%) (Dunner 2005), outbursts of anger (particularly early in treatment or after treatment discontinuation), restless leg syndrome, seizure (with treatment discontinuation), serotonin syndrome (rare: <1%) (Gelener 2011), sleep disorder (rapid eye movement) (Tan 2017), trismus, withdrawal syndrome (common: ≥10%) (Perahia 2005)

Ophthalmic: Acute angle-closure glaucoma (rare: <1%) (Mahmut 2017), cataract (Erie 2014)

Renal: Renal colic (Wilkening 2017)

Contraindications

Use of monoamine oxidase (MAO) inhibitors intended to treat psychiatric disorders (concurrently or within 14 days of discontinuing the MAO inhibitor); initiation of MAO inhibitor intended to treat psychiatric disorders within 5 days of discontinuing duloxetine; initiation of duloxetine in a patient receiving linezolid or intravenous methylene blue.

Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to duloxetine or any component of the formulation; hepatic impairment; severe renal

impairment (eg, CrCl <30 mL/minute) or end-stage renal disease (ESRD); uncontrolled narrow-angle glaucoma; concomitant use with thioridazine or with potent CYP1A2 inhibitors.

Warnings/Precautions

Major psychiatric warnings:

• Suicidal thinking/behavior: **[US Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years of age. Closely monitor for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1 to 2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with health care provider. A medication guide concerning the use of antidepressants in children and teenagers should be dispensed with each prescription.

• The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

• Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their health care provider if any of these symptoms or worsening depression occurs.

Concerns related to adverse effects:

• Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin or NSAIDs due to ulcerogenic potential. Bleeding related to SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

• CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

• Dermatologic: Severe skin reactions (including Stevens-Johnson syndrome and erythema multiforme) have been reported; discontinue immediately if blisters, peeling rash, mucosal erosions, or any other signs of hypersensitivity reactions are suspected.

• Fractures: Bone fractures have been associated with antidepressant treatment. Consider the possibility of a fragility fracture if an antidepressant-treated patient presents with unexplained bone pain, point tenderness, swelling, or bruising (Rabenda 2013; Rizzoli 2012).

• Hepatotoxicity: Avoid use in patients with substantial alcohol intake, evidence of liver disease or hepatic impairment. Rare cases of hepatic failure (including fatalities) have been reported with use. Hepatitis with abdominal pain, hepatomegaly, elevated transaminase levels >20 times ULN with and without jaundice have all been observed. Discontinue therapy with the presentation of jaundice or other signs of hepatic dysfunction and do not reinitiate therapy unless another source or cause is identified.

• Hyperglycemia: Modest increases in serum glucose and HbA_{1c} levels have been observed in some diabetic patients receiving duloxetine for diabetic peripheral neuropathic pain (DPNP).

• Ocular effects: May cause mild pupillary dilation which in susceptible individuals can lead to an episode of narrow-angle glaucoma. Consider evaluating patients who have not had an iridectomy for narrow-angle glaucoma risk factors.

• Orthostatic hypotension/syncope: May cause orthostatic hypotension/syncope, especially within the first week of therapy and after dose increases. Carefully monitor blood pressure with initiation of therapy, dose increases (especially in patients receiving >60 mg/day), or when using concomitant vasodilators or CYP1A2 inhibitors. Consider dose reduction or discontinuation of duloxetine if orthostatic hypotension or syncope occurs.

• Serotonin syndrome (SS) reactions: Potentially life-threatening serotonin syndrome (SS) has occurred with serotonergic agents (eg, SSRIs, SNRIs), particularly when used in combination with other serotonergic agents (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St John's wort) or drugs that impair serotonin metabolism (eg, monoamine oxidase inhibitors, specifically linezolid, methylene blue, and others used for psychiatric disorders). Monitor patients closely for signs/symptoms of SS, which may include mental status changes (eg, agitation, hallucinations, delirium), seizures, autonomic instability (eg, tachycardia, dizziness, diaphoresis), neuromuscular symptoms (eg, tremor, rigidity, myoclonus), or GI

symptoms (eg, nausea, vomiting, diarrhea). Discontinue treatment (and any concomitant serotonergic agents) immediately if signs/symptoms arise.

• Sexual dysfunction: May cause or exacerbate sexual dysfunction.

• SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

• Urinary hesitancy: May cause increased urinary resistance; advise patient to report symptoms of urinary hesitation/difficulty.

Disease-related concerns:

• Cardiovascular disease: Use caution in patients with cardiovascular conditions or cerebrovascular disease.

• Gastroparesis: Use caution in patients with impaired gastric motility (eg, some diabetics); may affect stability of the capsule's enteric coating.

• Hepatic impairment: Avoid use in patients with chronic liver disease or cirrhosis; clearance is decreased and half-life and plasma concentrations are increased.

• Hypertension: Use caution in patients with hypertension; preexisting hypertension should be treated prior to initiating therapy. Although no statistically significant differences in the frequency of sustained elevations of BP were observed in clinical trials when compared with placebo, modest increases in BP have been reported with use. Additionally, rare cases of hypertensive crisis have been reported; BP should be evaluated prior to initiating therapy and periodically thereafter; consider dose reduction or gradual discontinuation of therapy in individuals with sustained hypertension during therapy.

• Mania/hypomania: May precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Combination therapy with an antidepressant and a mood stabilizer may be effective for acute treatment of bipolar major depressive episodes, but should be avoided in acute mania or mixed episodes, as well as maintenance treatment in bipolar disorder due to the mood-destabilizing effects of antidepressants (CANMAT [Yatham 2018]; WFSBP [Grunze 2018]). Patients presenting with depressive symptoms should be screened for

bipolar disorder. **Duloxetine is not FDA approved for the treatment of bipolar depression.**

• Renal impairment: Use with caution; clearance is decreased and plasma concentrations are increased; dose reduction may be required.

• Seizure disorders: Use caution in patients with a previous seizure disorder or condition predisposing to seizures, such as brain damage or alcohol use disorder (Montgomery 2005).

Special populations:

• Fall risk: Falls with serious consequences, including bone fractures and hospitalization, have been reported in patients receiving therapeutic doses of duloxetine. The risk of falling appears related to the degree of orthostatic decrease in BP. Risks may also be greater in elderly patients, patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors, and in patients taking doses >60 mg/day. Consider dose reduction or discontinuation of duloxetine if falls occur.

• Sucrose intolerance: Some formulations may contain sucrose; patients with fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should avoid use.

Other warnings/precautions:

• Discontinuation syndrome: Abrupt discontinuation or interruption of antidepressant therapy has been associated with a discontinuation syndrome. Symptoms arising may vary with antidepressant; however, they commonly include nausea, vomiting, diarrhea, headaches, lightheadedness, dizziness, diminished appetite, sweating, chills, tremors, paresthesias, fatigue, somnolence, and sleep disturbances (eg, vivid dreams, insomnia). Less common symptoms include electric shock-like sensations, cardiac arrhythmias (more common with tricyclic antidepressants), myalgias, parkinsonism, arthralgias, and balance difficulties. Psychological symptoms may also emerge such as agitation, anxiety, akathisia, panic attacks, irritability, aggressiveness, worsening of mood, dysphoria, mood lability, hyperactivity, mania/hypomania, depersonalization, decreased concentration, slowed thinking, confusion, and memory or concentration difficulties. Greater risks for developing a discontinuation syndrome have been associated with antidepressants with shorter half-lives, longer durations of treatment, and abrupt discontinuation. For antidepressants of short or intermediate half-lives,

symptoms may emerge within 2 to 5 days after treatment discontinuation and last 7 to 14 days (APA 2010; Fava 2006; Haddad 2001; Shelton 2001; Warner 2006).

