Chapter

Serotonin Reuptake Inhibitors and Their Role in Chronic Pain Management

Adela Hilda Onuțu, Dan Sebastian Dîrzu and Cristina Petrișor

Abstract

Serotonin has a particular place in the modulation of pain. Experimental studies have described 5-HT1–7 receptors and their effects on facilitation or inhibition of nociceptive input. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors showed efficient and safer than tricyclic antidepressants in neuropathic pain. Although there is evidence regarding the beneficial impact of SSRIs in the multimodal acute pain management, studies are still searching for the potentially favorable effect of these drugs in the prevention of chronic postoperative pain. The scope of this chapter would be to update the knowledge regarding serotonin involving in pain pathways and to highlight the importance and contribution of serotonin reuptake inhibitors in the multimodal pain management schemes.

Keywords: serotonin, pain, SSRIs, SNRIs, pain management

1. Introduction

Chronic pain is recognized today as a disease [1], affects almost 20% of the population [2], and represents a significant cause of disability bringing along high secondary social costs. The management of chronic pain involves pharmacological and interventional tools and become a priority for healthcare systems. This chapter aims to summarize the role of serotonin reuptake inhibitors (SRI) in the treatment of chronic pain. SRI includes selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI).

2. Chronic pain conditions

Defined as the pain that lasts more than 3 months, frequent after the disappearance of the causal factor, chronic pain shows numerous risk factors (socio-demographic, biological, clinical, and psychological). Thus, most affected are females, older people, and people with low socio-economic level. A significant risk for developing chronic pain is the pain itself (acute and chronic at other sites), and also are incriminated the geographical background, occupational factors, and the history of abuse and violence. Neuroimaging studies have already proved the changes in the

brain with severe pain, reversible with proper treatment, and also suggested its importance for preventing the chronicization of pain [3]. The treatment of chronic pain is multi/interdisciplinary and multimodal, targeting different mechanisms of pain. We summarized some critical pain syndromes, which benefit from the SRI medication.

2.1 Diabetic neuropathy

Diabetes mellitus affects billions of people worldwide. The painful diabetic neuropathy (PDPN) occurs in 20% of diabetes patients during the disease. Risk factors include age, hypertension, obesity, alcohol abuse, and smoking.

Pathogenesis implies endoneurial microangiopathy and axonal loss, especially in sensory nerves. Aldose reductase activation by increasing polyol flux and the deposition of advanced glycated end-products are the primary determinants of PDPN. Secondary ischemia leads to enhanced oxidative stress and high production of free radicals, which leads to nerve damage [4].

Clinical PDPN may present as burning, stabbing, dull and aching, or sharp pain. In some instances, allodynia (painful response to a normally non-noxious stimulus) might accompany pain. PDPN is symptomatic mainly in the lower limbs and progresses proximally. Patients with PDPN show skin changes and loss of sensory that could lead further to diabetic ulcers.

The medication of painful diabetic neuropathy includes duloxetine, venlafaxine, tricyclic antidepressants (TAD), oxcarbazepine, and tapentadol. Overall, the quality of life in patients with PDPN is poor [5].

2.2 Fibromyalgia

Fibromyalgia (FM) is a syndrome composed of widespread chronic pain, muscle fatigue, and functional symptoms. It shows a genetic predisposition, but environmental factors play a prominent place during the disease. FM pathogenesis involves modified inflammatory response and oxidative stress [6].

Diagnosis is difficult because of the variety of clinical symptoms—75% of these patients do not meet the inclusion criteria, thus often they lack the diagnosis. Besides, these patients develop sleep disturbances and sexual dysfunction, altering further the quality of life.

The current evidence suggest for FM management antidepressants, cardiovascular exercise, and cognitive behavioral therapy [7]. Meta-analysis results agree that the medication approved by FDA—milnacipran—and duloxetine are effective in FM while there are concerns that the results showed only a moderate effect on pain and sleep, and no impact on fatigue [8].

2.3 Tension-type headache

Tension-type headache (TTH) is a typical headache (up to 78%), caused by the contractions of muscles of the scalp, neck, and jaw, and triggered mainly by stress and emotional conflicts. It is described as a moderate pressure applied to the frontal area, around the head or neck, and according to its frequency is classified as infrequent, frequent, and chronic.

