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Review Article

Toxicity of serotonin-norepinephrine reuptake inhibitors (SNRIs) during pregnancy and lactation

Göksu Canıtez[1], Rahime Şimşek[2], Deniz Arca Çakır[3], Hülya Tezel Yalçın[4], Terken Baydar[4], Pınar Erkekoğlu[4]

[1]Hacettepe University Graduate School of Science and Engineering, Department of Bioengineering, Ankara, Türkiye
[2]Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara, Türkiye
[3]Hacettepe University, Vaccine Institute, Department of Vaccine Technology, Ankara, Türkiye
[4]Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Ankara, Türkiye

ABSTRACT

Major depressive disorder (depression) is a severe mood disorder. Lifestyle changes during the COVID-19 pandemic contributed to the high incidence of depression in the population. The primary care treatment is provided by both psychotherapy and antidepressants. In the last 35 years, selective serotonin reuptake inhibitors (SSRIs) were used because of lower adverse effects when compared to tricyclic antidepressants and monoamine oxidase (MAO) inhibitors. However, selective serotonin–norepinephrine reuptake inhibitors (SNRIs), which are second-generation antidepressants, are preferred over first-generation antidepressants by some physicians as they have broad uses nowadays. Anxiety disorders, depression, social phobia, attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), fibromyalgia syndrome, chronic neuropathic pain, and menopausal symptoms are among the conditions that can be treated with SNRIs. Although the effects of genetic factors and family history on these diseases, especially recurrence, are undeniable, these drugs provide a great deal of improvement. However, the use of SNRIs during pregnancy and lactation is still a debate. There is no definite judgment on whether a pregnant woman should use these drugs during pregnancy or not. As the rate of depression among pregnant women increases, this issue becomes more serious. A definitive answer has not been reached yet because studies on pregnant women cannot be carried out within the framework of ethical rules. In this review, the effects, toxicity, and safety of SNRIs during pregnancy and lactation are discussed.

Keywords: SNRI, antidepressant, serotonin, norepinephrine, pregnancy, lactation

INTRODUCTION

"Depression (major depressive disorder)" is associated with changes in a person's mood, interests, tastes, and cognitive behavior and with a loss of physical strength (Otte et al., 2016; American Psychiatric Association, 2023). Quality of life is negatively affected by depression (Yang et al., 2021; American Psychiatric Association, 2023). Premature birth, inadequate newborn weight, relapse, and postnatal problems are outcomes of untreated perinatal major depressive disorder and anxiety disorders during pregnancy (Robiyanto et al., 2023). Antidepressants can be prescribed during pregnancy for anxiety and major depressive disorders (Otte et al., 2016). The prevalence of antidepressant usage during pregnancy is estimated to be 3% worldwide for selective serotonin reuptake inhibitors (SSRIs), 0.73% for serotonin and norepinephrine reuptake inhibitors (SNRIs), and 0.38% for tricyclic antidepressants (TCAs) (Molenaar et al., 2020). Although the pathophysiology of depression and the toxic effects of antidepressants are subjects of intense research, there are different hypotheses for the neurobiology of depression, particularly in susceptible period, like pregnancy and lactation. This review will focus on SNRIs, which are second-generation antidepressants. The toxicity and safety of SNRIs are evaluated and their effects during pregnancy and lactation are discussed.

DEPRESSION AND PREGNANCY

"Antenatal depression" defines mild or major depression during pregnancy or a few months after pregnancy ends. This depression can be caused by changing hormonal activities or social and economic conditions. In addition, a family history of depression is an important factor (Ghimire, Papabathini, Kawuki, Obore & Musa, 2021).

Corresponding Author: Pınar Erkekoğlu **E-mail:** erkekp@yahoo.com
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SECOND GENERATION ANTIDEPRESSANTS

Today, second-generation antidepressants with high efficacy and selectivity are chosen due to their lower adverse effects on both the mother and the child (Fasipe, 2018). New antidepressants are shown in Table 1.

SEROTONIN–NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs are compounds that inhibit presynaptic neuronal uptake of serotonin and norepinephrine (Figure 1). This mechanism ensures the activities of monoamines by staying in the central nervous system (CNS) for a longer period (Li et al., 2020).

SNRIs are now utilized as first-choice medications for treating major depressive disorder and anxiety, along with SSRIs. SNRIs provide a faster antidepressant effect compared to SSRIs due to the suppression of serotonin as well as norepinephrine reuptake, which is the primary distinction between SSRIs and SNRIs' mechanisms of action (MoA). Both classes have quite similar pharmacological activities on serotonin. The effect of SNRIs on serotonin is significantly greater than on norepinephrine (Snamina, Wietecha-Posłuszny & Zawadzki, 2019; American Psychiatric Association, 2023). MoA of SNRIs is dose dependent. They act as SSRIs at low doses, whereas norepinephrine reuptake inhibition occurs at higher doses (Fasipe, 2018). The fact that SNRIs suppress reuptake of serotonin as well as norepinephrine, unlike SSRIs, is due to their different affinities and selectivity levels of these two antidepressant class drugs to serotonin and norepinephrine transporters (SERT and NET, respectively) (Dale, Bang-Andersen & Sánchez, 2015).

Like SSRIs, SNRIs are well-tolerated, rapidly effective, and have fewer adverse effects (Fasipe, 2018). SNRIs inhibit the penetration of serotonin and norepinephrine into neurons and thus increase their levels in synaptic space (Banzi et al., 2015). These drugs also show activity in the hypothalamus, *amygdala*, and *locus coeruleus* as stress factors in these regions that are strongly affected by increased norepinephrine secretion. It was suggested that these drugs alter stress response and act in these specific regions of the brain such as the *amygdala* which is responsible for regulating responses to negative situations and activities of norepinephrine pathways located along peptide circuits (Gałecki, Mossakowska-Wójcik & Talarowska, 2018). In a study, it was reported that adverse effects such as nausea, fatigue, and diarrhea appeared in normal doses of SSRIs, while cardiac problems were experienced with increasing doses. This is attributed to the inhibition of norepinephrine reuptake (Park, Kim, Ko & Park,2021).

Globally, SNRIs are prescribed nearly >16 million times in a year (Park et al., 2021). The drugs classified as SNRIs by The Food and Drug Administration (FDA) are duloxetine, venlafaxine, desvenlafaxine, and levomilnacipran. In 2009, the FDA approved the SNRI milnacipran for the treatment of fibromyalgia. It is not used in the treatment of depression in the USA but acts as an antidepressant for treating depression (Lantz et al., 2003).

EFFECTS OF SNRIs DURING PREGNANCY AND LACTATION PERIOD

There is no definitive recommendation for the use of antidepressants during pregnancy. Although this is the case, the use of SNRIs and SSRIs in pregnancy has increased in recent years. However, women who use antidepressants before pregnancy usually discontinue this treatment at the beginning of the pregnancy due to concerns about the use of the medicine during this susceptible period (Zoega et al., 2015).

The hypothesis that SNRIs may pose potential risks in an unborn or newborn baby arises from their ability to pass the placenta and the blood–brain barrier (BBB). They are also secreted to human milk at certain levels. There are concerns that SNRIs can affect the functional development of the brain and can cause neurobehavioral, cognitive, emotional, and mental problems both in perinatal and early postnatal periods (Dubovicky, Belovicova, Csatlosova & Bogi, 2017). In a study, the relationship between antidepressant exposure during the third trimester of pregnancy and the risk of poor neonatal adaptation was investigated. The study's results showed that throughout the third trimester, there was a greater incidence of poor neonatal adaptation with SNRI therapy and antidepressant combination therapy than with bupropion monotherapy (Brumbaugh et al., 2023). Moreover, there are also risks for preterm birth, stillbirth, congenital malformations, low birth weight, seizures and respiratory difficulties, persistent pulmonary hypertension in newborns and infant deaths. In addition, conditions such as feeding and sleep disorders, excessive crying, unbalanced body temperature, vomiting, hypertonia, hypotonia, tremors, restlessness, and lower IQ scores in later life are considered characteristic features in newborns who are prenatally exposed to antidepressants. Infants with these symptoms have a longer hospital stay and need intragastric feeding and respiratory support (Dubovicky et al., 2017).

Although data on whether prenatal exposure to SSRIs/SNRIs causes some birth abnormalities, including heart defects, are conflicting, and persistent pulmonary hypertension (PPHN) in infants has been reported. This is explained by the mechanism suggesting "both SSRIs and SNRIs increase levels of serotonin in fetal circulation and cause vasoconstriction as well as an increase in the infant's pulmonary vascular resistance." (Masarwa et al., 2019).