Metabolism/Transport Effects

Substrate of CYP1A2 (major), CYP2D6 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP2D6 (moderate)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Abametapir: May increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Acalabrutinib: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.): May enhance the antiplatelet effect of other Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Ajmaline: May increase the serum concentration of CYP2D6 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Ajmaline: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Ajmaline. *Risk C: Monitor therapy*

Alcohol (Ethyl): May enhance the adverse/toxic effect of Serotonin/Norepinephrine Reuptake Inhibitors. Specifically, risks of psychomotor impairment may be enhanced. Alcohol (Ethyl) may enhance the hepatotoxic effect of Serotonin/Norepinephrine Reuptake Inhibitors. Particularly duloxetine and milnacipran. Management: Patients receiving serotonin/norepinephrine reuptake inhibitors (SNRIs) should be advised to avoid alcohol. Monitor for increased psychomotor impairment and hepatotoxicity in patients who consume alcohol during treatment with SNRIs. *Risk D: Consider therapy modification*

Almotriptan: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Alosetron: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. Management: If possible, avoid coadministration of direct-acting alpha-/beta-agonists and serotonin/norepinephrine reuptake inhibitors. If coadministered, monitor for increased sympathomimetic effects (eg, increased blood pressure, chest pain, headache). *Risk D: Consider therapy modification*

Alpha2-Agonists: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the antihypertensive effect of Alpha2-Agonists. *Risk C: Monitor therapy*

Amphetamines: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Amphetamines. Management: Monitor for amphetamine toxicities (including serotonin syndrome) if used with a moderate CYP2D6 inhibitor. Initiate amphetamine therapy at lower doses, monitor frequently, and adjust doses as needed. Discontinue amphetamines if serotoinin syndrome occurs *Risk C: Monitor therapy*

Amphetamines: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability). Initiate amphetamines at lower doses, monitor frequently, and adjust doses as needed. *Risk C: Monitor therapy*

Anticoagulants: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Antipsychotic Agents: Serotonergic Agents (High Risk) may enhance the adverse/toxic effect of Antipsychotic Agents. Specifically, serotonergic agents may enhance dopamine blockade, possibly increasing the risk for neuroleptic malignant syndrome. Antipsychotic Agents may

enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. *Risk C: Monitor therapy*

Apixaban: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Apixaban. Specifically, the risk for bleeding may be increased. Management: Carefully consider risks and benefits of this combination and monitor closely. *Risk C: Monitor therapy*

ARIPiprazole: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole pharmacologic effects. Aripiprazole dose adjustments may or may not be required based on concomitant therapy, indication, or dosage form. Consult full interaction monograph for specific recommendations. *Risk C: Monitor therapy*

ARIPiprazole Lauroxil: CYP2D6 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of ARIPiprazole Lauroxil. *Risk C: Monitor therapy*

Aspirin: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

AtoMOXetine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of AtoMOXetine. *Risk C: Monitor therapy*

Bemiparin: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Bemiparin. Management: Avoid concomitant use of bemiparin with antiplatelet agents. If concomitant use is unavoidable, monitor closely for signs and symptoms of bleeding. *Risk D: Consider therapy modification*

Blood Pressure Lowering Agents: May enhance the hypotensive effect of DULoxetine. *Risk C: Monitor therapy*

Brexanolone: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the CNS depressant effect of Brexanolone. *Risk C: Monitor therapy*

Brexpiprazole: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Brexpiprazole. Management: If brexpiprazole is to be used together with both a moderate CYP2D6 inhibitor and a strong or moderate CYP3A4 inhibitor, the brexpiprazole dose should be reduced to 25% of the usual dose when treating indications other than major depressive disorder. *Risk C: Monitor therapy*

Broccoli: May decrease the serum concentration of CYP1A2 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Bromopride: May enhance the adverse/toxic effect of Serotonin/Norepinephrine Reuptake Inhibitors. *Risk X: Avoid combination*

BusPIRone: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Cannabis: May decrease the serum concentration of CYP1A2 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Carvedilol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Carvedilol. *Risk C: Monitor therapy*

Cephalothin: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Cephalothin. Specifically, the risk for bleeding may be increased. *Risk C: Monitor therapy*

CloZAPine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of CloZAPine. *Risk C: Monitor therapy*

Cobicistat: May increase the serum concentration of CYP2D6 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Collagenase (Systemic): Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Collagenase (Systemic). Specifically, the risk of injection site bruising and/or bleeding may be increased. *Risk C: Monitor therapy*

Cyclobenzaprine: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

CYP1A2 Inducers (Moderate): May decrease the serum concentration of DULoxetine. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May increase the serum concentration of DULoxetine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May increase the serum concentration of DULoxetine. *Risk C: Monitor therapy*

Dabigatran Etexilate: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Dabigatran Etexilate. Agents with Antiplatelet Properties may increase the serum concentration of Dabigatran Etexilate. This mechanism applies specifically to clopidogrel. Management: Carefully consider risks and benefits of this combination and monitor closely; Canadian labeling recommends avoiding prasugrel or ticagrelor. *Risk C: Monitor therapy*

Dapoxetine: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Do not use serotonergic agents (high risk) with dapoxetine or within 7 days of serotonergic agent discontinuation. Do not use dapoxetine within 14 days of monoamine oxidase inhibitor use. Dapoxetine labeling lists this combination as contraindicated. *Risk X: Avoid combination*

Dasatinib: May enhance the anticoagulant effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Deoxycholic Acid: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Deoxycholic Acid. Specifically, the risk for bleeding or bruising in the treatment area may be increased. *Risk C: Monitor therapy*

Deutetrabenazine: CYP2D6 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of Deutetrabenazine. *Risk C: Monitor therapy*

Dexmethylphenidate-Methylphenidate: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Dextromethorphan: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

DOXOrubicin (Conventional): CYP2D6 Inhibitors (Moderate) may increase the serum concentration of DOXOrubicin (Conventional). *Risk X: Avoid combination*

Edoxaban: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Edoxaban. Specifically, the risk of bleeding may be increased. *Risk C: Monitor therapy*

Eletriptan: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Eliglustat: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Eliglustat. Management: Eliglustat dose is 84 mg daily with CYP2D6 inhibitors. Use is contraindicated (COI) when also combined with strong CYP3A4 inhibitors. When also combined with a moderate CYP3A4 inhibitor, use is COI in CYP2D6 EMs or IMs and should be avoided in CYP2D6 PMs. *Risk D: Consider therapy modification*

Enoxaparin: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Enoxaparin. Management: Discontinue antiplatelet agents prior to initiating enoxaparin whenever possible. If concomitant administration is unavoidable, monitor closely for signs and symptoms of bleeding. *Risk D: Consider therapy modification*

Ergot Derivatives: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Fat Emulsion (Fish Oil Based): May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Fenfluramine: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. *Risk C: Monitor therapy*

FentaNYL: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) if these agents are combined. *Risk C: Monitor therapy*

Flecainide: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Flecainide. *Risk C: Monitor therapy*

FluvoxaMINE: DULoxetine may enhance the antiplatelet effect of FluvoxaMINE. DULoxetine may enhance the serotonergic effect of FluvoxaMINE. This could result in serotonin syndrome. FluvoxaMINE may increase the serum concentration of DULoxetine. *Risk X: Avoid combination*

Glucosamine: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Haloperidol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Haloperidol. *Risk C: Monitor therapy*

Heparin: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Heparin. Management: Decrease the dose of heparin or agents with antiplatelet properties if coadministration is required. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. Bleeding may occur. Management: Avoid combination when possible. If used, monitor more closely for evidence of bleeding. Discontinue herbal products with anticoagulant or antiplatelet actions 2 weeks prior to surgical, dental, or invasive procedures. *Risk D: Consider therapy modification*

Ibritumomab Tiuxetan: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Ibritumomab Tiuxetan. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ibrutinib: May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Icosapent Ethyl: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Iloperidone: CYP2D6 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Iloperidone. Specifically, concentrations of the metabolite P95 may be decreased. CYP2D6 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of Iloperidone. Specifically, concentrations of the metabolite P88 may be increased. CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Iloperidone. *Risk C: Monitor therapy*

Indoramin: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Indoramin. *Risk C: Monitor therapy*

Inotersen: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Iobenguane Radiopharmaceutical Products: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane Radiopharmaceutical Products. Management: Discontinue all drugs that may inhibit or interfere with catecholamine transport or uptake for at least 5 biological half-lives before iobenguane administration. Do not administer these drugs until at least 7 days after each iobenguane dose. *Risk X: Avoid combination*

Ioflupane I 123: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the diagnostic effect of Ioflupane I 123. *Risk C: Monitor therapy*

Lasmiditan: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Levomethadone: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Limaprost: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Linezolid: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Lorcaserin (Withdrawn From US Market): May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Lumefantrine: May increase the serum concentration of CYP2D6 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Meperidine: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) if these agents are combined. *Risk C: Monitor therapy*

Mequitazine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Mequitazine. *Risk X: Avoid combination*

Metaxalone: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Methadone: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Methylene Blue: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the serotonergic effect of Methylene Blue. This could result in serotonin syndrome. *Risk X: Avoid combination*

Metoclopramide: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Metoclopramide. *Risk C: Monitor therapy*

Metoprolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Metoprolol. *Risk C: Monitor therapy*

Mirtazapine: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Monoamine Oxidase Inhibitors (Antidepressant): May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Multivitamins/Fluoride (with ADE): May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Multivitamins/Minerals (with ADEK, Folate, Iron): May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Multivitamins/Minerals (with AE, No Iron): May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nefazodone: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents (Nonselective): Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Nonsteroidal Anti-Inflammatory Agents (Nonselective). *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents (Topical): Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Nonsteroidal Anti-Inflammatory Agents (Topical). *Risk C: Monitor therapy*