Chronic TTH results as a consequence of sensitization of the pain pathway due to persistent pericranial myofascial nociceptive input. This TTH shows a frequency of at least 15 days/month for at least 3 months. If nausea and vomiting are present, exclude the diagnosis of TTH. Photophobia may occur in TTH.

Treatment of the acute episodes of TTH includes nonsteroidal anti-inflammatory drugs and acetaminophen, while their prevention associates pharmacologic and non-pharmacologic (physical and psychologic therapy) interventions. Tricyclic antidepressants (amitriptyline) are the most studied drugs in TTH, but new studies showed efficacy for other antidepressants including SRI—citalopram, sertraline, venlafaxine, and paroxetine [9].

2.4 Somatoform pain

Somatoform pain (SP) is the primary symptom in an ambiguous and unclarified category called somatization spectrum disorders (SSD), defined as the displaying of somatic complaints as a result of social stress. It shows a growing incidence (up to 60%) and is a symptom generally unexplained by the medical condition of these patients (which must be ruled out). The symptomatology—headache and musculoskeletal pain—overlaps with other chronic pain syndromes and may be associated with psychiatric symptoms (depression, anxiety, personality disorders) and thus makes the diagnosis difficult. The mechanism of this condition is a subject of debate, but a genetic predisposition plus an altered interpersonal relationship in childhood and adolescence are the determining factors [10].

Treatment is focused on psychotherapy and modulation of interpersonal relations, by learning to develop robust, safe, and supportive social relationships. Besides, acupuncture and massage proved efficacy. Medication includes TADs and SSRIs [11].

3. Selective serotonin reuptake inhibitors in chronic pain management

Due to the association between chronic pain states and depression and also due to the continuous need and search for effective analgesic drugs, antidepressants have long been considered for the treatment of chronic pain. Some antidepressants are useful in the management of pain syndromes showing analgesic effects, but not all antidepressants have analgesic properties [12]. TADs are recognized to have analgesic effects in doses lower than the antidepressant ones. However, frequent side effects preclude their widespread use.

Consequently, newer generations of antidepressants, like SSRIs and SNRIs, have been studied in chronic pain management. For SSRIs, efficiency in chronic pain conditions has been debated, and results are still inconclusive. It is felt that antidepressants with both noradrenergic and serotoninergic activities are superior analgesics compared to drugs that possess only serotoninergic activity [13].

Currently available SSRIs are fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. Fluvoxamine is approved for the treatment of obsessive-compulsive disorders but has sometimes been used off-label for the treatment of depression. SSRIs are currently approved and used for the treatment of a wide range of diseases: depression, anxiety and panic disorders, obsessive-compulsive disorders, post-traumatic stress disorder, premenstrual dysphoric syndrome, dysthymia, irritable bowel syndrome, eating disorders, alcohol abuse, and some personality disorders [14].

SSRIs utility for the treatment of chronic pain has been questioned but seems attractive due to their better side-effect profile compared to first-generation antidepressants like TADs, as SSRIs selectively block serotonin reuptake (reabsorption in the synaptic cleft).

How could SSRIs be useful in chronic pain management? Do they possess both antidepressant and intrinsic analgesic properties?

Even though widely prescribed, the mechanism of action of SSRIs is not yet fully understood. The traditional theories claim the fact that antidepressant drugs act by influencing certain brain neurotransmitters [15]. Serotonin (5-HT) is one of the neurotransmitters which carry signals between neurons. The monoamine signaling theory of depression explains how SSRIs and other antidepressants work at the synaptic level by inhibiting the reuptake of one or several neurotransmitters, an effect which is almost immediate and leads to the increase of the extracellular level of the mediator. SSRIs are selective inhibitors of the presynaptic 5-HT reuptake transporter (SERT) that leads to an acute increase in serotonin concentrations in the synaptic cleft. This effect does not explain why antidepressant drugs work 2–4 weeks after treatment commencement, which might be better explained by receptor downregulation and delayed desensitization of presynaptic serotonin receptors [16]. Recent findings also suggest changes in brain-derived neurotrophic factor expression, which might even lead to SSRI antidepressant effect. Another newer theory suggests that SSRIs impact brain levels of allopregnanolone, enhancing gamma-amino butyric functions in the brain [14]. Apart from monoamine neurotransmitter's imbalance, the inflammatory theory of depression claims the increased serum levels of proinflammatory mediators in the depressed patients [17]. As inflammation is the well-known cause of acute and some type of chronic pain, proinflammatory mediators play the capital role in initiating nociception and peripheral sensitization. *In vitro* experimental studies and early *in vivo* studies suggested that SSRIs could inhibit the release of TNF-α, interferon γ, interleukin 1β, and free radical superoxide [16, 18]. Probably one of the most plausible humoral links between chronic pain conditions and depression is inflammation. If SSRIs have intrinsic anti-inflammatory and anti-oxidative properties and could modulate inflammatory processes, then this could be an explanation for their therapeutic effect in chronic pain management. The detailed specificity of action for this mechanism remains unknown [19]. Intrinsic antihyperalgesic effects in animal models have recently been described for SSRIs [20–23].

