Serotonin-Norepinephrine Reuptake Inhibitors

Subjects: Others

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Serotonin-norepinephrine reuptake inhibitors (SNRIs) are among the most commonly prescribed medications in the United States annually. As their name suggests, the principle mechanism of action is the inhibition of presynaptic neuronal uptake of 5-HT (serotonin) and norepinephrine following release from the synaptic cleft.

Keywords: serotonin-norepinephrine reuptake inhibitors ; serotonin ; desvenlafaxine

1. Introduction

Prevention of reuptake prolongs the persistence of these monoamines in the synaptic cleft within the central nervous system (CNS). Accordingly, this results in increased postsynaptic receptor stimulation and additional post synaptic neuronal transmission. There are five principal SNRIs that are currently approved by the Food and Drug Administration (FDA) for use in the United States (**Table 1**) [1][2][3][4][5][6][7]. SNRIs are often considered to have a 'dual action' on account of their mechanism, however the specific degree of reuptake inhibition of norepinephrine and serotonin is both dose- and agent-dependent.

Table 1. Commonly-prescribed serotonin-norepinephrine reuptake inhibitors.

Drug (FDA Approval)	FDA Approved Indications for Use	Bioavailability (Oral)	Protein Binding	Metabolism	Elimination	$T_{1/2}$ (Hours)	Severe Side Effects
Desvenlafaxine (2008)	**Major Depressive Disorder**	**80%**	**30%**	**Hepatic; conjugation, primary; CYP3A4, minor pathway**	**Renal: 45%, unchanged; up to 24% changed**	**10–11.1**	**Hypertension, angioedema, suicidal ideation, serotonin syndrome**
Duloxetine (2004)	**Major Depressive Disorder, Generalized Anxiety Disorder, Fibromyalgia, Diabetic Peripheral Neuropathy, Musculoskeletal pain**	**30–80%**	**>90%**	**Hepatic: P450 CYP2D6 and CYP1A2 via conjugation and oxidation**	**Fecal: 20% Renal: 70% as metabolites**	**12**	**Hypertensive crisis, Steven-Johnson Syndrome, withdrawal syndrome, serotonin syndrome, liver failure**
Levomilnacipran (2013)	**Major Depressive Disorder**	**92%**	**22%**	**Desethylation by CYP3A4, and hydroxylation with further conjugation**	**Renal: 58% unchanged, 27% identifiable metabolites**	**12**	**Hypertension, suicidal ideation, serotonin syndrome, drug withdrawal, seizure**

Drug (FDA Approval)	FDA Approved Indications for Use	Bioavailability (Oral)	Protein Binding	Metabolism	Elimination	$T_{1/2}$ (Hours)	Severe Side Effects
Milnacipran (1996)	Fibromyalgia	85–90%	13%	Hepatic	Renal: 50% to 60% unchanged drug	6–8	Hypertensive crisis, Erythema multiforme, Stevens-Johnson syndrome, Fulminant hepatitis, suicidal ideation, serotonin syndrome
Tramadol (1977)	Pain management	70–75%	20%	Hepatic: extensive via CYP2D6 and CYP3A4, conjugation, N- and O-demethylation, and glucuronidation or sulfation	Renal excretion: 60% as metabolite; approximately 30% unchanged	5.6–6.7	Dyspnea, respiratory depression, serotonin syndrome
Venlafaxine (1994)	Panic disorder, generalized anxiety disorder, major depressive disorder, social phobia	42%	27–30%	Hepatic: extensive first-pass via P450 CYP2D6	Fecal: 2% Renal: 87%, 82% as metabolites, 5% unchanged	5	Neuroleptic malignant syndrome, Serotonin syndrome, suicidal ideation

SNRIs are a versatile class of medications with a wide variety of clinical applications. Specific clinical applications vary between SNRIs; however, these drugs are commonly prescribed as first-line agents for the treatment of depression, anxiety and fibromyalgia, among other medical conditions [9][8]. Additionally, there are emerging applications for their use in the treatment of chronic pain. Anxiety and depression rates have been rising nationally, and this trend has been exacerbated by the COVID-19 pandemic, which significantly increased the incidence of these diseases [10][11][12].