Obinutuzumab: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Obinutuzumab. Specifically, the risk of serious bleeding-related events may be increased. *Risk C: Monitor therapy*

Oliceridine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Oliceridine. *Risk C: Monitor therapy*

Olmutinib: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Olmutinib. *Risk C: Monitor therapy*

Omega-3 Fatty Acids: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Ondansetron: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Opioid Agonists: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Opioid Agonists (metabolized by CYP3A4 and CYP2D6): May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Opioid Agonists (metabolized by CYP3A4): May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Oxitriptan: Serotonergic Agents (High Risk) may enhance the serotonergic effect of Oxitriptan. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Ozanimod: May enhance the adverse/toxic effect of Serotonergic Agents (High Risk). *Risk C: Monitor therapy*

Peginterferon Alfa-2b: May decrease the serum concentration of CYP2D6 Substrates (High risk with Inhibitors). Peginterferon Alfa-2b may increase the serum concentration of CYP2D6 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pentoxifylline: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Perhexiline: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Perhexiline. *Risk C: Monitor therapy*

Perphenazine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Perphenazine. *Risk C: Monitor therapy*

Pimozide: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Pimozide. *Risk C: Monitor therapy*

Pitolisant: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Pitolisant. *Risk C: Monitor therapy*

Propafenone: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Propafenone. *Risk C: Monitor therapy*

Propranolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Ramosetron: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Rasagiline: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

RisperiDONE: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of RisperiDONE. *Risk C: Monitor therapy*

Rivaroxaban: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Rivaroxaban. Management: Carefully consider risks and benefits of this combination and monitor closely; Canadian labeling recommends avoiding prasugrel or ticagrelor. *Risk C: Monitor therapy*

Safinamide: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Salicylates: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of DULoxetine. Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of DULoxetine. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, mental status changes) when these agents are combined. In addition, monitor for signs and symptoms of bleeding. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors (Strong CYP2D6 Inhibitors): DULoxetine may enhance the antiplatelet effect of Selective Serotonin Reuptake Inhibitors (Strong CYP2D6 Inhibitors). DULoxetine may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors (Strong CYP2D6 Inhibitors). This could result in serotonin syndrome. Selective Serotonin Reuptake Inhibitors (Strong CYP2D6 Inhibitors) may increase the serum concentration of DULoxetine. Management: Monitor for increased duloxetine effects/toxicities and signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperthermia, tremor, mental status changes) when these agents are combined. In addition, monitor for signs and symptoms of bleeding. *Risk C: Monitor therapy*

Selegiline: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Selumetinib: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Serotonergic Agents (High Risk, Miscellaneous): Serotonin/Norepinephrine Reuptake Inhibitors may enhance the serotonergic effect of Serotonergic Agents (High Risk, Miscellaneous). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Serotonin 5-HT1D Receptor Agonists (Triptans): May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of other Serotonin/Norepinephrine Reuptake Inhibitors. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the serotonergic effect of other Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, mental status changes) when these agents are combined. In addition, monitor for signs and symptoms of bleeding. *Risk C: Monitor therapy*

St John's Wort: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. St John's Wort may decrease the serum concentration of Serotonergic Agents (High Risk). Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Syrian Rue: May enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the metabolic formation of highly potent active metabolites. Management: Consider alternatives to the use of moderate CYP2D6 inhibitors with tamoxifen when possible, as the combination may be associated with reduced clinical effectiveness of tamoxifen. *Risk D: Consider therapy modification*

Tamsulosin: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Tamsulosin. *Risk C: Monitor therapy*

Tetrabenazine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. *Risk C: Monitor therapy*

Thioridazine: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Timolol (Systemic): CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Timolol (Systemic). *Risk C: Monitor therapy*

Tipranavir: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Tobacco (Smoked): May decrease the serum concentration of DULoxetine. *Risk C: Monitor therapy*

TraMADol: DULoxetine may enhance the adverse/toxic effect of TraMADol. The risk for serotonin syndrome/serotonin toxicity and seizures may be increased with this combination. DULoxetine may diminish the therapeutic effect of TraMADol. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes), reduced tramadol effectiveness and seizures if these agents are combined. *Risk C: Monitor therapy*

TraZODone: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Tricyclic Antidepressants: DULoxetine may enhance the serotonergic effect of Tricyclic Antidepressants. This could result in serotonin syndrome. DULoxetine may increase the serum concentration of Tricyclic Antidepressants. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) and increased TCA concentrations and effects if these agents are combined. *Risk C: Monitor therapy*

Urokinase: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Urokinase. *Risk X: Avoid combination*

Valbenazine: CYP2D6 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of Valbenazine. *Risk C: Monitor therapy*

Vitamin E (Systemic): May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Zanubrutinib: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Zuclopenthixol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Zuclopenthixol. *Risk C: Monitor therapy*

Reproductive Considerations

If treatment for major depressive disorder is initiated for the first time in females planning a pregnancy, agents other than duloxetine are preferred (Larsen 2015).

Pregnancy Considerations

Duloxetine crosses the placenta (Boyce 2011; Briggs 2009; Collin-Lévesque 2018).

Nonteratogenic adverse events have been observed with venlafaxine or other SNRIs/SSRIs when used during pregnancy. Cyanosis, apnea, respiratory distress, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor have been reported in the neonate immediately following delivery after exposure to venlafaxine, SSRIs, or other SNRIs late in the third trimester. Prolonged hospitalization, respiratory support, or tube feedings may be required. Some symptoms may be due to the toxicity of the SNRIs/SSRIs or a discontinuation syndrome and may be consistent with serotonin syndrome associated with treatment.

Duloxetine may impair platelet aggregation, resulting in an increased risk of bleeding; the risk of postpartum hemorrhage may be increased when used within the month prior to delivery.

Untreated or inadequately treated mental illness may lead to poor compliance with prenatal care. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized. Use of a single agent is preferred. According to their recommendations, treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary care provider, and pediatrician (ACOG 2008). If treatment for major depressive disorder is initiated for the first time during pregnancy, agents other than duloxetine are preferred (Larsen 2015; MacQueen 2016).

Untreated fibromyalgia may be associated with adverse pregnancy outcomes, including placental abruption, venous thrombosis, premature rupture of membranes, preterm birth, and intrauterine growth restriction/small for gestational age. It is not known if these outcomes are

due specifically to fibromyalgia or comorbid conditions. Due to limited data, use of duloxetine for the treatment of fibromyalgia syndrome (FMS) in pregnancy should be reserved for women with severe forms of FMS complicated by depressive symptoms which worsen during pregnancy. Close monitoring is recommended (Gentile 2019).

Health care providers are encouraged to enroll women exposed to duloxetine during pregnancy in the Cymbalta Pregnancy Registry (866-814-6975 or http://cymbaltapregnancyregistry.com).

Pregnant women exposed to antidepressants during pregnancy are encouraged to enroll in the National Pregnancy Registry for Antidepressants (NPRAD). Women 18 to 45 years of age or their health care providers may contact the registry by calling 844-405-6185. Enrollment should be done as early in pregnancy as possible.

Breast-Feeding Considerations

Duloxetine is present in breast milk.

The relative infant dose (RID) of duloxetine is 2.3% when calculated using the highest breast milk concentration located and compared to a weight-adjusted maternal dose of 60 mg/day.

In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000). However, some sources note breastfeeding should only be considered if the RID is <5% for psychotropic agents (Larsen 2015).

The RID of duloxetine was calculated using a milk concentration of ~120 mcg/L, providing an estimated daily infant dose via breast milk of 0.02 mg/kg/day. This milk concentration was obtained following maternal administration of duloxetine 60 mg/day (Briggs 2009). Duloxetine has also been detected in the serum of a breastfeeding infant (Boyce 2011).

Information related to the use of duloxetine in breastfeeding women is limited. Infants of mothers using psychotropic medications should be monitored daily for changes in sleep, feeding patterns, and behavior (Bauer 2013) as well as infant growth and neurodevelopment (Sachs 2013; Sriraman 2015).

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. When first initiating an antidepressant in a breastfeeding woman, agents other than duloxetine are preferred. Women successfully treated with duloxetine

during pregnancy may continue use while breastfeeding if there are no other contraindications (Berle 2011).

Monitoring Parameters

Blood pressure (baseline, then periodically, especially in patients with high baseline blood pressure); liver and renal function tests (baseline; as clinically indicated); suicidal ideation (baseline and with dose changes); serum sodium in at-risk populations (as clinically indicated); blood glucose and HbA_{1c} in diabetic patients (baseline and as clinically indicated)

Mechanism of Action

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake. Duloxetine has no significant activity for muscarinic cholinergic, H_1-histaminergic, or $alpha_2$-adrenergic receptors. Duloxetine does not possess MAO-inhibitory activity.