Possible side effects observed during antidepressant treatment with SSRIs also need to be considered when prescribing SSRIs for chronic pain management.

These side effects include [12, 14, 24]:

- Drowsiness, dry mouth, blurred vision, dizziness
- Gastrointestinal effects: nausea, diarrhea or constipation, vomiting
- Central nervous system effects: insomnia, agitation or restlessness, headache, tremors, increased sweating, rarely extrapyramidal symptoms, anorexia
- Syndrome of inappropriate antidiuretic hormone secretion with hyponatremia, somnolence, delirium, confusion
- Sexual dysfunction
- Weight gain
- Platelet dysfunction and increased risk of bleeding
- Drug interactions due to the concomitant hepatic metabolism involving the cytochrome P450
- Safety issues in pregnancy

- Serotonin syndrome

Suicide might be a risk occurring early in the treatment, even though larger epidemiological studies do not confirm this assumption [14].

SSRIs discontinuation syndrome is characterized by sensory and gastrointestinal symptoms, dizziness, lethargy, and sleep disturbances [25].

3.1 Individual SSRIs and their efficiency in chronic pain conditions as highlighted in clinical trials

3.1.1 Fluoxetine

Fluoxetine (Prozac™, Sarafem™) has been one of the first SSRIs available for the treatment of depression. Its use for chronic pain management has been highlighted in several clinical trials including modest numbers of patients (**Table 1**). For chronic tension-type headache, fluoxetine administered in 20 mg daily dose is equally efficient to desipramine [26]. For the treatment of painful diabetic neuropathy, fluoxetine is no more effective than placebo and ameliorates pain in 48% of the patients, especially the depressed ones [27]. For somatoform pain disorders, the analgesic effect is related to treatment duration and is related to its antidepressant effect as depressive patients show greater improvement compared to non-depressed ones [28]. Fluoxetine was found to be efficient for the treatment of fibromyalgia when compared to placebo or amitriptyline [29, 30].

3.1.2 Fluvoxamine

Fluvoxamine (Luvox™) is currently used for the treatment of obsessive-compulsive disorders, and the therapeutic dose varies widely between 50 and 300 mg. Non-depressed patients with severe chronic tension-type headache respond to fluvoxamine 50–100 mg daily [31], and it is efficient in central post-stroke pain, cancer pain, and osteoarthritis [32–34]. However, for chronic cancer pain, its beneficial effect has not yet been proven [35].

	Study	Chronic pain condition	Dose used for chronic pain (mg)	No patients	Comparator	Efficiency
Fluoxetine 10–80 mg/day for depression [14]	Walker et al. [26]	Chronic tension-type headache	20	25	Desipramine	Equally efficient
	Max et al. [27]	Diabetic neuropathy	40	46	Placebo	Equally efficient
	Luo et al. [28]	Somatoform pain disorders	20	80	Placebo	Efficient for depressed patients
	Goldenberg et al. [29]	Fibromyalgia	20	19	Amitriptyline	Effective
	Arnold et al. [30]	Fibromyalgia	45 ± 25	60	Placebo	Effective

Table 1.
Randomized controlled trials for fluoxetine in chronic pain management.

3.1.3 Sertraline

Sertraline (Zoloft™) is recommended in single daily doses of 50–200 mg for the treatment of depression. In small sample size studies, it has proven to be efficient in non-cardiac chronic chest pain and chronic pelvic pain of prostatic origin in men [36, 37], but not in women with chronic pelvic pain [38].