2. Serotonin-Norepinephrine Reuptake Inhibitors

2.1. Desvenlafaxine

Approved by the Food and Drug Administration (FDA) in 2008, desvenlafaxine is a potent SNRI that potentiates neurotransmitter activity of serotonin and norepinephrine within the CNS. The drug is the synthetic form of the SNRI venlafaxine's major active metabolite, and is principally used in the treatment of major depressive disorder (MDD). Desvenlafaxine is renally eliminated, but first undergoes hepatic conjugation with minor metabolism through the CYP3A4 pathway. Current evidence suggests equal efficacy between desvenlafaxine and venlafaxine in treatment of MDD [13]. However, desvenlafaxine may be a better drug selection in patients with decreased P450 CYP2D6 activity (crucial in the metabolism of venlafaxine and many other medications), who may be poor metabolizers [14]. Overall, desvenlafaxine has a favorable side effect profile. However, there are several key theoretical concerns for anesthesiologists, including the development of hypertension, angioedema and serotonin syndrome. At least one case report implicated desvenlafaxine in the development of refractory intraoperative hypertension [15]. Additionally, there is anecdotal evidence regarding the development of Takotsubo Cardiomyopathy with resultant intraoperative cardiac arrest, although this appears rare [16]. Specific guidelines for the perioperative management of desvenlafaxine apart from recommendations for SNRIs as a class are lacking. A 14-day tapering process is recommended if the decision is made to discontinue the medication in the perioperative period [13][15].

2.2. Duloxetine

Duloxetine is amongst the mostly commonly prescribed drugs annually in the United States. Accordingly, anesthesiologists are likely to encounter patients taking this drug, which was approved by the FDA in 2004 and is currently the first-line therapy for a variety of psychiatric diagnoses including MDD, generalized anxiety disorder, fibromyalgia, diabetic peripheral neuropathy and musculoskeletal pain. Additionally, duloxetine has a number of off-label uses, including treatment of peripheral neuropathy secondary to chemotherapy administration and urinary incontinence [17]. Like many other SNRIs, metabolism is through the CYP450 family of enzymes, specifically through the CYP2D6 and CYP2A2 pathways via oxidation and conjugation. Accordingly, interpatient variations in enzyme activity may contribute to varied clinical effects [18]. Duloxetine has an established safety profile and is generally well-tolerated. However, there are a number of significant severe adverse reactions including hypertensive crisis, Stevens-Johnson syndrome, serotonin syndrome, and fulminant liver failure that are of particular concern for anesthesiologists [19]. Recent research of duloxetine is largely centered on applications as an adjunct therapy in chronic pain management [20][21][22][23]. There is also an expanding role for duloxetine as an adjunct therapy in the acute postoperative period as part of a multimodal analgesia regimen, although results are mixed [24][25][26]. Trials supporting its efficacy are mostly centering on opioid-sparing effects

with concurrent therapy [27]. More evidence is likely necessary to definitively conclude that antidepressants have a distinct role in the management of postoperative pain, with better characterization of the risk benefit ratio [28]. An additional consideration regarding duloxetine for anesthesiologists is the interaction of the drug with electroconvulsive therapy. Although largely continued throughout electroconvulsive therapy without an issue, an isolated case occurred where a duloxetine-lithium combination therapy precipitated ventricular tachycardia during an electroconvulsive therapy session [29]. Duloxetine can likely be continued through the perioperative period; however, if discontinuation is required, a 14-day taper is suggested [30].

2.3. Levomilnacipran

Levomilnacipran is the most recently FDA-approved SNRI (2013), and is currently indicated for the treatment of MDD. However, additional applications for levomilnacipran are currently under investigation [31]. The drug is principally metabolized by CYP3A4 via desethylation and hydroxylation with further conjugation. Levomilnacipran differs from other SNRIs because it has a doubled potency of norepinephrine reuptake inhibition compared to serotonin [32]. Specific studies evaluating levomilnacipran in the perioperative, intraoperative, and postoperative settings are currently lacking. The more recent FDA approval and relatively lower number of prescriptions may be contributing factors to an overall low volume of evidence. Furthermore, levomilnacipran has not yet been investigated for off-label uses, unlike many other SNRIs. Levomilnacipran does have a number of side effects that are relevant to anesthesiologists, including hypertension and serotonin syndrome. As previously discussed, these adverse reactions are common to the SNRI class of medications. Recommendations on the continuation of levomilnacipran in the perioperative period are lacking, but likely mirror other SNRIs.