Pharmacodynamics and Pharmacokinetics

Onset of action:

Anxiety disorders (generalized anxiety disorder): Initial effects may be observed within 2 weeks of treatment, with continued improvements through 4 to 6 weeks (WFSBP [Bandelow 2012]); some experts suggest up to 12 weeks of treatment may be necessary for response (BAP [Baldwin 2014]; Katzman 2014; WFSBP [Bandelow 2012]).

Depression: Initial effects may be observed within 1 to 2 weeks of treatment, with continued improvements through 4 to 6 weeks (Papakostas 2006; Posternak 2005; Szegedi 2009).

Absorption: Well absorbed; food has no effect on C_{max}, but decreases AUC by 10%.

Distribution: V_d:

Children ≥7 years and Adolescents: 1,200 L (Lobo 2014).

Adults: ~1,640 L.

Protein binding: >90%; primarily to albumin and $alpha_1$-acid glycoprotein.

Metabolism: Hepatic, via CYP1A2 and CYP2D6; forms multiple metabolites (inactive).

Half-life elimination:

Children ≥7 years and Adolescents: 10.4 hours (Lobo 2014).

Adults: ~12 hours (range: 8 to 22 hours); ~4 hours longer in elderly women.

Time to peak: 5 to 6 hours; food delays by 1.7 to 4 hours.

Excretion: Urine (~70%; <1% of total dose as unchanged drug); feces (~20%).

Pharmacodynamics and Pharmacokinetics: Additional Considerations

Renal function impairment: C_{max} and AUC were ~100% greater in patients with ESRD receiving intermittent hemodialysis.

Hepatic function impairment: Six patients with cirrhosis and moderate hepatic impairment had a 5-fold higher exposure (AUC) and a 3-fold longer half-life compared to patients with normal hepatic function (Suri 2005).

Geriatric: AUC was ~25% higher in elderly women.

Cigarette smoking: Duloxetine bioavailability is reduced by ~33% in smokers.

Pricing: US

Capsule Delayed Release Sprinkle (Drizalma Sprinkle Oral)

20 mg (per each): $7.02

30 mg (per each): $7.02

40 mg (per each): $7.02

60 mg (per each): $7.02

Capsule, enteric pellets (Cymbalta Oral)

20 mg (per each): $9.43

30 mg (per each): $10.58

60 mg (per each): $10.58

Capsule, enteric pellets (DULoxetine HCl Oral)

20 mg (per each): $6.22 - $7.00

30 mg (per each): $6.98 - $7.85

40 mg (per each): $7.85

60 mg (per each): $6.98 - $7.85

Disclaimer: A representative AWP (Average Wholesale Price) price or price range is provided as reference price only. A range is provided when more than one manufacturer's AWP price is available and uses the low and high price reported by the manufacturers to determine the range. The pricing data should be used for benchmarking purposes only, and as such should not be used alone to set or adjudicate any prices for reimbursement or purchasing functions or considered to be an exact price for a single product and/or manufacturer. Medi-Span expressly disclaims all warranties of any kind or nature, whether express or implied, and assumes no liability with respect to accuracy of price or price range data published in its solutions. In no event shall Medi-Span be liable for special, indirect, incidental, or consequential damages arising from use of price or price range data. Pricing data is updated monthly.

Brand Names: International

Abrretia (MX); Alacir (UY); Ambidext (LK); Andepra (AU); Ariclaim (AT, BE, BG, CH, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, MT, NL, NO, PL, PT, RO, RU, SE, SK, TR); Aritavi (CZ, IE); Cicleno (CL); Cimal (CO); Cymbalta (AE, AR, AT, AU, BB, BE, BG, BH, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, EG, ES, FI, FR, GB, GT, HK, HN, HR, HU, IE, IL, IT, JO, JP, KR, KW, LB, LT, LU, LV, MT, MX, MY, NI, NL, NO, PA, PE, PH, PL, QA, RO, RU, SA, SE, SG, SK, TH, TR, TW, ZA); Cymbatex (EG); Cymgen (ZA); Delok (IN); Deloxi (BD); Deuloks (ZW); Doxet (PE); Dulan (LK); Dulonorm (LB); Dulopressive (EG); Duloprex (KR); Dulox (BD); Duloxa (KR, LB); Duloxta (ID); Dulsevir (LV); Duroceptol (KR); Duseta (KR); Duxela (KR); Duxetin (AR, UY); Duxetine (TW); Duxtin (BD); Inmox (CO); Kastandi (CR, DO, GT, HN, NI, PA, SV); Loxentia (IE); Loxyt (LB); Lyta (LK); Nitidex (AR); Psynil (PH); Sebata (KR); Xeristar (AT, BE, BG, CH, CZ, DE, DK, EE, ES, FI, FR, GB, HR, IE, IT, MT, NL, NO, RO, RU, SE, SK, TR); Xinolax DR (BD); Yelate (ZA); Yentreve (AE, AT, BE, BG, CH, CL, CZ, DE, DK, EE, FI, FR, GB, HR, IE, IL, IT, LU, MT, MX, NL, NO, PL, RU, SE, SK, TR)

For country abbreviations used in Lexicomp (show table)

REFERENCES

1. *2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674-694. doi:10.1111/jgs.15767 [PubMed 30693946]*
2. *American College of Obstetricians and Gynecologists, ACOG Practice Bulletin: Clinical Management Guidelines for Obstetricians-Gynecologists No. 92 April 2008 (Replaces Practice Bulletin Number 87, November 2007), "Use of*

Psychiatric Medications During Pregnancy and Lactation," Obstet Gynecol, 2008, 111(4):1001-20. [PubMed 18378767]

3. *American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Published October 2010. Accessed March 27, 2019.*
4. *Anderson PO, Sauberan JB. Modeling drug passage into human milk. Clin Pharmacol Ther. 2016;100(1):42-52. [PubMed 27060684]*
5. *Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry. 2010;71(12):1565-1575. doi:10.4088/JCP.09r05786blu [PubMed 21190637]*
6. *Baldessarini RJ, Faedda GL, Offidani E, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. J Affect Disord. 2013;148(1):129-135. doi:10.1016/j.jad.2012.10.033 [PubMed 23219059]*
7. *Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-439. doi:10.1177/0269881114525674 [PubMed 24713617]*
8. *Balhara Y, Sagar R, Varghese ST. Bleeding gums: duloxetine may be the cause. J Postgrad Med. 2007;53(1):44-45. doi:10.4103/0022-3859.30328 [PubMed 17244971]*
9. *Bandelow B, Sher L, Bunevicius R, et al; WFSBP Task Force on Mental Disorders in Primary Care; WFSBP Task Force on Anxiety Disorders, OCD and PTSD. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care [published corrections appear in Int J Psychiatry Clin Pract. 2012;16(3):242. Int J Psychiatry Clin Pract. 2013;17(1):76]. Int J Psychiatry Clin Pract. 2012;16(2):77-84. doi:10.3109/13651501.2012.667114 [PubMed 22540422]*
10. *Bartlett D. Drug-Induced Serotonin Syndrome. Crit Care Nurse. 2017;37(1):49-54. doi:10.4037/ccn2017169 [PubMed 28148614]*
11. *Bauer M, Severus E, Köhler S, et al; WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder-update 2015. World J Biol Psychiatry. 2015;16(2):76-95. doi:10.3109/15622975.2014.1001786 [PubMed 25677972]*
12. *Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ; World Federation of Societies of Biological Psychiatry Task Force on Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry. 2013;14(5):334-385. doi:10.3109/15622975.2013.804195 [PubMed 23879318]*
13. *Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ; World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2:*

Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. World J Biol Psychiatry. 2002;3(2):69-86. [PubMed 12479080]