Pregnant women exposed to SSRIs and SNRIs in the first trimester have a risk of giving birth to an infant with musculoskeletal problems as well as heart, craniofacial, digestive, and respiratory system disorders. Animal experiments suggested that altered serotonin levels could affect organogenesis and morphogenesis. Serotonin is vital for cellular development in early

Table 1. Pharmacological classes of second-generation antidepressants.

Pharmacological Class	Examples
SSRIs	Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram, Fluvoxamine
SNRIs	Venlafaxine, Desvenlafaxine, Duloxetine, Levomilnacipran
SARI	Trazodone, Nefazodone, Vortioxetine
SPARI	Vilazodone
SNRISA with potent antipsychotic D_2 receptor blockade/antagonism	Amoxapine
NRISA	Maprotiline
NASSA	Mirtazapine, Mianserin
NRIs	Reboxetine, Atomoxetine
NDRI	Bupropion
Atypical antipsychotics that exhibit weak D_2 receptor antagonism with potently strong 5-HT_{2A} receptor blockade	Olanzapine, Quetiapine, Risperidone, Lurasidone, Aripiprazole
NMDA-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist that exhibit a direct action on excitatory glutamatergic neurotransmission system	Ketamine

SSRIs, Selective Serotonin Reuptake Inhibitors; SNRIs, Serotonin-Norepinephrine Reuptake Inhibitors; SARI, Serotonin receptor antagonists with serotonin reuptake inhibition; SPARI, Serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition; SNRISA, Serotonin-norepinephrine reuptake inhibitor and serotonin receptos antagonism; NRISA, Norepinephrine reuptake inhibitor with serotonin receptors antagonism; NASSA, Noradrenergic α2-receptor antagonist with specific serotonergic receptors-2 and-3 antagonism; NRIs, Selective Norepinephrine Reuptake Inhibitors; NDRI, Norepinephrine-Dopamine Reuptake Inhibitor; NMDA,N-methyl-D-aspartate.

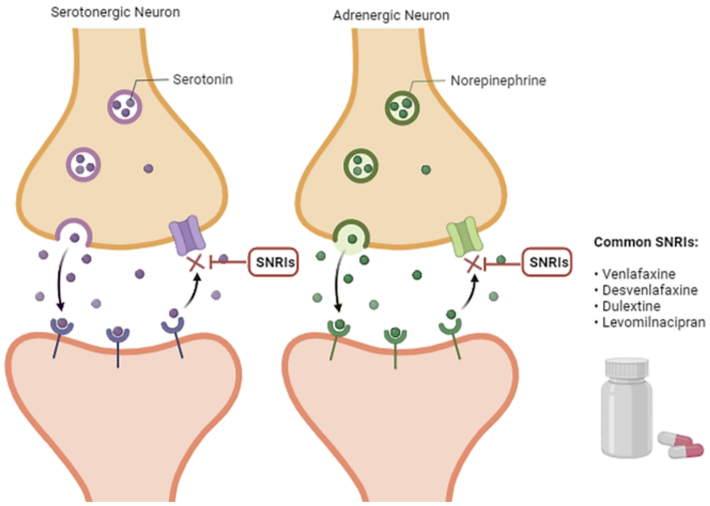

Figure 1. Action mechanism of serotonin-norepinephrine reuptake inhibitors (SNRIs)

organogenesis. Therefore, prenatal alterations in serotonin levels may cause various malformations in the newborn (Bérard, Zhao & Sheehy, 2017).

Although a significant relationship was not found in some studies, a study found an increased risk of ADHD in children of mothers who used antidepressants including SNRIs during their pregnancy (Uguz, 2018). A study on pregnant women prescribed at least two SNRI/SSRI drugs found that their children had a higher risk of developmental problems, such as language, and cognitive development aside from communication problems, lower social competence, and emotional maturity (Singal et al., 2020). Moreover, postpartum hemorrhage with an increase in gastrointestinal bleeding and preeclampsia may arise due to the use of SNRIs during pregnancy (Perrotta et al., 2019). Regarding their biological mechanism, SNRIs are especially anticipated to raise the risk of hypertensive disorders of pregnancy among antidepressants. It was suggested that SNRIs were associated with the risk of preeclampsia during the second trimester of pregnancy (Avalos, Chen & Li, 2015). Also in another study, an elevated risk for hypertensive disorders in pregnant women treated with SNRIs compared to those treated with SSRIs was found (Benevent et al., 2023).

The potential link between the use of antidepressants and metabolic problems has long been a contentious issue. The-

oretically, antidepressants can affect blood glucose levels directly through weight gain, by raising cellular insulin resistance, or by blocking pancreatic insulin production. Antidepressants have been shown to cause hyperglycemia in several animal experiments. Serotonin homeostasis is impacted by serotonin reuptake inhibitors blocking the serotonin reuptake transporter. However, when insulin resistance develops naturally during pregnancy, serotonin compensates this resistance. Their susceptibility to histamine and noradrenergic receptors may increase the incidence of gestational diabetes mellitus. Therefore, in a systematic review and meta-analysis, the gestational diabetes mellitus risk linked to antidepressant treatment during pregnancy was evaluated. The effects of TCAs, particularly amitriptyline, on glucose dysregulation appear to be more significant in the general population than those of SSRIs and SNRIs (Wang, Ying & Jiang, 2023).

FDA evaluates the use of antidepressants during pregnancy on a case–by–case basis, by making a risk–benefit analysis. According to these evaluations, most antidepressants are in category C, which means, "negative effects on fetus have been observed in animal studies, but there are no adequate and good human studies. The drug can only be used during pregnancy if it is essential" (Ray & Stowe, 2014). FDA pregnancy categories of SNRIs are given in Table 2 (Dandjinou, Sheehy & Bérard, 2019).

Amounts of SNRIs in breast milk may differ. Amounts of venlafaxine and desvenlafaxine passing into breast milk are usually moderate. There are insufficient studies on the safety of duloxetine in lactation and no reports for levomilnacipran (Drugs and Lactation Database, 2006). Lactation risk categories for some SNRIs given by the American College of Obstetricians and Gynecologists (ACOG) and the FDA are summarized in Table 3 (Armstrong, 2008).

UNDERSTANDING SNRIs

SNRI drugs show higher efficacy with improved response and remission rates vs. TCAs. In patients with high recurrence potential, SNRIs can be prescribed in high doses for long–term treatments. It is because they are well tolerated as they do not interact with muscarinic, histaminic, and α1-adrenergic receptors and they do not affect MoA. Only venlafaxine may exhibit some dopamine reuptake inhibition at high doses. Their specific MOA provides lower adverse effects. The likelihood of committing suicide in SNRI-using patients is less than TCAs although SNRI possess more risk than SSRIs. General adverse effects are nausea, vomiting, diarrhea, headache, dry mouth, cardiovascular symptoms, sexual problems, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Lambert & Bourin, 2002; Lee & Chen, 2010).

Venlafaxine

Venlafaxine (1-(2-(dimethylamino)-1-(4- methoxyphenyl) ethyl)cyclohexan-1-ol) has phenylethylamine structure and is structurally different from other SNRI drugs because it contains two chemical rings (bicyclic) (Figure 2a). Venlafaxine is the first SNRI approved for major depression, anxiety, panic disorder, and social phobia by the FDA in 1993. A few years later, micro capsulated XR formulation was on the market. XR formula is used once a day while non–XR formulation should be taken twice daily. XR formula has clinical advantage of causing less nausea and dizziness at the start of treatment (Sansone & Sansone, 2014).