2.4. Milnacipran

Milnacipran is an older SNRI that obtained FDA approval for use in the treatment of fibromyalgia in 1996, and is the first-line treatment for this indication. An additional off-label use includes the treatment of MDD, and is often a second-line therapy for this use [33]. Current research into milnacipran is exploring its role in the treatment of neuropathic pain, although early results are not promising [34]. Of note, unlike many other SNRIs, milnacipran does not undergo metabolism via the CYP450 system. The side effect profile is similar to other SNRIs, with the most severe effects being hypertensive crisis, erythema multiforme, Stevens-Johnson syndrome, fulminant hepatitis, and serotonin syndrome. Evidence related specifically to anesthesia, outside of general concerns regarding the SNRI class, are lacking. A 14-day taper is recommended if the decision is made to discontinue in the perioperative period.

2.5. Sibutramine

Sibutramine is an SNRI that prevents dopamine reuptake, in addition to blocking the reuptake of serotonin and norepinephrine. Sibutramine reduces the reuptake of norepinephrine (by 73%), serotonin (by 54%), and dopamine (by 16%). The drug was initially approved for use in 1998 as an appetite suppressant for the treatment of obesity. However, it was voluntarily withdrawn from the US markets in 2010. Studies were suggestive of an increased risk of cardiovascular adverse events including non-fatal stroke and non-fatal heart attack [35]. Despite this risk profile, sibutramine is still available in countries outside of the United States. Unlike many other drugs in the SNRI class, there is no utility as an antidepressant, despite its initial evidence of efficacy [36].

2.6. Tramadol

Tramadol was patented in the 1960s but was not approved by the FDA until 1995. The drug's principle mechanism of action is through opioid μ-receptor agonism; however, the drug also functions as a serotonin and norepinephrine reuptake inhibitor. Although not a traditional SNRI, tramadol's partial SNRI mechanism of action merits consideration in this paper. Accordingly, tramadol's principle mechanism of action as a μ-receptor agonist precludes its use as a first-line antidepressant, unlike most other drugs in the SNRI class. Instead, tramadol is FDA-approved for the management of both acute and chronic pain.

Due to its unique mechanism of action and prolonged time on the market, tramadol has been extensively investigated for off-label uses, more so than other drugs with an SNRI mechanism of action. These include treatment of cancer pain, adjunct therapy for peripheral nerve blocks, and neuraxial anesthesia. Additionally, tramadol has also been extensively evaluated for the treatment of neuropathic pain. However, a recent meta-analysis suggested only modest benefit [37]. The combined mechanisms are thought to be more effectively modulate to the transmission of pain [38]. Tramadol is metabolized through the CYP450 family of enzymes (mostly CYP2D6 and CYP3A4) via conjugation, N- and O-demethylation, and glucuronidation or sulfation. Although well-tolerated, adverse effects of tramadol include respiratory

depression, physical dependence, seizures and serotonin syndrome. Risk of serotonin syndrome and seizures are unique to tramadol amongst other opioids, and is attributed to its serotonin-norepinephrine mechanism of action [39][40].

Tramadol is more widely utilized in the preoperative, intraoperative, and postoperative period compared to other medications with serotonin-norepinephrine reuptake pharmacodynamics. Intraoperative use of tramadol is limited in favor of other pure opioid agonists; however, tramadol may be administered in the perioperative period as part of an effective multimodal pain regimen [38]. Tramadol has also been utilized as an adjunct to local anesthetic for a neuraxial blockade via an intrathecal approach, epidural, or combined spinal-epidural with varying success [41][42][43]. Adjunct agents are a method to prolong the duration of the blockade while minimizing unwanted side effects. These blocks are commonly employed by anesthesiologists for a variety of surgeries.

In addition to applications as an adjunct to neuraxial anesthesia, tramadol has been utilized in combination with local anesthetics for applications in regional anesthesia. While tramadol does not have efficacy as a solo agent for regional anesthesia, it may improve the efficacy of local anesthetics [44]. This has been found regarding upper extremity blocks in particular [45]. However, not all data is supportive of tramadol as an effective adjunct for regional anesthesia [46]. There is some evidence suggestive of tramadol as a solo effective local anesthetic for maxillary infiltration [47]. The concurrent use of tramadol with other antidepressants is of specific interest due to the variety of applications of tramadol in the perioperative period and theoretical concerns over the development of serotonin syndrome. Current evidence suggests tramadol use with monoamine oxidase inhibitors should be avoided, but concurrent use with other antidepressants is not contraindicated [48].

Applications of tramadol in the postoperative period are related to its successful prevention of postoperative shivering [49][50][51]. Additionally, this benefit appears following a variety of different anesthetics, including remifentanil-induced shivering as well as following subarachnoid blocks [52][53]. Tramadol continues to draw interest as one component of a multimodal postoperative pain management strategy [54].

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