14. *Berle JO, Spigset O. Antidepressant use during breastfeeding. Curr Womens Health Rev. 2011;7(1):28-34. [PubMed 22299006]*
15. *Bixby AL, VandenBerg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. Ann Pharmacother. 2019;53(2):186-194. doi:10.1177/1060028018794005 [PubMed 30081645]*
16. *Boyce PM, Hackett LP, and Ilett KF, Duloxetine transfer across the placenta during pregnancy and into milk during lactation. Arch Womens Ment Health. 2011;14(2):169-172. [PubMed 21359876]*
17. *Boyer EW, Shannon M. The serotonin syndrome [published correction appears in N Engl J Med. 2007;356(23):2437] [published correction appears in N Engl J Med. 2009;361(17):1714]. N Engl J Med. 2005;352(11):1112-1120. doi:10.1056/NEJMra041867 [PubMed 15784664]*
18. *Briggs GG, Ambrose PJ, Ilett KF, et al. Use of duloxetine in pregnancy and lactation. Ann Pharmacother. 2009;43(11):1898-1902. [PubMed 19809008]*
19. *Bunchorntavakul C, Reddy KR. Drug hepatotoxicity: newer agents. Clin Liver Dis. 2017;21(1):115-134. doi:10.1016/j.cld.2016.08.009 [PubMed 27842767]*
20. *Bystritsky A. Pharmacotherapy for generalized anxiety disorder in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate, Inc. http://www.uptodate.com. Accessed September 6, 2018.*
21. *Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: A critical review of the literature. Psychother Psychosom. 2016;85(5):270-288. doi:10.1159/000447034 [PubMed 27508501]*
22. *Castro-Diaz D, Palma PC, Bouchard C, et al; Duloxetine Dose Escalation Study Group. Effect of dose escalation on the tolerability and efficacy of duloxetine in the treatment of women with stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(8):919-929. [PubMed 17160693]*
23. *Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain. 2009;146(3):253-260. doi:10.1016/j.pain.2009.06.024 [PubMed 19625125]*
24. *Chen VC, Ng MH, Chiu WC, et al. Effects of selective serotonin reuptake inhibitors on glaucoma: A nationwide population-based study. PLoS One. 2017;12(3):e0173005. doi:10.1371/journal.pone.0173005 [PubMed 28257449]*
25. *Cheng YL, Hu HY, Lin XH, et al. Use of SSRI, but not SNRI, increased upper and lower gastrointestinal bleeding: A nationwide population-based cohort study in Taiwan. Medicine (Baltimore). 2015;94(46):e2022. doi:10.1097/MD.0000000000002022 [PubMed 26579809]*
26. *Chou R. Subacute and chronic low back pain: Nonpharmacologic and pharmacologic treatment. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed September 8, 2019.*
27. *Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. Lancet. 2016;388(10047):881-890. doi:10.1016/S0140-6736(16)30385-3 [PubMed 27289172]*

28. *Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. J Sex Med. 2007;4(4 Pt 1):917-929. doi:10.1111/j.1743-6109.2007.00520.x [PubMed 17627739]*

29. *Collin-Lévesque L, El-Ghaddaf Y, Genest M, et al. Infant exposure to methylphenidate and duloxetine during lactation. Breastfeed Med. 2018;13(3):221-225. [PubMed 29485905]*

30. *Costagliola C, Parmeggiani F, Semeraro F, Sebastiani A. Selective serotonin reuptake inhibitors: a review of its effects on intraocular pressure. Curr Neuropharmacol. 2008;6(4):293-310. doi:10.2174/157015908787386104 [PubMed 19587851]*

31. *Coupland CA, Dhiman P, Barton G, et al. A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. Health Technol Assess. 2011;15(28):1-iv. doi:10.3310/hta15280 [PubMed 21810375]*

32. *Cymbalta (duloxetine) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; April 2020.*

33. *Cymbalta (duloxetine) [product monograph]. Toronto, Ontario, Canada: Eli Lilly Canada Inc; March 2020.*

34. *Davison SN, Koncicki H, Brennan F. Pain in chronic kidney disease: a scoping review. Semin Dial. 2014;27(2):188-204. doi:10.1111/sdi.12196 [PubMed 24517512]*

35. *de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Arch Gen Psychiatry. 2008;65(7):795-803. doi:10.1001/archpsyc.65.7.795 [PubMed 18606952]*

36. *Delgado PL, Brannan SK, Mallinckrodt CH, et al. Sexual functioning assessed in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine for major depressive disorder. J Clin Psychiatry. 2005;66(6):686-692. doi:10.4088/jcp.v66n0603 [PubMed 15960560]*

37. *Deveza LA, Bennell K. Management of moderate to severe knee osteoarthritis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed October 10, 2019.*

38. *Douros A, Ades M, Renoux C. Risk of intracranial hemorrhage associated with the use of antidepressants inhibiting serotonin reuptake: A systematic review. CNS Drugs. 2018;32(4):321-334. doi:10.1007/s40263-018-0507-7 [PubMed 29536379]*

39. *Drizalma Sprinkle (duloxetine delayed-release capsules) [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries Inc; July 2020.*

40. *Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003;96(9):635-642. doi:10.1093/qjmed/hcg109 [PubMed 12925718]*

41. *Dunner DL, D'Souza DN, Kajdasz DK, Detke MJ, Russell JM. Is treatment-associated hypomania rare with duloxetine: secondary analysis of controlled trials in non-bipolar depression. J Affect Disord. 2005;87(1):115-119. doi:10.1016/j.jad.2005.02.017 [PubMed 15967235]*

42. *Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol. 2014;24(4):170-179. doi:10.1089/cap.2013.0096 [PubMed 24815533]*

43. *Emslie GJ, Wells TG, Prakash A, et al. Acute and longer-term safety results from a pooled analysis of duloxetine studies for the treatment of children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol. 2015;25(4):293-305. doi:10.1089/cap.2014.0076 [PubMed 25978741]*

44. *Erie JC, Brue SM, Chamberlain AM, Hodge DO. Selective serotonin reuptake inhibitor use and increased risk of cataract surgery: a population-based, case-control study. Am J Ophthalmol. 2014;158(1):192-197.e1. doi:10.1016/j.ajo.2014.03.006 [PubMed 24631758]*

45. *Fava GA, Benasi G, Lucente M, Offidani E, Cosci F, Guidi J. Withdrawal symptoms after serotonin-noradrenaline reuptake inhibitor discontinuation: Systematic review. Psychother Psychosom. 2018;87(4):195-203. doi:10.1159/000491524 [PubMed 30016772]*

46. *Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. Psychother Psychosom. 2015;84(2):72-81. doi:10.1159/000370338 [PubMed 25721705]*

47. *Fava M. Prospective studies of adverse events related to antidepressant discontinuation. J Clin Psychiatry. 2006;67(Suppl 4):14-21. [PubMed 16683858]*

48. *Fenske JN, Schwenk TL. Obsessive compulsive disorder: diagnosis and management. Am Fam Physician. 2009;80(3):239-245. [PubMed 19621834]*

49. *Filocamo MT, Li Marzi V, Del Popolo G, et al. Pharmacologic treatment in postprostatectomy stress urinary incontinence. Eur Urol. 2007;51(6):1559-1564. [PubMed 16942833]*

50. *Fink KG, Huber J, Würnschimmel E, Schmeller NT. The use of duloxetine in the treatment of male stress urinary incontinence. Wien Med Wochenschr. 2008;158(3-4):116-118. doi: 10.1007/s10354-007-0494-7. [PubMed 18330528]*

51. *Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors-metoclopramide interaction. Ann Pharmacother. 2002;36(1):67-71. doi:10.1345/aph.1A161 [PubMed 11816261]*

52. *Food and Drug Administration. DMETS Medication Error Postmarketing Safety Review. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103473.pdf. Published March 8, 2007. Accessed February 2, 2016.*

53. *Friedman RA, Leon AC. Expanding the black box - depression, antidepressants, and the risk of suicide. N Engl J Med. 2007;356(23):2343-2346. doi:10.1056/NEJMp078015 [PubMed 17485726]*

54. *Gabriel M, Sharma V. Antidepressant discontinuation syndrome. CMAJ. 2017;189(21):E747. doi:10.1503/cmaj.160991 [PubMed 28554948]*

55. *Gaffney RR, Schreibman IR. Serotonin syndrome in a patient on trazodone and duloxetine who received fentanyl following a percutaneous liver biopsy. Case Rep Gastroenterol. 2015;9(2):132-136. doi:10.1159/000382069 [PubMed 26078731]*

56. *Gandhi S, Shariff SZ, Al-Jaishi A, et al. Second-generation antidepressants and hyponatremia risk: A population-based cohort study of older adults. Am J Kidney Dis. 2017;69(1):87-96. doi:10.1053/j.ajkd.2016.08.020 [PubMed 27773479]*

57. *Gelener P, Gorgulu U, Kutlu G, Ucler S, Inan LE. Serotonin syndrome due to duloxetine. Clin Neuropharmacol. 2011;34(3):127-128. doi:10.1097/WNF.0b013e31821b3aa0 [PubMed 21586918]*

58. *Gentile S, Fusco ML. Managing fibromyalgia syndrome in pregnancy no bridges between USA and EU. Arch Womens Ment Health. 2019;22(6):711-721. [PubMed 30607517]*

59. *Gicquel C, Moulis F, Chenaf C, et al. Duloxetine and gingival bleeding: a case-report and reviews of the French and World PharmacoVigilance Databases and literature. Eur J Clin Pharmacol. 2017;73(9):1197-1198. doi:10.1007/s00228-017-2290-7 [PubMed 28639120]*