3.1.4 Paroxetine

Paroxetine (Paxil™, Seroxat™) is one of the most extensively studied SSRI for chronic pain management (**Table 2**). For tension-type daily headache, two studies failed to prove any beneficial effect [39, 40]. Foster et al. suggested that by extending treatment periods up to 3–9 months, patients may benefit [41]. For chronic low back pain, doses of 20 mg are less efficient than maprotiline, and the effects are similar to placebo [42, 43]. In fibromyalgia, paroxetine improves overall symptomatology, but the effect on pain is less robust [44]. Paroxetine has been shown to be useful for the treatment of diabetic peripheral neuropathy, but not more efficient than imipramine [45]. In a mixed study comparing paroxetine and citalopram versus gabapentin, the comparable efficiency of these two SSRIs with gabapentin was shown [46].

	Study	Chronic pain condition	Dose used for chronic pain (mg)	No of patients	Comparator	Efficiency
Paroxetine 10–50 mg daily for depression [14]	Langemark and Olesen [39]	Chronic tension-type headache	20–30	50	Sulpiride	Less efficient
	Holroyd et al. [40]	Chronic headache, non-responding to amitriptyline	Up to 40	31	Placebo	Modest effect
	Foster and Bafaloukos [41]	Chronic daily headache	10–50	48	Placebo	Efficient when used for 3–9 months
	Dickens et al. [42]	Chronic low back pain	20	91	Placebo	Not efficient
	Atkinson et al. [43]	Chronic low back pain	20	74	Maprotiline	Less efficient
	Patkar et al. [44]	Fibromyalgia	12.5–2.5 mg	116	Placebo	Inconclusive
	Sindrup et al. [45]	Diabetic peripheral neuropathy	40	29	Placebo and imipramine	Efficient compared to placebo, less efficient compared to imipramine
	Giannopoulos et al. [52]	Diabetic peripheral neuropathy	20–40	101	Citalopram or paroxetine *versus* gabapentin	Comparable efficiency

Table 2.
Randomized controlled trials for paroxetine in chronic pain management.

	Study	Chronic pain condition	Dose used for chronic pain (mg)	No of patients	Comparator	Efficiency
Citalopram 10–80 mg for depression [14]	Nørregaard et al. [46]	Fibromyalgia	20–40	43	Placebo	No effect
	Anderberg et al. [47]	Fibromyalgia	20–40	40	Placebo	Inconclusive
	Aragona et al. [48]	Somatoform pain disorder	20	35	Reboxetine	Moderate effect
	Bendsten et al. [49]	Chronic tension-type headache	20	40	Placebo and amitriptyline	No significant effect
	Viazis et al. [50]	Gastroesophageal reflux disease	20	63		Efficient when administered with proton pump inhibitors
	Roohafza et al. [51]	Pediatric functional abdominal pain	20	86	Placebo	Effective
	Giannopoulos et al. [52]	Diabetic peripheral neuropathy	20–40	101	Citalopram or paroxetine *versus* gabapentin	Comparable efficiency

Table 3.
Randomized controlled trials for citalopram in chronic pain management.

3.1.5 Citalopram

Citalopram (Celexa™, Cipramil™) is administered in 10–80 mg dose once daily for the treatment of depression (**Table 3**). It has been investigated for the treatment of fibromyalgia and chronic tension-type headache, with no beneficial results [47–49], while for somatoform pain disorders it has only moderate analgesic effect [50–52].

3.1.6 Escitalopram

Escitalopram (Cipralex™, Lexapro™) has antidepressive effects in 10–20 mg daily dose. For chronic low back pain, citalopram has similar results compared to duloxetine [53]. It has pain-relieving effects in painful diabetic neuropathy and somatoform disorders [54, 55]. For the treatment of pain symptoms associated with depression, escitalopram is equally effective with nortriptyline [56].

4. Serotonin norepinephrine reuptake inhibitors in pain management

SNRIs are first-line antidepressants known to inhibit the reuptake of serotonin and norepinephrine almost exclusively by binding to their transporters (SERT and NET). This category includes drugs with very different chemical structure and includes venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran.

SNRIs show different pharmacokinetics and dynamics and also different affinity to SERT and NET with consequences on their therapeutic actions (**Table 4**).

SNRI	Bioavailability (%)	Elimination half life	Elimination	SERT affinity	NAT affinity	Active metabolite
Venlafaxine	45	5 h (IR) 11 h (ER)	Renal	High	Low	Yes
Duloxetine IR	50	12 h	Renal + feces	High	High	No
Milnacipran	85	8 h	Renal (55% unchanged)	Moderate	Moderate	No
Desvenlafaxine	80	11 h (IR) 13–14 h (ER)	Renal (45% unchanged) at 72 h	High	Low	No
Levomilnacipran	92	12 h	Renal 58% unchanged	Low	High	No

SERT, serotonin transporter; NAT, noradrenaline transporter; IR, immediate release; ER, extended release.