Pharmacokinetics

Venlafaxine is effectively absorbed after being administered orally. It has a 45% absolute bioavailability. A single oral dose of venlafaxine was at least 92% absorbed. Following twice-daily oral administration of an immediate-release formulation of 150 mg venlafaxine, the Cmax was 150 ng/mL and the Tmax was 5.5 hours. The active metabolite, desvenlafaxine (ODV), has a Cmax and Tmax of 260 ng/mL and 9 hours, respectively. The rate of absorption is slower with venlafaxine XR. However, it has a similar level of absorption as the formulation for immediate release. After once-daily administration of 75 mg venlafaxine XR, Cmax was 225 ng/mL and Tmax was two hours. The bioavailability of venlafaxine or ODV is not affected by food. The oral half–life is 5 hours while the half-life of the XR formulation is 11 hours. Venlafaxine's apparent volume of distribution (Vd) at steady state is 7.53.7 L/kg while ODV's is 5.71.8 L/kg. Venlafaxine is 27% bound to plasma proteins. Venlafaxine undergoes extensive presystemic hepatic metabolism by CYP2D6, 3A3, and 3A4. After CYP2D6-mediated demethylation, venlafaxine is metabolized to ODV (Yue et al., 2023). Even though it's not a frequent metabolic pathway, CYP2C9, CYP2C19, and CYP3A4 can N-demethylate venlafaxine to form N-desmethylvenlafaxine (NDV) (Fogelman et al., 1999). ODV and NDV are further metabolized by CYP isoenzymes 2C19, 2D6 and/or 3A4 to form N,O-didesmethylvenlafaxine (NODV). NODV is also metabolized to form N,N,O-tridesmethylvenlafaxine, possibly with glucuronidation. Within 48 hours, venlafaxine (87%) can be detected in urine [unconjugated ODV (29%), minor inactive metabolites (27%), conjugated ODV (26%), and unchanged venlafaxine (5%)] (Preskorn et al., 2009). Venlafaxine and ODV have an elimination half-life of 5±2 hours and 11±2 hours, respectively (Stahl, Entsuah & Rudolph, 2002; Sansone & Sansone, 2014).

Pharmacodynamics

Venlafaxine has 30-fold selectivity for serotonin reuptake compared to norepinephrine reuptake at the presynaptic terminal.

Table 2. Teratogenicity categories for SNRIs.

Drug Name	FDA Category	Possible Teratogenic Effects	Approved condition
Duloxetine	C	No teratogenic effect observed.	Major – depressive disorder, not clear for pediatric patients
Venlafaxine	C	No teratogenic effect observed.	Major – depressive disorder, not approved for pediatric patients
Desvenlafaxine	C	No teratogenic effect observed.	Major – depressive disorder, not approved for pediatric patients
Levomilnacipran	C	No teratogenic effect observed.	Major – depressive disorder, not approved for pediatric patients

Table 3. Lactation risk categories of SNRIs.

Drug Name	Lactation Risk Category
Venlafaxine	L3
Desvenlafaxine	No information
Duloxetine	Not applicable
Levomilnacipran	No information

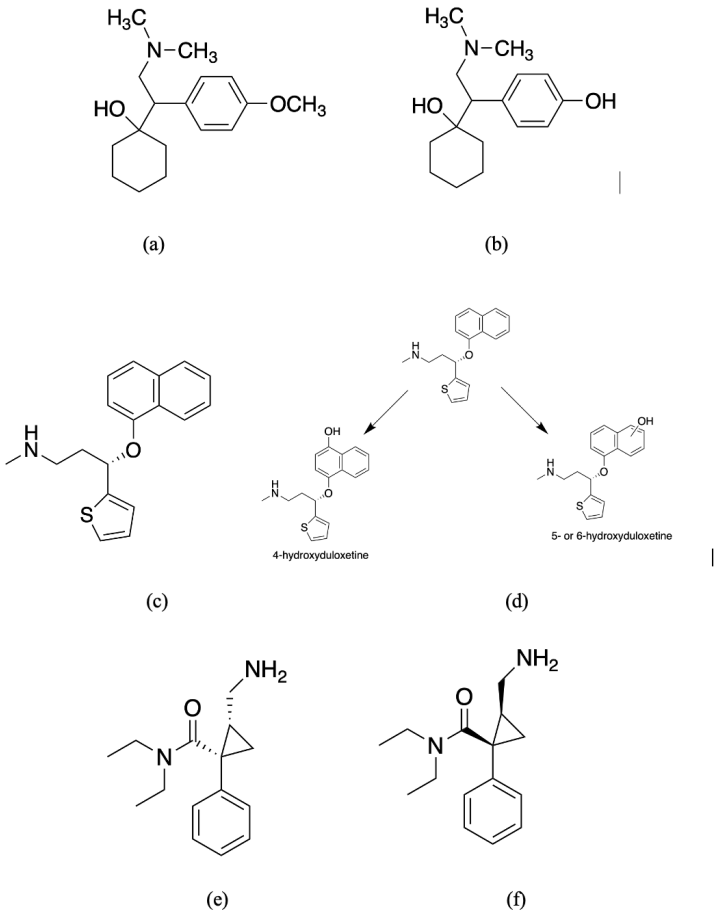

Figure 2. Chemical structure of SNRIsa. Venlafaxine; b. Desvenlafaxine; c. Duloxetine; d. Major metabolites of duloxetine. e. Levomilnacipran; f. Milnacipran.

At low doses, venlafaxine initially inhibits serotonin reuptake while at higher doses, it inhibits norepinephrine reuptake as well as serotonin. Therefore, adverse effects just as headache and nausea are related to serotonin uptake suppression while adverse effects such as dry mouth and sweating are due to norepinephrine reuptake suppression. At high doses, venlafaxine also inhibits dopamine reuptake (Sansone & Sansone, 2014).

In a study comparing venlafaxine and SSRIs, venlafaxine showed a much higher efficacy, possibly due to the "double effect". 75 mg daily intake fulfilled serotonin reuptake inhibition (Stahl et al., 2002; FDA, 2017).

Pregnancy

During the second and third trimesters, venlafaxine may increase the risk of pre-eclampsia and eclampsia. In one study investigating the relationship between gestational diabetes and antidepressants, pregnant women using venlafaxine had an increased risk compared to the control group (Dandjinou et al., 2019).

In another study investigating the relationship between venlafaxine therapy in the early period of pregnancy and preterm delivery, increased risks were observed. Children whose mothers used venlafaxine in the third trimester had withdrawal syndrome, preterm birth, neonatal seizures, and necrotizing enterocolitis (Bellantuono, Vargas, Mandarelli, Nardi & Martini, 2015). Partial clubfoot, hypospadias, and neural tube defects were also observed in children after their mother intake venlafaxine in first trimester. However, there is no clear evidence that prenatal venlafaxine exposure is the only reason for these malformations. In another study, researchers suggested that exposure of venlafaxine might lead to hypospadias (Lind et al., 2013).

Prenatal exposure caused slightly reduced IQ scores and a higher incidence of problematic behavior. Moreover, prenatally exposed newborns may experience poor neonatal adaptation syndrome. Scientists mention a "possibility" of all these conditions for SNRIs as there is lack of empirical studies where firm evidence can be reached (Dubovicky et al., 2017). Most of the research conducted on pregnant women exposed to venlafaxine have not found a conclusive link between miscarriage or serious birth abnormalities (Bellantuono et al., 2015).

Lactation

O-desmethylvenlafaxine can be found in most breastfed newborns' plasma, but rare adverse effects have been documented. Venlafaxine was not to be taken during nursing, and newborn or preterm infants who were breastfed should be watched for excessive sedation and proper weight gain. Evaluation of serum ODV levels is suggested. Venlafaxine was also suggested to cause withdrawal symptoms, but this has not been rigorously demonstrated (Koren, Moretti & Kapur, 2006; Boucher, Koren, & Beaulac-Baillargeon, 2009).

Desvenlafaxine

Desvenlafaxine [4-(2-(dimethylamino)-1-(1-hydroxycyclo hexyl) thylphenol] is an SNRI authorized by the FDA for the management of depression (Figure 2b). Desvenlafaxine was introduced into therapy in 2008 and is used as succinate salt. Because it is a metabolite of venlafaxine, they are structurally similar. After biotransformation, desvenlafaxine concentration in plasma is 2-3 times that of venlafaxine (Figure 3) (DeMaio, Kane, Nichols & Jordan, 2011; Sansone & Sansone, 2014; Magalhães, Alves, LLerena & Falcão, 2015).

Desvenlafaxine is superior to venlafaxine due to its proven high efficacy, safety profile, good tolerance, low effect on CYP450s, and once-daily use (Seo, Sohi, Patkar, Masand & Pae, 2010). According to the FDA, this single daily dose is 50 mg. Once a day treatment is sufficient.

Pharmacokinetics

Oral bioavailability is ~80% (Pae, 2011). Food does not affect the bioavailability of the drug, but the important thing is that orally taken drug is swallowed directly without chewing (FDA, 2011). Within 7.5 hours, peak plasma concentration is reached (Reddy et al., 2010). Cmax and Tmax of desvenlafaxin (ODV) were 290 ng/mL and three hours, respectively. Vd is 3.4 L/kg and binds 30% of plasma proteins. Drug concentration has no impact on the degree of protein binding (Liebowitz & Tourian, 2010; Reddy et al., 2010).