60. *Grunze H, Vieta E, Goodwin GM, et al; Members of the WFSBP Task Force on Bipolar Affective Disorders working on this topic. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Acute and long-term treatment of mixed states in bipolar disorder. World J Biol Psychiatry. 2018;19(1):2-58. doi: 10.1080/15622975.2017.1384850. [PubMed 29098925]*

61. *Guo MH, Monir RL, Wright A, Holland NP. Case of serotonin syndrome initially presenting as diffuse body pain. Am J Case Rep. 2018;19:1227-1231. doi:10.12659/AJCR.911204 [PubMed 30318504]*

62. *Haddad PM. Antidepressant discontinuation syndromes. Drug Saf. 2001;24(3):183-197. [PubMed 11347722]*

63. *Halperin D, Reber G. Influence of antidepressants on hemostasis. Dialogues Clin Neurosci. 2007;9(1):47-59. [PubMed 17506225]*

64. *Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63(3):332-339. doi:10.1001/archpsyc.63.3.332 [PubMed 16520440]*

65. *Hanje AJ, Pell LJ, Votolato NA, Frankel WL, Kirkpatrick RB. Case report: fulminant hepatic failure involving duloxetine hydrochloride. Clin Gastroenterol Hepatol. 2006;4(7):912-917. doi:10.1016/j.cgh.2006.04.018 [PubMed 16797245]*

66. *Hanley GE, Smolina K, Mintzes B, Oberlander TF, Morgan SG. Postpartum hemorrhage and use of serotonin reuptake inhibitor antidepressants in pregnancy. Obstet Gynecol. 2016;127(3):553-561. doi:10.1097/AOG.0000000000001200 [PubMed 26855096]*

67. *Hathaway EE, Walkup JT, Strawn JR. Antidepressant Treatment Duration in Pediatric Depressive and Anxiety Disorders: How Long is Long Enough? Curr Probl Pediatr Adolesc Health Care. 2018;48(2):31-39. [PubMed 29337001]*

68. *Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2012;11:CD004851. doi:10.1002/14651858.CD004851.pub3 [PubMed 23152227]*

69. *Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. Drug Healthc Patient Saf. 2010;2:141-150. doi:10.2147/DHPS.S7634 [PubMed 21701626]*

70. *Hirsch M, Birnbaum RJ. Discontinuing antidepressant medications in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed March 27, 2019.*

71. *Hirsch M, Birnbaum RJ. Switching antidepressant medications in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed May 11, 2018.*

72. *Hou YC, Lai CH. Long-term duloxetine withdrawal syndrome and management in a depressed patient [published correction appears in J Neuropsychiatry Clin Neurosci. 2014;26(2):133. Lai, Chien-Han [added]]. J Neuropsychiatry Clin Neurosci. 2014;26(1):E4. doi:10.1176/appi.neuropsych.12110265 [PubMed 24515685]*

73. *Hu D, Wurster S. Hyponatremia induced by duloxetine: A case report. Consult Pharm. 2018;33(8):446-449. doi:10.4140/TCP.n.2018.446 [PubMed 30068437]*

74. *Huybrechts KF, Bateman BT, Pawar A, et al. Maternal and fetal outcomes following exposure to duloxetine in pregnancy: cohort study. BMJ. 2020;368:m237. doi:10.1136/bmj.m237 [PubMed 32075794]*

75. *Issac Z, Atlas S, Kunis L. Management of non-radicular neck pain in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed December 27, 2019.*

76. *Ito S. Drug therapy for breast-feeding women. N Engl J Med. 2000;343(2):118-126. [PubMed 10891521]*

77. *Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother. 2006;40(9):1618-1622. doi:10.1345/aph.1G293 [PubMed 16896026]*

78. *Jha MK, Rush AJ, Trivedi MH. When discontinuing SSRI antidepressants is a challenge: Management tips. Am J Psychiatry. 2018;175(12):1176-1184. doi:10.1176/appi.ajp.2018.18060692 [PubMed 30501420]*

79. *Jiang HY, Xu LL, Li YC, Deng M, Peng CT, Ruan B. Antidepressant use during pregnancy and risk of postpartum hemorrhage: A systematic review and meta-analysis. J Psychiatr Res. 2016;83:160-167. doi:10.1016/j.jpsychires.2016.09.001 [PubMed 27637098]*

80. *Jing E, Straw-Wilson K. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review. Ment Health Clin. 2016;6(4):191-196. doi:10.9740/mhc.2016.07.191 [PubMed 29955469]*

81. *Joharchi K, Memari M, Azargashb E, Saadat N. Efficacy and safety of duloxetine and pregabalin in Iranian patients with diabetic peripheral neuropathic pain: a double-blind, randomized clinical trial [published correction appears in J Diabetes Metab Disord. 2019;18(2):583]. J Diabetes Metab Disord. 2019;18(2):575-582. doi:10.1007/s40200-019-00427-w [PubMed 31890684]*

82. *Kang SG, Park YM, Lee HJ, Yoon B. Duloxetine-induced liver injury in patients with major depressive disorder. Psychiatry Investig. 2011;8(3):269-271. doi:10.4306/pi.2011.8.3.269 [PubMed 21994516]*

83. *Katzman MA, Bleau P, Blier P, et al; Canadian Anxiety Guidelines Initiative Group. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(suppl 1):S1. doi:10.1186/1471-244X-14-S1-S1 [PubMed 25081580]*

84. *Kennedy GJ, Marcus P. Use of antidepressants in older patients with co-morbid medical conditions: guidance from studies of depression in somatic illness. Drugs Aging. 2005;22(4):273-287. [PubMed 15839717]*

85. *Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry. 2003;160(4):790-792. doi:10.1176/appi.ajp.160.4.790 [PubMed 12668373]*

86. *Kirkham J, Seitz D. Evidence of ocular side effects of SSRIs and new warnings. Evid Based Ment Health. 2017;20(1):27. doi:10.1136/eb-2016-102528 [PubMed 27993931]*

87. *Kulkarni M. Duloxetine induced hyponatremia. Indian J Nephrol. 2015;25(4):259. doi:10.4103/0971-4065.151352 [PubMed 26199483]*

88. *Lahon K, Shetty HM, Paramel A, Sharma G. Sexual dysfunction with the use of antidepressants in a tertiary care mental health setting - a retrospective case series. J Pharmacol Pharmacother. 2011;2(2):128-131. doi:10.4103/0976-500X.81913 [PubMed 21772780]*

89. *Larsen ER, Damkier P, Pedersen LH, et al. Use of psychotropic drugs during pregnancy and breast-feeding. Acta Psychiatr Scand Suppl. 2015;(445):1-28. [PubMed 26344706]*

90. *Leon AC. The revised warning for antidepressants and suicidality: unveiling the black box of statistical analyses. Am J Psychiatry. 2007;164(12):1786-1789. doi:10.1176/appi.ajp.2007.07050775 [PubMed 18056231]*

91. *Leong C, Alessi-Severini S, Enns MW, et al. Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: A propensity score-matched population-based study. J Clin Psychopharmacol. 2017;37(3):332-340. doi:10.1097/JCP.0000000000000701 [PubMed 28383363]*

92. *Leth-Møller KB, Hansen AH, Torstensson M, et al. Antidepressants and the risk of hyponatremia: A Danish register-based population study. BMJ Open. 2016;6(5):e011200. doi:10.1136/bmjopen-2016-011200 [PubMed 27194321]*

93. *Li H, Cheng Y, Ahl J, Skljarevski V. Observational study of upper gastrointestinal tract bleeding events in patients taking duloxetine and nonsteroidal anti-inflammatory drugs: a case-control analysis. Drug Healthc Patient Saf. 2014;6:167-174. doi:10.2147/DHPS.S66835 [PubMed 25382984]*

94. *Li J, Yang L, Pu C, Tang Y, Yun H, Han P. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. Int Urol Nephrol. 2013;45(3):679-686. [PubMed 23504618]*

95. *Liu PT, Argento V, Skudlarska B, Blagodatny M. Serotonin syndrome in an octogenarian after switch from fluoxetine to duloxetine. J Am Geriatr Soc. 2009;57(12):2384. doi:10.1111/j.1532-5415.2009.02601.x [PubMed 20122009]*

96. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Duloxetine. https://www.ncbi.nlm.nig.gov/books/. Updated January 8, 2018.*

97. *Lobo ED, Heathman M, Kuan HY, et al. Effects of varying degrees of renal impairment on the pharmacokinetics of duloxetine: analysis of a single-dose phase I study and pooled steady-state data from phase II/III trials. Clin Pharmacokinet. 2010;49(5):311-321. doi:10.2165/11319330-000000000-00000 [PubMed 20384393]*

98. *Lobo ED, Quinlan T, Prakash A. Pharmacokinetics of orally administered duloxetine in children and adolescents with major depressive disorder. Clin Pharmacokinet. 2014;53(8):731-740. doi: 10.1007/s40262-014-0149-y. [PubMed 24989060]*

99. *Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol. 2020;38(28):3325-3348. doi:10.1200/JCO.20.01399 [PubMed 32663120]*

100. *MacQueen GM, Frey BN, Ismail Z, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. Special populations: youth, women, and the elderly. Can J Psychiatry. 2016;61(9):588-603. [PubMed 27486149]*

101. *Mahmut A , Tunc V , Demiryurek E , Gursoy A . Bilateral acute angle-closure glaucoma induced by duloxetine. Duloxetin által kiváltott, kétoldali, akut zárt zugú glaucoma. Ideggyogy Sz. 2017;70(9-10):358-360. doi:10.18071/isz.70.0358 [PubMed 29870629]*

102. *Mannesse CK, Jansen PA, Van Marum RJ, et al. Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. Maturitas. 2013;76(4):357-363. doi:10.1016/j.maturitas.2013.08.010 [PubMed 24094459]*

103. *Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D. Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med. 2004;158(8):773-780. doi:10.1001/archpedi.158.8.773 [PubMed 15289250]*

104. *Mawardi G, Markman TM, Muslem R, et al. SSRI/SNRI therapy is associated with a higher risk of gastrointestinal bleeding in LVAD patients [published online ahead of print, 2019 Aug 8]. Heart Lung Circ. 2019;S1443-9506(19)31374-5. doi:10.1016/j.hlc.2019.07.011 [PubMed 31635997]*

105. *McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-388. doi: 10.1016/j.joca.2014.01.003. [PubMed 24462672]*

106. *McIntyre RS, Panjwani ZD, Nguyen HT, et al. The hepatic safety profile of duloxetine: a review. Expert Opin Drug Metab Toxicol. 2008;4(3):281-285. doi:10.1517/17425255.4.3.281 [PubMed 18363543]*

107. *Micca JL, Ruff D, Ahl J, Wohlreich MM. Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials. BMC Musculoskelet Disord. 2013;14:137. doi: 10.1186/1471-2474-14-137. [PubMed 23590727]*

108. *Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. Int J Clin Pract. 2005; 59(12):1435-1440. [PubMed 16351676]*

109. *Mori M, Koide T, Imanishi Y, Matsui Y, Matsuda T. Duloxetine-induced hyponatremia in an elderly patient treated with thiazide diuretics. Indian J Pharmacol. 2014;46(6):657-659. doi:10.4103/0253-7613.144947 [PubMed 25538343]*

110. *Murakami M, Osada K, Ichibayashi H, et al. An open-label, long-term, phase III extension trial of duloxetine in Japanese patients with fibromyalgia. Mod Rheumatol. 2017;27(4):688-695. doi: 10.1080/14397595.2016.1245237. [PubMed 27796152]*

111. *Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nephrol Dial Transplant. 2012;27(10):3736-3745. doi:10.1093/ndt/gfs295 [PubMed 22859791]*

112. *National Collaborating Centre for Mental Health (UK). Depression: The Treatment and Management of Depression in Adults (Updated Edition). Leicester (UK): British Psychological Society; 2010. [PubMed 22132433]*

113. *National Institute for Health and Care Excellence (NICE). Urinary incontinence in women: management. https://www.nice.org.uk/guidance/cg171. Published September 2013. Updated November 2015. Accessed March 30, 2018.*

114. *Nelson C. Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration and side effects. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed December 17, 2020.*

115. *Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. J Am Geriatr Soc. 2011;59(4):577-585. [PubMed 21453380]*

116. *Nelson JC, Lu Pritchett Y, Martynov O, Yu JY, Mallinckrodt CH, Detke MJ. The safety and tolerability of duloxetine compared with paroxetine and placebo: a pooled analysis of 4 clinical trials. Prim Care Companion J Clin Psychiatry. 2006;8(4):212-219. doi:10.4088/pcc.v08n0404 [PubMed 16964316]*

117. *Nguyen T, Shoukhardin I, Gouse A. Duloxetine uses in patients with kidney disease: different recommendations from the United States versus Europe and Canada. Am J Ther. 2019;26(4):e516-e519. doi:10.1097/MJT.0000000000000737 [PubMed 29419534]*

118. *Norman TR, Olver JS. Duloxetine in the treatment of generalized anxiety disorder. Neuropsychiatr Dis Treat. 2008;4(6):1169-1180. doi:10.2147/ndt.s2820 [PubMed 19337457]*

119. *Ogle NR, Akkerman SR. Guidance for the discontinuation or switching of antidepressant therapies in adults. J Pharm Pract. 2013;26(4):389-396. doi:10.1177/0897190012467210 [PubMed 23459282]*

120. *Ormseth MJ, Scholz BA, Boomershine CS. Duloxetine in the management of diabetic peripheral neuropathic pain. Patient Prefer Adherence. 2011;5:343-356. doi:10.2147/PPA.S16358 [PubMed 21845034]*

121. *Papakostas GI, Perlis RH, Scalia MJ, Petersen TJ, Fava M. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. J Clin Psychopharmacol. 2006;26(1):56-60. doi:10.1097/01.jcp.0000195042.62724.76 [PubMed 16415707]*

122. *Parikh AR, Thatcher BT, Tamano EA, Liskow BI. Suicidal ideation associated with duloxetine use: a case series. J Clin Psychopharmacol. 2008;28(1):101-102. doi:10.1097/jcp.0b013e318160d5c3 [PubMed 18204351]*

123. *Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf. 2013;8(3):207-223. doi:10.2174/1574886311308030011 [PubMed 23914755]*

124. *Park YM, Lee BH, Lee HJ, Kang SG. Cholestatic jaundice induced by duloxetine in a patient with major depressive disorder. Psychiatry Investig. 2010;7(3):228-230. doi:10.4306/pi.2010.7.3.228 [PubMed 20927314]*

125. *Patel R, Reiss P, Shetty H, et al. Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. BMJ Open. 2015;5(12):e008341. doi:10.1136/bmjopen-2015-008341 [PubMed 26667012]*

126. *Perahia DG, Bangs ME, Zhang Q, et al. The risk of bleeding with duloxetine treatment in patients who use nonsteroidal anti-inflammatory drugs (NSAIDs): analysis of placebo-controlled trials and post-marketing adverse event reports. Drug Healthc Patient Saf. 2013;5:211-219. doi:10.2147/DHPS.S45445 [PubMed 24348072]*

127. *Peritogiannis V, Antoniou K, Mouka V, Mavreas V, Hyphantis TN. Duloxetine-induced hypomania: case report and brief review of the literature on SNRIs-induced mood switching. J Psychopharmacol. 2009;23(5):592-596. doi:10.1177/0269881108089841 [PubMed 18562441]*

128. *Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry. 2005;66(2):148-158. doi:10.4088/jcp.v66n0201 [PubMed 15704999]*

129. *Prakash A, Lobo E, Kratochvil CJ, et al. An open-label safety and pharmacokinetics study of duloxetine in pediatric patients with major depression. J Child Adolesc Psychopharmacol. 2012;22(1):48-55. doi:10.1089/cap.2011.0072 [PubMed 22251023]*

130. *Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians [published correction appears in Ann Intern Med. 2014;161(10):764]. Ann Intern Med. 2014;161(6):429-440. doi:10.7326/M13-2410 [PubMed 25222388]*

131. *Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166(7):514-530. doi:10.7326/M16-2367 [PubMed 28192789]*

132. *Qadir A, Haider N. Duloxetine withdrawal seizure. Psychiatry (Edgmont). 2006;3(9):10. [PubMed 20975823]*

133. *Rabenda V, Nicolet D, Beaudart C, et al. Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int. 2013;24(1):121-137. [PubMed 22638709]*

134. *Reeves RR, Brister JC. Serious suicide attempt with duloxetine treatment. South Med J. 2008;101(7):769. doi:10.1097/SMJ.0b013e318177872f [PubMed 19209119]*

135. *Rizzoli R, Cooper C, Reginster JY, et al. Antidepressant medications and osteoporosis. Bone. 2012;51(3):606-613. [PubMed 22659406]*

136. *Sachs HC; Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics. 2013;132(3):e796-809. [PubMed 23979084]*

137. *Schäfer W, Princk C, Kollhorst B, Schink T. Antidepressants and the risk of hemorrhagic stroke in the elderly: A nested case-control study. Drug Saf. 2019;42(9):1081-1089. doi:10.1007/s40264-019-00837-y [PubMed 31165430]*