Just a small fraction of desvenlafaxine goes through oxidative N-demethylation via CYP43A4. Its metabolites are N,O-didesmethylvenlafaxine, benzylhydroxy desvenlafaxine, desvenlafaxine N-oxide and cyclohexane ring hydroxy desvenlafaxine, Desvenlafaxine also undergoes glucuronidation and desvenlafaxine O-glucuronide is the major metabolite. The main excretion route is by the kidneys. While 19% of the dose is excreted as the glucuronide metabolite and 5% as N,O-didesmethylvenlafaxine, the remaining 45% of the dose remains unchanged in the urine (Liebowitz & Tourian, 2010). Desvenlafaxine has an 11.1-hour half-life (Liebowitz & Tourian, 2010; Sansone & Sansone, 2014).

Pharmacodynamics

Desvenlafaxine has ten times greater affinity for inhibiting the reuptake of serotonin than norepinephrine transporters. Dopamine and norepinephrine transporters have lower affitinity. In *in vitro* experiments, desvenlafaxine did not inhibit MAO and desvenlafaxin nearly had no affinity for muscarinic, cholinergic, H1-histaminergic, and α1-adrenergic receptors, desvenlafaxin nearly had no affinity (Liebowitz & Tourian, 2010). In a study on male rats, desvenlafaxine reached to hypothalamus rapidly after oral administration (30 mg) and it significantly increased the amount of extracellular norepinephrine, suggest-

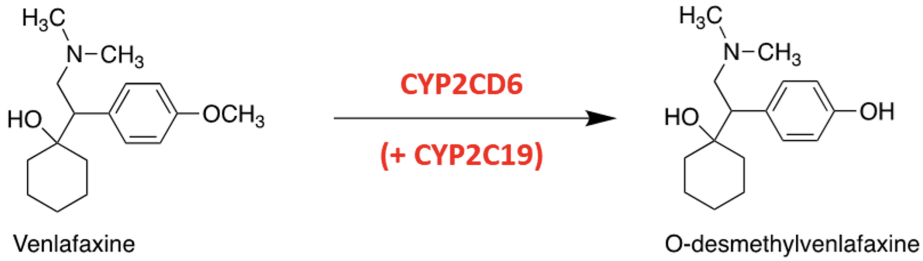

Figure 3. Biotransformation of venlafaxine to desvenlafaxine (ODV).

ing a good brain–plasma ratio and therefore it can be used in various CNS disorders (Deecher et al., 2006).

In a study conducted to improve the treatment of vasomotor symptoms that occur during menopause, desvenlafaxine was preferred despite being a new SNRI because its therapeutic efficacy is assumed to be due to its role in thermoregulation of norepinephrine and serotonin neurotransmitters in hypothalamus and dysfunction resulting from vasomotor symptoms. Women treated with desvenlafaxine showed a much higher rate of improvement compared to control group (Speroff et al., 2008).

Many studies have demonstrated safety, tolerability, and effectiveness of desvenlafaxine in both daily and fixed doses and flexible doses (100 mg, 200 mg, and 400 mg) (Liebowitz et al., 2008).

Pregnancy

There were no teratogenic effects when oral doses up to 300 mg/kg/day and 75 mg/kg/day were given to pregnant rats and rabbits during organogenesis. In reproductive developmental studies in rats and rabbits treated with desvenlafaxine succinate, there was no evidence of teratogenicity at a plasma exposure (AUC) that is up to 19-times (rats) and 0.5-times (rabbits) the exposure at an adult human dose of 100 mg per day. Yet, at highest dose, fetus weights showed decreases and delayed skeletal ossification was observed along with maternal toxicity (Pfizer Medical Information, 2021).

Lactation

Desvenlafaxine is eliminated in breast milk. Nursing mothers must discontinue using the medicine or stop breastfeeding based on the risks and benefits to the mother and child because controlled clinical trials are not available (Ilett, Watt, Hackett, Kohan & Teoh, 2010).

When given orally to pregnant rats during gestation and lactation at the maximum dose (300 mg/kg/day), there were increases in pup mortality during the first four days of lactation and decreases in pup weights, both of which had no apparent cause. The AUC exposure at the level that had no effect on rat pup mortality was 4.5 times higher than the exposure at a daily dose of 100 mg for adults. Desvenlafaxine medication for the mother had no impact on the pups' post-weaning development or ability for reproduction (Pfizer Medical Information, 2021).

Ten breastfeeding women (with a mean age of 4.3 months) receiving desvenlafaxine at a dose of 50 to 150 mg every day participated in a lactation study. Foremilk and hindmilk were collected over a 24-hour dosing period at steady state (up to 8 samples). The average relative baby dose was 6.8%, with a range of 5.8% to 8.1%. No adverse reactions were reported in newborns (Rampono, Teoh, Hackett, Kohan, & Ilett, 2011).

Duloxetine

Duloxetine, ((3S)-N-methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine), is one of the first-line treatments for many diseases including fibromyalgia and major depressive disorder (Figure 2c). Duloxetine was introduced to treatment in USA in 2004 (Lantz et al., 2003; Lee & Chen, 2010; Fanelli, Weller & Liu, 2021; Knadler, Lobo, Chappell & Bergstrom, 2011). In addition to these disorders, SNRIs especially venlafaxine and duloxetine can also be used in the treatment of pain associated with cancer. Duloxetine may be preferred because of its higher affinity for noradrenergic transporters, but both medicines are recommended as equivalent first-line treatments (Zerfas, McGinn & Smith, 2023).

Pharmacokinetics

Mean bioavailability is 50%, with a wide variability between individuals (30-80%). As duloxetine can hydrolyze in acidic conditions, there is a necessity for enteric coating although enteric coating causes two hours of delay in absorption. Tmax is 6 hours including delay time. Food also leads to a delay in Tmax and 10% decrease in AUC. Along with those, taking duloxetine before sleep at night leads to a 4-hour lag time and 18% decrease in AUC with a 29% reduction in Cmax. The reason for the delay is delayed gastric emptying. However, they do not practically affect the clinical efficacy. Duloxetine is highly bound to proteins (90-99%, primarily albumin and α1-acid-glycoprotein) and is highly distributed. Duloxetine can cross

BBB. In both humans and animals, the amount of duloxetine in the cerebral cortex was found to be higher than in plasma. V_d is 1,620-1,800 L (Knadler et al., 2011).

Cytochrome P450 2D6 (CYP2D6) and cytochrome P450 1A2 (CYP1A2), two mitochondrial isoforms of cytochrome P450 isoenzymes, are primarily responsible for the metabolism of duloxetine (Yue et al., 2023). Five phenotypes (ultrarapid metabolizers, rapid metabolizers, normal metabolizers, intermediate metabolizers, and poor metabolizers) have been determined based on the enzymatic activity of different CYP2D6 polymorphisms. Because treatment response may vary due to CYP2D6 polymorphisms, personalized treatment approaches are very important to optimize major depression disorder management (Maciaszek et al., 2023). CYP2C9 is known to be a minor contributor in formation of 5-hydroxy metabolite. Hydroxylation occurs at 4-, 5-, or 6- positions on naphthalene ring (Figure 2d) and 4-hydroxy metabolite directly undergoes glucuronidation. 5- and 6-hydroxy metabolites undergo glucuronide or sulfate conjugation. Unknown metabolites lack clinical significance in overall profile of duloxetine. The half-life of duloxetine ranges between 78-17 hours, with a mean of 12 hours. Inter-individual variations are reported in the clearance of duloxetine (57-114 L/h). The concentration of the drug in the blood at a steady state increased by 2.3 and 2.6 times, respectively, with the dose doubling from 30 to 60 mg and from 60 to 120 mg. The 20% of duloxetine is eliminated in the feces as the parent drug, a 4-hydroxy metabolite, and an unidentified metabolite. Urine excretes 70% of duloxetine as conjugated metabolites. Biliary secretion may also be involved (Knadler et al., 2011).

Pharmacodynamics

Duloxetine inhibits the reuptake of serotonin and norepinephrine in neurons. It also has a weaker inhibitory effect on dopamine reuptake. The dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and -aminobutyric acid (GABA) receptors are not particularly stimulated by duloxetine. The dual action of duloxetine on serotonin and norepinephrine regulates emotions. Compared to venlafaxine, the affinity of duloxetine for suppression of serotonin and norepinephrine reuptake is partially more balanced (Frampton & Plosker, 2007).

CNS effects of duloxetine are mediated by its action on the external urinary sphincter. Due to increments in serotonin and norepinephrine levels in α1-adrenergic receptors, *Onuf's* nucleus, activation of 5-HT2 and 5-HT3 show increases. Both 5-HT2 and α1 are G_q (G_i/G_o) coupled receptors. When they are activated, the activity of the inositol trisphosphate/phospholipase C (IP3/PLC) pathway increases. This activation of the IP3/PLC pathway causes the release of intracellular calcium, which raises intracellular calcium levels and promotes neuronal excitability. On the other hand, 5-HT3 is a ligand-gated sodium channel allowing sodium to flow into neurons when it is activated. Increased sodium flow into neurons causes depolarization and the activation of voltage-gated channels is essential to produce action potentials. When each of these receptors is activated, they work together to enhance the pudendal motor nerve's response to glutamate. This response also provides duloxetine to act on the spinal cord and enables modulation of pain. Increased serotonin and norepinephrine levels in the dorsal horn of the spinal cord provide pain inhibition by activation of several receptors (i.e. α1-adrenergic and α2-adrenergic receptors, 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2 and 5-HT3). GABAergic inhibitory interneuron connections that are activated block the transmission of painful impulses to the brain and the nociceptive projection neuron. Activation of G_q-coupled 5-HT1 and α2 receptors cause elevated potassium through inward rectifier channels and reduced adenylyl cyclase/protein kinase A signaling which participates in neuronal inhibition. These inhibitory receptors are present on the projection neuron itself as well as the dorsal root ganglion, which act to prevent the direct transmission of painful inputs (Wong et al., 1993; Millan, 2002; Gupta, Nihalani & Masand, 2007; Bellingham & Peng, 2010).

The safety, tolerability, and effectiveness of duloxetine are demonstrated in both daily and fixed doses and flexible doses (30 mg and 60 mg). The intended pharmacological effect of duloxetine and its hypertensive effect are connected. The vascular endothelium's adrenergic receptors are activated when norepinephrine availability increases. Vasoconstriction occurs as the Gq-coupled receptor mediating calcium releases from the sarcoplasmic reticulum to enhance smooth muscle contraction because the action of α1-adrenergic receptors predominates (Cowen, Ogilvie & Gama 2005).

Pregnancy

It has been demonstrated that duloxetine has adverse effects on postnatal and embryo/fetal development in animals. There is no sufficient and reliable research on pregnant women. Some neonates can need respiration support, tube feeding, and a longer hospital stay. Some of them wailed nonstop, experienced convulsions, had trouble breathing or eating, or had stiff or overly relaxed muscles. Therefore, if there is no immediate necessity, duloxetine should not be given to pregnant women or those planning to have children. (Cymbalta Product Monograph, 2021).

A recent study revealed information on pre/post-term births, ectopic pregnancies, and pregnancy outcomes of women exposed to duloxetine from the Lilly Safety System (LSS) and the FDA Adverse Events Reporting System. There were 400 pregnancies found in the LSS database. Most of the pregnancy outcomes that were categorized as "abnormal" were spontaneous abortions (n=41), perinatal complications (n=25), or premature births (n=19). In patients with abnormal pregnancy outcomes, relevant concomitant medication use, and relevant medical history were more frequently reported, compared to those with nor-

mal pregnancy outcomes. Considering all the available data, it was suggested that the "frequency of abnormal results reported in pregnancy cases with duloxetine exposure is generally consistent with historic control rates in the general population" (Hoog, Cheng, Elpers & Dowsett, 2013). In addition, there are similar results reported in 256 pregnant women taking duloxetine with a majority of intake during either of the trimesters (n=206) while others throughout pregnancy (Einarson et al., 2012). The rate of major congenital malformations (1.8% as hydronephrosis, kidney agenesis, and clubfoot) was within the general population's baseline rate (Einarson et al., 2012). Similar findings were obtained from two case reports performed by Briggs et al. (2009) and Bellantuono et al. (2013) who reported two cases of pregnant women exposed to duloxetine during pregnancy (60mg/day) (Briggs et al., 2009; Bellantuono, Marini & Lucarelli, 2013). Both suggested that healthy newborns were born from two mothers who took duloxetine during pregnancy.

In one case report, Eyal and Yaeger (2008) found that a newborn developed a neonatal "behavioral syndrome," characterized by poor muscle tone, respiratory distress, jitteriness, weak cry, low *Apgar* score, and seizures, born to a mother who took duloxetine throughout pregnancy (90 mg/day). Authors suggested that these symptoms could have developed as a result of discontinuation syndrome (Eyal & Yaeger, 2008).

Ankarfeldt et. al (2021) investigated the potential link between duloxetine exposure during pregnancy and birth defects or stillbirth in children. A population-based observational study was carried out using information from more than 2 million Danish and Swedish medical birth registrations from 2004 to 2016. It was found that there were no correlations between duloxetine exposure during pregnancy and the risk of abnormalities or stillbirth (Ankarfeldt et al., 2021).

Lactation

Duloxetine is eliminated in breast milk. The baby receives nearly 0.14% of the maternal dose on a mg/kg basis. Boyce et al., (2011) reported a newborn with no adverse effects whose mother was prescribed duloxetine in the second half of pregnancy (60 mg/day). The dose of duloxetine taken during pregnancy may be a crucial factor in adverse effects in prenatally exposed infants (Boyce, Hackett & Ilett, 2011). The safety of duloxetine in infants is not clearly established. Therefore, duloxetine is not recommended during nursing (Larsen et al., 2015).

Levomilnacipran (Fetzima)

Levomilnacipran ((1*S*,2*R*)-2-(aminomethyl)-*N,N*-diethyl-1-phenylcyclopropane-1 carboxamide, Figure 2e), is the enantiomer of milnacipran ((1*R*,2*S*)-2-(aminomethyl)-*N,N*-diethyl-1-phenylcyclopropane-1-carboxamide; Figure 2f) and is superior in the management of depression. Since it is used once a day, patient compliance is high and the drug is well tolerated (Bruno, Morabito, Spina & Muscatello, 2016). In addition, it has been shown to have -site amyloid precursor protein cleaving enzyme-1 (BACE-1) inhibitory activity. Thus, it has been experimentally shown that the compound may have a pleiotropic effect by inhibiting β-amyloid plaque formation (Fasipe, 2018).

Pharmacokinetics

After oral administration of an extended-release capsule of levomilnacipran, relative bioavailability was 92%. Intake of the drug with food does not affect its blood concentrations. After using extended-release capsules, the mean C_{max} was determined as 341 ng/mL, and the mean steady-state AUC was 5196 ng·h/mL. After oral intake, the drug has a T_{max} of 6-8 hours. In humans, there is no interconversion of stereoisomers. V_d is 387-473 L. Between 10 to 1,000 ng/mL of plasma concentrations, levomilnacipran is carried as 22% protein bound. Levomilnacipran is bio transformed by desethylation (mainly by CYP3A4 and by CYP2C8, CYP2C19, CYP 2D6 and CYP 2J2 to a lesser extent) to N-desethyl levomilnacipran and by hydroxylation to p-hydroxy-levomilnacipran. Both metabolites are glucuronidated later. The main excretion route for levomilnacipran and its metabolites is by kidneys. In the urine, about 58% of the dosage is eliminated unchanged, with the remaining 18% being accounted for by the primary metabolite N-desethyl levomilnacipran. Levomilnacipran glucuronide (4%), desethyl-levomilnacipran glucuronide (3%), p-hydroxy levomilnacipran glucuronide (1%), and p-hydroxylevomilnacipran (1%), are also urine detectable metabolites. It is found that these metabolites are inactive. 12 hours is the half-life, while 21 to 29 L/h is the average apparent total clearance (Bruno et al., 2016).

Pharmacodynamics

The exact antidepressant action mechanism is uncertain. However, it is hypothesized that it is connected to the accumulation of serotonin and norepinephrine in the central nervous system (CNS) due to an inhibition of their reuptake by transporters. Its inhibitory reuptake effect is more on norepinephrine rather than serotonin (Lee & Chen, 2010; Montgomery et al., 2013; Bruno et al., 2016;). In a rat study, levomilnacipran increased amounts of serotonin and norepinephrine in the frontal cortex but this increase was stronger for norepinephrine than serotonin (Auclair et al., 2013).