138. *Schagen van Leeuwen JH, Lange RR, Jonasson AF, Chen WJ, Viktrup L. Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Maturitas. 2008;60(2):138-147. [PubMed 18547757]*

139. *Schatzberg AF, Blier P, Delgado PL, Fava M, Haddad PM, Shelton RC. Antidepressant discontinuation syndrome: consensus panel recommendations for clinical management and additional research. J Clin Psychiatry. 2006;67(Suppl 4):27-30. [PubMed 16683860]*

140. *Schlenker B, Gratzke C, Reich O, Schorsch I, Seitz M, Stief CG. Preliminary results on the off-label use of duloxetine for the treatment of stress incontinence after radical prostatectomy or cystectomy. Eur Urol. 2006;49(6):1075-1078. [PubMed 16481094]*

141. *Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009;29(3):259-266. doi:10.1097/JCP.0b013e3181a5233f [PubMed 19440080]*

142. *Shamliyan T, Wyman J, Kane RL; Agency for Healthcare Research Quality. Nonsurgical treatments for urinary incontinence in adult women: diagnosis and comparative effectiveness. https://www.ncbi.nlm.nih.gov/books/NBK92960/. Published April 2012. Accessed January 21, 2015.*

143. *Shelton RC. Steps following attainment of remission: discontinuation of antidepressant therapy. Prim Care Companion J Clin Psychiatry. 2001;3(4):168-174. [PubMed 15014601]*

144. *Shelton RC, Andorn AC, Mallinckrodt CH, et al. Evidence for the efficacy of duloxetine in treating mild, moderate, and severe depression. Int Clin Psychopharmacol. 2007;22(6):348-355. [PubMed 17917553]*

145. *Shifera AS, Leoncavallo A, Sherwood M. Probable association of an attack of bilateral acute angle-closure glaucoma with duloxetine. Ann Pharmacother. 2014;48(7):936-939. doi:10.1177/1060028014529645 [PubMed 24732786]*

146. *Simon NM, Worthington JJ, Moshier SJ, et al. Duloxetine for the treatment of generalized social anxiety disorder: a preliminary randomized trial of increased dose to optimize response. CNS Spectr. 2010;15(7):367-373. [PubMed 20625362]*

147. *Smith EM, Pang H, Cirrincione C, et al; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309(13):1359-67. doi:10.1001/jama.2013.2813 [PubMed 23549581]*

148. *Sriraman NK, Melvin K, Meltzer-Brody S. ABM Clinical Protocol #18: Use of antidepressants in breastfeeding mothers. Breastfeed Med. 2015;10(6):290-299. [PubMed 26204124]*

149. *Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord. 1998;51(3):215-235. doi:10.1016/s0165-0327(98)00221-3 [PubMed 10333979]*

150. *Strawn JR, Prakash A, Zhang Q, et al. A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. J Am Acad Child Adolesc Psychiatry. 2015;54(4):283-293. doi:10.1016/j.jaac.2015.01.008 [PubMed 25791145]*

151. *Strawn JR, Whitsel R, Nandagopal JJ, Delbello MP. Atypical Stevens-Johnson syndrome in an adolescent treated with duloxetine. J Child Adolesc Psychopharmacol. 2011;21(1):91-92. doi:10.1089/cap.2010.0071 [PubMed 29210786]*

152. *Sun CF, Chen YL, Li YH, Kumaraswamy M, Lo YC, Chen YT. Duloxetine-induced hyponatremia in an elderly male patient with treatment-refractory major depressive disorder. Case Rep Psychiatry. 2019;2019:4109150. doi:10.1155/2019/4109150 [PubMed 31214374]*

153. *Sun-Edelstein C, Tepper SJ, Shapiro RE. Drug-induced serotonin syndrome: a review. Expert Opin Drug Saf. 2008;7(5):587-596. doi:10.1517/14740338.7.5.587 [PubMed 18759711]*

154. *Suri A, Reddy S, Gonzales C, Knadler MP, Branch RA, Skinner MH. Duloxetine pharmacokinetics in cirrhotics compared with healthy subjects. Int J Clin Pharmacol Ther. 2005;43(2):78-84. doi:10.5414/cpp43078 [PubMed 15726876]*

155. *Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J Clin Psychiatry. 2009;70(3):344-353. doi:10.4088/jcp.07m03780 [PubMed 19254516]*

156. *Takata J, Arashi T, Abe A, Arai S, Haruyama N. Serotonin syndrome triggered by postoperative administration of serotonin noradrenaline reuptake inhibitor (SNRI). JA Clin Rep. 2019;5(1):55. doi:10.1186/s40981-019-0275-5 [PubMed 32025920]*

157. *Takayama A, Nagamine T, Matsumoto Y, Nakamura M. Duloxetine and angiotensin II receptor blocker combination potentially induce severe hyponatremia in an elderly woman. Intern Med. 2019;58(12):1791-1794. doi:10.2169/internalmedicine.2059-18 [PubMed 30799349]*

158. *Tan L, Zhou J, Yang L, et al. Duloxetine-induced rapid eye movement sleep behavior disorder: a case report. BMC Psychiatry. 2017;17(1):372. doi:10.1186/s12888-017-1535-4 [PubMed 29162053]*

159. *Tondo L, Vázquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010;121(6):404-414. doi:10.1111/j.1600-0447.2009.01514.x [PubMed 19958306]*

160. *Tully PJ, Cardinal T, Bennetts JS, Baker RA. Selective serotonin reuptake inhibitors, venlafaxine and duloxetine are associated with in hospital morbidity but not bleeding or late mortality after coronary artery bypass graft surgery. Heart Lung Circ. 2012;21(4):206-214. doi:10.1016/j.hlc.2011.12.002 [PubMed 22285303]*

161. *Upadhyaya HP, Arnold LM, Alaka K, Qiao M, Williams D, Mehta R. Efficacy and safety of duloxetine versus placebo in adolescents with juvenile fibromyalgia: results from a randomized controlled trial. Pediatr Rheumatol Online J. 2019;17(1):27. doi: 10.1186/s12969-019-0325-6. [PubMed 31138224]*

162. *Viramontes TS, Truong H, Linnebur SA. Antidepressant-induced hyponatremia in older adults. Consult Pharm. 2016;31(3):139-150. doi:10.4140/TCP.n.2016.139 [PubMed 26975593]*

163. *Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry. 2014;171(4):404-415. doi:10.1176/appi.ajp.2013.13050709 [PubMed 24362450]*

164. *Vuppalanchi R, Hayashi PH, Chalasani N, et al. Duloxetine hepatotoxicity: a case-series from the drug-induced liver injury network. Aliment Pharmacol Ther. 2010;32(9):1174-1183. doi:10.1111/j.1365-2036.2010.04449.x [PubMed 20815829]*

165. *Wang D, Lai J, Lu S, Huang M, Hu S, Xu Y. Rapid-onset hyponatremia and delirium following duloxetine treatment for postherpetic neuralgia: Case report and literature review. Medicine (Baltimore). 2018;97(46):e13178. doi:10.1097/MD.0000000000013178 [PubMed 30431592]*

166. *Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant discontinuation syndrome. Am Fam Physician. 2006;74:449-456. [PubMed 16913164]*

167. *Wells KA and Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-1308. [PubMed 18691989]*

168. *Werneke U, Northey S, Bhugra D. Antidepressants and sexual dysfunction [published correction appears in Acta Psychiatr Scand. 2007;115(3):255]. Acta Psychiatr Scand. 2006;114(6):384-397. doi:10.1111/j.1600-0447.2006.00890.x [PubMed 17087787]*

169. *Wiciński M, Kaluzny BJ, Liberski S, Marczak D, Seredyka-Burduk M, Pawlak-Osińska K. Association between serotonin-norepinephrine reuptake inhibitors and acute angle closure: What is known?. Surv Ophthalmol. 2019;64(2):185-194. doi:10.1016/j.survophthal.2018.09.006 [PubMed 30278181]*

170. *Wilkening GL, Kucherer SA, Douaihy AB. Priapism and renal colic in a patient treated with duloxetine. Ment Health Clin. 2016;6(4):197-200. doi:10.9740/mhc.2016.07.197 [PubMed 29955470]*

171. *Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170. doi: 10.1111/bdi.12609. [PubMed 29536616]*

172. *Young JB, Singh TD, Rabinstein AA, Fugate JE. SSRI/SNRI use is not associated with increased risk of delayed cerebral ischemia After aSAH. Neurocrit Care. 2016;24(2):197-201. doi:10.1007/s12028-015-0190-1 [PubMed 26264066]*

Topic 8484 Version 440.0

→