In a study of patients with major depression, patients treated with levomilnacipran showed significantly higher rates of improvement compared to the placebo group. In addition, it has played an important role in eliminating functional impairments that can occur during depression. Another factor observed was that a small number of patients discontinued to treatment of levomilnacipran compared to placebo. This suggests that the

drug is well-tolerated. However, patients treated with levomilnacipran had a higher mean heart rate, which was associated with increased noradrenergic activity (Montgomery et al., 2013).

Pregnancy

There are no sufficient controlled trials of levomilnacipran in pregnant women. The drug was not teratogenic in rats or rabbits when administered during the organogenesis phase up to 100 mg/kg/day (doses up to 8 or 16 times the MRHD of 120 mg on a mg/m2 basis, respectively). Rat fetus body weights were decreased, and skeletal ossification was postponed in both rats and rabbits. However, these effects were not seen in either species at doses up to 30 mg/kg/day (2.4 times MRHD in rats or 5 times MRHD in rabbits), which indicated that neither species experienced any adverse effects. Early postnatal pup mortality increased when pregnant rats were given 60 mg/kg/day (5 times MRHD) orally during organogenesis, pregnancy, and lactation. At 20 mg/kg/day (1.6 times MRHD), there was no pup death. Up to 8 weeks of age, pre- and post-weaning pup weight increase was decreased in the surviving pups. The progeny's physical and functional growth including their ability to reproduce remained unaffected. At 7 mg/kg/day (0.6 times the MRHD), no effects on body weight growth were seen. Levomilnacipran should be used in pregnant women by deciding based on the risks-benefits. (FDA, 2012).

Lactation

Levomilnacipran has been found in the milk of nursing rats. There have been no studies with nursing mothers who exposed to levomilnacipran in the literature. On the other hand, racemic form of milnacipran has modest amounts in breastmilk and was not anticipated to have any adverse effects on breastfed infants. Levomilnacipran should be used with caution while breastfeeding (Drugs and Lactation Database, 2006).

DISCUSSION AND CONCLUSION

Depression in pregnancy as well as in lactation may lead to severe consequences. Therefore, use of antidepressants during these periods may be needed. The usage of SNRIs during nursing and pregnancy has not been well studied. Even though the categorization of drugs in pregnancy (A, B, C, D and X) are discontinued by the FDA in 2015, FDA continues to be the initial phase of risk assessment. The current additional processes and the initial risk assessment are taken into consideration when making the final judgment about whether the drug can be used during pregnancy or not. On the other hand, drug use during lactation is being evaluated according to the Pregnancy and Lactation Labeling Rule (PLLR). The healthcare providers assess benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication according to the PLLR. When an information become s outdated, the PLLR also requires the label to be updated.

SNRIs used to be evaluated as category C by the FDA as negative effects on fetus have been observed in animal studies. These drugs can only be used during pregnancy if there is a clear necessity (Ray Stowe, 2014). Lactating mothers may also have post-partum depression. If a SNRI is the drug of choice, it should be used with caution, as there have been no well-designed or well-controlled studies on effects of SNRIs in postnatal period.

In conclusion, although SNRIs have fewer adverse effects and high efficacy, they should be used with caution during pregnancy and lactation. Well-controlled studies on large number of subjects are needed to show their safety during these two susceptible periods of life.

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ORCID IDs of the authors

Göksu Canıtez	0009-0006-0672-2022
Rahime Şimşek	0000-0002-8467-6336
Deniz Arca Çakır	0000-0002-6110-1775
Hülya Tezel Yalçın	0000-0002-1843-3424
Terken Baydar	0000-0002-5497-9600
Pınar Erkekoğlu	0000-0003-4713-7672

REFERENCES

Ankarfeldt, M. Z., Petersen, J., Andersen, J. T., Li, H., Motsko, S. P., Fast, T. ... Jimenez-Solem, E. (2021). Exposure to duloxetine during pregnancy and risk of congenital malformations and stillbirth: A nationwide cohort study in Denmark and Sweden. *Plos Medicine*, 18(11), e1003851. https://doi.org/10.1371/journal.pmed.1003851

American Psychiatric Association (2023, September). Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) [Web log post]. Retrieved from: https://www.psychiatry.org/psychiatrists/practice/dsm/updates-to-dsm/updates-to-dsm-5-tr-criteria-text

Armstrong, C. (2008). ACOG guidelines on psychiatric medication use during pregnancy and lactation. *American Family Physician,*

78(6), 772-778.

Auclair, A. L., Martel, J. C., Assié, M. B., Bardin, L., Heusler, P., Cussac, D. ... Depoortère, R. (2013). Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology*, 70, 338–347. https://doi.org/10.1016/j.neuropharm.2013.02.024

Avalos, L. A., Chen, H., & Li, D. K. (2015). Antidepressant medication use, depression, and the risk of preeclampsia. *CNS Spectrums*, 20(1), 39–47. https://doi.org/10.1017/S1092852915000024

Banzi, R., Cusi, C., Randazzo, C., Sterzi, R., Tedesco, D., & Moja, L. (2015). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. *The Cochrane Database Of Systematic Reviews*, 4(4), CD002919. https://doi.org/10.1002/14651858.CD002919.pub3

Bellantuono, C., Marini, A., & Lucarelli, C. (2013). Infant health and neurodevelopmental outcomes following prenatal exposure to duloxetine. *Clinical Drug Investigation, 33*(9), 685 688. https://doi.org/10.1007/s40261-013-0112-y

Bellantuono, C., Vargas, M., Mandarelli, G., Nardi, B., & Martini, M. G. (2015). The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. *Human Psychopharmacology*, 30(3), 143–151. https://doi.org/10.1002/hup.2473

Bellingham, G. A., & Peng, P. W. (2010). Duloxetine: a review of its pharmacology and use in chronic pain management. *Regional Anesthesia And Pain Medicine, 35*(3), 294–303. https://doi.org/10.1097/AAP.0b013e3181df2645

Benevent, J., Araujo, M., Karki, S., Delarue-Hurault, C., Waser, J., Lacroix, I. ... Damase-Michel, C. (2023). Risk of Hypertensive Disorders of Pregnancy in Women Treated With Serotonin-Norepinephrine Reuptake Inhibitors: A Comparative Study Using the EFEMERIS Database. *The Journal Of Clinical Psychiatry*, 84(4), 22m14734. https://doi.org/10.4088/JCP.22m14734

Bérard, A., Zhao, J. P., & Sheehy, O. (2017). Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. *BMJ Open*, 7(1), e013372. *https://doi.org/10.1136/bmjopen-2016-013372*

Boucher, N., Koren, G., & Beaulac-Baillargeon, L. (2009). Maternal use of venlafaxine near term: correlation between neonatal effects and plasma concentrations. *Therapeutic Drug Monitoring*, 31(3), 404–409. https://doi.org/10.1097/FTD.0b013e3181a58fb4

Boyce, P. M., Hackett, L. P., & Ilett, K. F. (2011). Duloxetine transfer across the placenta during pregnancy and into milk during lactation. *Archives Of Women's Mental Health, 14*(2), 169–172. https://doi.org/10.1007/s00737-011-0215-5

Briggs, G. G., Ambrose, P. J., Ilett, K. F., Hackett, L. P., Nageotte, M. P., & Padilla, G. (2009). Use of duloxetine in pregnancy and lactation. *The Annals Of Pharmacotherapy*, 43(11), 1898–1902. https://doi.org/10.1345/aph.1M317

Brumbaugh, J. E., Ball, C. T., Crook, J. E., Stoppel, C. J., Carey, W. A., & Bobo, W. V. (2023). Poor Neonatal Adaptation After Antidepressant Exposure During the Third Trimester in a Geographically Defined Cohort. *Mayo Clinic Proceedings. Innovations, Quality & Outcomes*, 7(2), 127–139. https://doi.org/10.1016/j.mayocpiqo.2023.02.002

Bruno, A., Morabito, P., Spina, E., & Muscatello, M. R. (2016). The Role of Levomilnacipran in the Management of Major Depressive Disorder: A Comprehensive Review. *Current Neuropharmacology*, 14(2), 191–199. https://doi.org/10.2174/1570159x14666151117122458

Cowen, P. J., Ogilvie, A. D., & Gama, J. (2005). Efficacy, safety, and tolerability of duloxetine 60 mg once daily in major depression. *Current Medical Research And Opinion*, 21(3), 345–356. https://doi.org/10.1185/030079905X30680

Dale, E., Bang-Andersen, B., & Sánchez, C. (2015). Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochemical Pharmacology*, 95(2), 81–97. https://doi.org/10.1016/j.bcp.2015.03.011

Dandjinou, M., Sheehy, O., & Bérard, A. (2019). Antidepressant use during pregnancy and the risk of gestational diabetes mellitus: a nested case-control study. *BMJ Open*, 9(9), e025908. https://doi.org/10.1136/bmjopen-2018-025908

Deecher, D. C., Beyer, C. E., Johnston, G., Bray, J., Shah, S., Abou-Gharbia, M., & Andree, T. H. (2006). Desvenlafaxine succinate: A new serotonin and norepinephrine reuptake inhibitor. *The Journal Of Pharmacology And Experimental Therapeutics*, 318(2), 657–665. https://doi.org/10.1124/jpet.106.103382

DeMaio, W., Kane, C., Nichols, A., & Jordan, R. (2011). Metabolism studies of desvenlafaxine. *Journal Of Bioequivalence & Bioavailability, 3*(7), 151-160. https://doi.org/10.4172/jbb.1000076

Dubovicky, M., Belovicova, K., Csatlosova, K., & Bogi, E. (2017). Risks of using SSRI / SNRI antidepressants during pregnancy and lactation. *Interdisciplinary Toxicology*, 10(1), 30–34. https://doi.org/10.1515/intox-2017-0004

Einarson, A., Smart, K., Vial, T., Diav-Citrin, O., Yates, L., Stephens, S. ... Einarson, T. R. (2012). Rates of major malformations in infants following exposure to duloxetine during pregnancy: a preliminary report. *The Journal of Clinical Psychiatry*, 73(11), 1471. https://doi.org/10.4088/JCP.12l08013

Eyal, R., & Yaeger, D. (2008). Poor neonatal adaptation after in utero exposure to duloxetine. The American Journal Of Psychiatry, 165(5), 651. https://doi.org/10.1176/appi.ajp.2008.07071194

Fanelli, D., Weller, G., & Liu, H. (2021). New Serotonin-Norepinephrine Reuptake Inhibitors and Their Anesthetic and Analgesic Considerations. *Neurology International*, 13(4), 497–509. https://doi.org/10.3390/neurolint13040049

Fasipe, O. J. (2018). Neuropharmacological classification of antidepressant agents based on their mechanisms of action. *Archives Of Medicine And Health Sciences, 6*(1), 81-94. https://doi.org/10.4103/amhs.amhs_7_18

FDA Approved Drug Products. (2011). PRISTIQ® (desvenlafaxine) Extended-Release Tablets. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021992s030lbl.pdf

FDA Center for Drug Evaluation and Research. (2012). F2695 (Levomilnacipran HCl). Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204168Orig1s000PharmR.pdf

FDA Approved Drug Products. (2017). EFFEXOR XR® (venlafaxine Extended-Release) Capsules. Retrieved from : https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf

Fogelman, S. M., Schmider, J., Venkatakrishnan, K., von Moltke, L. L., Harmatz, J. S., Shader, R. I., & Greenblatt, D. J. (1999). O- and N-demethylation of venlafaxine in vitro by human liver microsomes and by microsomes from cDNA-transfected cells: effect of metabolic inhibitors and SSRI antidepressants. *Neuropsychopharmacology: Official Publication Of The American College Of Neuropsychopharmacology*, 20(5), 480–490. https://doi.org/10.1016/S0893-133X(98)00113-4

Frampton, J. E., Plosker, G. L. (2007). Duloxetine: a review of its use in the treatment of major depressive disorder. *CNS Drugs*, 21(7),

581–609. https://doi.org/10.2165/00023210-200721070-00004

Gałecki, P., Mossakowska-Wójcik, J., & Talarowska, M. (2018). The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. *Progress In Neuro-Psychopharmacology & Biological Psychiatry*, 80(Pt C), 291–294. https://doi.org/10.1016/j.pnpbp.2017.03.016

Ghimire, U., Papabathini, S. S., Kawuki, J., Obore, N., & Musa, T. H. (2021). Depression during pregnancy and the risk of low birth weight, preterm birth and intrauterine growth restriction- an updated meta-analysis. *Early Human Development*, 152, 105243. https://doi.org/10.1016/j.earlhumdev.2020.105243

Gupta, S., Nihalani, N., & Masand, P. (2007). Duloxetine: review of its pharmacology, and therapeutic use in depression and other psychiatric disorders. *Annals Of Clinical Psychiatry : Official Journal Of The American Academy Of Clinical Psychiatrists*, 19(2), 125–132. https://doi.org/10.1080/10401230701333319

Hoog, S. L., Cheng, Y., Elpers, J., & Dowsett, S. A. (2013). Duloxetine and pregnancy outcomes: safety surveillance findings. *International Journal Of Medical Sciences, 10*(4), 413–419. https://doi.org/10.7150/ijms.5213

Ilett, K. F., Watt, F., Hackett, L. P., Kohan, R., & Teoh, S. (2010). Assessment of infant dose through milk in a lactating woman taking amisulpride and desvenlafaxine for treatment-resistant depression. *Therapeutic Drug Monitoring,* 32(6), 704–707. https://doi.org/10.1097/FTD.0b013e3181f88f70

Knadler, M. P., Lobo, E., Chappell, J., & Bergstrom, R. (2011). Duloxetine: clinical pharmacokinetics and drug interactions. *Clinical Pharmacokinetics*, 50(5), 281–294. https://doi.org/10.2165/11539240-000000000-00000

Koren, G., Moretti, M., & Kapur, B. (2006). Can venlafaxine in breast milk attenuate the norepinephrine and serotonin reuptake neonatal withdrawal syndrome. *Journal Of Obstetrics And Gynaecology Canada : JOGC = Journal D'obstetrique Et Gynecologie Du Canada : JOGC,* 28(4), 299–301. https://doi.org/10.1016/S1701-2163(16)32135-1

Lambert, O., & Bourin, M. (2002). SNRIs: mechanism of action and clinical features. *Expert Review Of Neurotherapeutics*, 2(6), 849–858. https://doi.org/10.1586/14737175.2.6.849

Lantz, R. J., Gillespie, T. A., Rash, T. J., Kuo, F., Skinner, M., Kuan, H. Y., & Knadler, M. P. (2003). Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. Drug Metabolism And Disposition: The Biological Fate Of Chemicals, 31(9), 1142–1150. https://doi.org/10.1124/dmd.31.9.1142

Larsen, E. R., Damkier, P., Pedersen, L. H., Fenger-Gron, J., Mikkelsen, R. L., Nielsen, R. E., ... Danish Society of Clinical Pharmacology (2015). Use of psychotropic drugs during pregnancy and breast-feeding. *Acta Psychiatrica Scandinavica. Supplementum*, (445), 1–28. https://doi.org/10.1111/acps.12479

Lee, Y. C., & Chen, P. P. (2010). A review of SSRIs and SNRIs in neuropathic pain. *Expert Opinion On Pharmacotherapy*, 11(17), 2813–2825. https://doi.org/10.1517/14656566.2010.507192

Li, J., Lu, C., Gao, Z., Feng, Y., Luo, H., Lu, T. ... Luo, Y. (2020). SNRIs achieve faster antidepressant effects than SSRIs by elevating the concentrations of dopamine in the forebrain. *Neuropharmacology*, 177, 108237. https://doi.org/10.1016/j.neuropharm.2020.108237

Liebowitz, M. R., Manley, A. L., Padmanabhan, S. K., Ganguly, R., Tummala, R., Tourian, K. A. (2008). Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder. *Current Medical Research And Opinion*, 24(7), 1877–1890. https://doi.org/10.1185/03007990802161923

Liebowitz, M. R., & Tourian, K. A. (2010). Efficacy, safety, and tolerability of Desvenlafaxine 50 mg/d for the treatment of major depressive disorder:a systematic review of clinical trials. *Primary Care Companion To The Journal Of Clinical Psychiatry*, 12(3), PCC.09r00845. https://doi.org/10.4088/PCC.09r00845blu

Lind, J. N., Tinker, S. C., Broussard, C. S., Reefhuis, J., Carmichael, S. L., Honein, M. A., ... National Birth Defects Prevention Study (2013). Maternal medication and herbal use and risk for hypospadias: data from the National Birth Defects Prevention Study, 1997-2007. *Pharmacoepidemiology And Drug Safety*, 22(7), 783–793. https://doi.org/10.1002/pds.3448

Maciaszek, J., Pawłowski, T., Hadryś, T., Machowska, M., Wiela-Hojeńska, A., & Misiak, B. (2023). The Impact of the CYP2D6 and CYP1A2 Gene Polymorphisms on Response to Duloxetine in Patients with Major Depression. *International Journal Of Molecular Sciences*, 24(17), 13459. https://doi.org/10.3390/ijms241713459

Magalhães, P., Alves, G., LLerena, A., & Falcão, A. (2015). Clinical drug-drug interactions: focus on venlafaxine. *Drug Metabolism And Personalized Therapy*, 30(1), 3–17. https://doi.org/10.1515/dmdi-2014-0011

Masarwa, R., Bar-Oz, B., Gorelik, E., Reif, S., Perlman, A., & Matok, I. (2019). Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis. *American Journal Of Obstetrics And Gynecology, 220*(1), 57.e1–57.e13. https://doi.org/10.1016/j.ajog.2018.08.030

Millan M. J. (2002). Descending control of pain. *Progress In Neurobiology*, 66(6), 355–474. https://doi.org/10.1016/s0301-0082(02)00009-6

Molenaar, N. M., Bais, B., Lambregtse-van den Berg, M. P., Mulder, C. L., Howell, E. A., Fox, N. S. ... Kamperman, A. M. (2020). The international prevalence of antidepressant uses before, during, and after pregnancy: A systematic review and meta-analysis of timing, type of prescriptions and geographical variability. *Journal Of Affective Disorders, 264*, 82–89. https://doi.org/10.1016/j.jad.2019.12.014

Montgomery, S. A., Mansuy, L., Ruth, A., Bose, A., Li, H., & Li, D. (2013). Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. *The Journal Of Clinical Psychiatry, 74*(4), 363–369. https://doi.org/10.4088/JCP.12m08141

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M. ... Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews. Disease Primers, 2*, 16065. https://doi.org/10.1038/nrdp.2016.65

Pae C. U. (2011). Desvenlafaxine in the treatment of major depressive disorder. *Expert Opinion On Pharmacotherapy*, 12(18), 2923–2928. https://doi.org/10.1517/14656566.2011.636033

Park, K., Kim, S., Ko, Y. J., & Park, B. J. (2021). Comparison of risk of cardiovascular disease related adverse events between selective serotonin reuptake inhibitor users and serotonin norepinephrine reuptake inhibitor users in Korean adult patients with depression: retrospective cohort study. *Psychiatry Research, 298*, 113744. https://doi.org/10.1016/j.psychres.2021.113744

Perrotta, C., Giordano, F., Colombo, A., Carnovale, C., Castiglioni, M., Di Bernardo, I. ... Viganò, C. (2019). Postpartum Bleeding in Pregnant Women Receiving SSRIs/SNRIs: New Insights From a Descriptive Observational Study and an Analysis of Data from the FAERS Database. *Clinical Therapeutics, 41*(9), 1755–1766. https://doi.org/10.1016/j.clinthera.2019.06.008

Preskorn, S., Patroneva, A., Silman, H., Jiang, Q., Isler, J. A., Burczynski, M. E. ... Nichols, A. I. (2009). Comparison of the

pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. *Journal Of Clinical Psychopharmacology, 29*(1), 39–43. https://doi.org/10.1097/JCP.0b013e318192e4c1

Rampono, J., Teoh, S., Hackett, L. P., Kohan, R., & Ilett, K. F. (2011). Estimation of desvenlafaxine transfer into milk and infant exposure during its use in lactating women with postnatal depression. *Archives Of Women's Mental Health, 14*(1), 49–53. https://doi.org/10.1007/s00737-010-0188-9

Ray, S., & Stowe, Z. N. (2014). The use of antidepressant medication in pregnancy. *Best Practice & Research. Clinical Obstetrics & Gynecology, 28*(1), 71–83. https://doi.org/10.1016/j.bpobgyn.2013.09.005

Reddy, S., Kane, C., Pitrosky, B., Musgnung, J., Ninan, P. T., & Guico-Pabia, C. J. (2010). Clinical utility of desvenlafaxine 50 mg/d for treating MDD: a review of two randomized placebo-controlled trials for the practicing physician. *Current Medical Research And Opinion, 26*(1), 139–150. https://doi.org/10.1185/03007990903408678

Robiyanto, R., Roos, M., Bos, J. H. J., Hak, E., van Puijenbroek, E. P., & Schuiling-Veninga, C. C. M. (2023). Switching pattern and dose adjustment of antidepressants before and during pregnancy. *Archives Of Women's Mental Health, 26*(5), 685–696. https://doi.org/10.1007/s00737-023-01355-8

Sansone, R. A., & Sansone, L. A. (2014). Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. *Innovations In Clinical Neuroscience, 11*(3-4), 37–42. https://www.ncbi.nlm.nih.gov/pubmed/24800132

Seo, H. J., Sohi, M. S., Patkar, A. A., Masand, P. S., & Pae, C. U. (2010). Desvenlafaxine succinate: a newer antidepressant for the treatment of depression and somatic symptoms. *Postgraduate Medicine, 122*(1), 125–138. https://doi.org/10.3810/pgm.2010.01.2106

Singal, D., Chateau, D., Struck, S., Lee, J. B., Dahl, M., Derksen, S. ... Brownell, M. (2020). In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners. *Pediatrics, 145*(5), e20191157. https://doi.org/10.1542/peds.2019-1157

Snamina, M., Wietecha-Posłuszny, R., & Zawadzki, M. (2019). Postmortem analysis of human bone marrow aspirate - Quantitative determination of SSRI and SNRI drugs. Talanta, 204, 607–612. https://doi.org/10.1016/j.talanta.2019.06.054

Speroff, L., Gass, M., Constantine, G., Olivier, S., & Study 315 Investigators (2008). Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. *Obstetrics And Gynecology*, 111(1), 77–87. https://doi.org/10.1097/01.AOG.0000297371.89129.b3

Stahl, S. M., Entsuah, R., & Rudolph, R. L. (2002). Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. *Biological Psychiatry, 52*(12), 1166–1174. https://doi.org/10.1016/s0006-3223(02)01425-7

Uguz F. (2018). Maternal Antidepressant Use During Pregnancy and the Risk of Attention-Deficit/Hyperactivity Disorder in Children: A Systematic Review of the Current Literature. *Journal Of Clinical Psychopharmacology, 38*(3), 254–259. https://doi.org/10.1097/JCP.0000000000000868

Wang, X. Y., Ying, X. H., & Jiang, H. Y. (2023). Antidepressant use during pregnancy and the risk for gestational diabetes: a systematic review and meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians, 36*(1), 2162817. https://doi.org/10.1080/14767058.2022.2162817

Wong, D. T., Bymaster, F. P., Mayle, D. A., Reid, L. R., Krushinski, J. H., & Robertson, D. W. (1993). LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropsychopharmacology: Official Publication Of The American College Of Neuropsychopharmacology, 8*(1), 23–33. https://doi.org/10.1038/npp.1993.4

Yang, L., Wu, Z., Cao, L., Wang, Y., Su, Y., Huang, J. ... Fang, Y. (2021). Predictors and moderators of quality of life in patients with major depressive disorder: An AGTs-MDD study report. *Journal Of Psychiatric Research, 138*, 96–102. https://doi.org/10.1016/j.jpsychires.2021.03.063

Yue, M., Kus, L., Katta, S., Su, I., Li, L., Haas, D. M., & Quinney, S. K. (2023). Pharmacokinetics of Antidepressants in Pregnancy. *Journal Of Clinical Pharmacology, 63 Suppl 1*(Suppl 1), S137–S158. https://doi.org/10.1002/jcph.2282

Zerfas, I., McGinn, R., Smith, M. A. (2023). Pharmacologic Management of Cancer-Related Pain in Pregnant Patients. *Drugs, 83*(12), 1067–1076. https://doi.org/10.1007/s40265-023-01906-4

Zoega, H., Kieler, H., Nørgaard, M., Furu, K., Valdimarsdottir, U., Brandt, L., & Haglund, B. (2015). Use of SSRI and SNRI Antidepressants during Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden. *Plos One, 10*(12), e0144474. https://doi.org/10.1371/journal.pone.0144474

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