Table 4.
SNRIs pharmacokinetics and pharmacodynamics.

Side effects of SNRIs are common to all antidepressants, but these drugs add dry mouth and constipation due to increased levels of noradrenaline. The risk of withdrawal because of side effects, in patients with chronic pain, was highest for milnacipran and followed by venlafaxine and duloxetine [57].

4.1 Venlafaxine

Venlafaxine (Effexor™) is an SNRI with mixed action on amine reuptake. When administrated in low doses, it inhibits SERT and at higher doses NAT. It is indicated for major depressive disorder (MDD) and also for anxiety, panic disorders, and social phobia management.

An experimental study showed its antihyperalgesic effect after a single administration in a diabetic neuropathic pain model, a result reversed by pretreatment with yohimbine and chloroamphetamine, but not by naloxone [58].

Long ago, a short case report raised attention to the potential beneficial effect of venlafaxine in chronic pain management [59], and later others confirmed its beneficial effects in managing neuropathic pain: peripheral neuropathy, postherpetic neuropathy, headache, and multiple sclerosis. In a systematic review on neuropathic pain, the authors found four trials (high quality evidence): two with positive results at doses of 150–225 mg venlafaxine ER daily and two with negative results (lower doses). The number needed to treat (NNT) was 6.4 and the number needed to harm (NNH) was 11.8 [60].

In elderly patients with low back pain and depression, 150 mg venlafaxine showed efficacy, but the authors suggested that patients who did not respond to small doses may benefit from dose augmentation after a 2-week period [61].

Venlafaxine may be useful in the treatment of spinal cord injury (SCI) associated with MDD because this medication improved SCI-related disability and pain. Still, further trials are needed to determine optimal doses and efficiency in patients with SCI without MDD [62, 63].

Studies in patients with taxane-oxaliplatin-induced neurotoxicity showed clinical improvement after venlafaxine (37.5 mg bid) [64], and further studies are in progress [65].

Venlafaxine had good results in acute pain; in patients with cancer breast surgery, the preoperative administration of 37.5 mg venlafaxine reduced the postoperative opioid consumption and the incidence of chronic postoperative pain at 6 months [66].

A former Cochrane meta-analysis reported little evidence to support the recommendation of venlafaxine in neuropathic pain management and noted that venlafaxine promoted fatigue, nausea, dizziness, and somnolence with a low incidence [67].

Eventually, two recent reviews (11 and 13 trials) found that venlafaxine was beneficial in neuropathic pain management with good tolerability claiming the necessity for further research to expand these findings [68, 69]. There are contradictory findings in these recent reviews, but there is need for further good quality evidence.

4.2 Desvenlafaxine

Desvenlafaxine (Pristiq™) is the third SNRI with FDA approval and only indication for MDD management (50–400 mg daily). The daily recommended dose is 50 mg. Desvenlafaxine is the salt of an active metabolite of venlafaxine, and the ER form allows 1 day administration. It presents a good bioavailability (**Table 4**) and shows a low binding to plasma proteins (30%). Desvenlafaxine binds to SERT 10 times more than to NAT and also has a weak affinity for dopamine transporter. Adverse effects are dose-dependent and typical to all antidepressants. Doses of 200–400 mg showed efficacy in DPN management, with effect sizes similar to duloxetine [70] and with increased side effects at higher doses. At the moment, there is a lack of evidence to support the use of desvenlafaxine in chronic pain management.

4.3 Duloxetine

Duloxetine (Cymbalta™; DLX) is probably the most used drug from this class of antidepressants. Aside from MDD and urinary incontinence, duloxetine is indicated for anxiety disorder, chronic pain in diabetic neuropathy, fibromyalgia, musculoskeletal pain, and osteoarthritis. DLX is a potent SNRI, with a high affinity for both SERT and NAT. It has a moderate bioavailability, with an elimination half-time of 12 h. It is metabolized in the liver and does not possess any active metabolite. Duloxetine exerts antihyperalgesic and allodynic effects, by impairing nociception at a peripheral level (blocks NaV 1.7 current) and by inhibiting neuronal firing [71]. With acute administration, DLX leads to elevated levels of NA and 5-HT, and with chronic treatment, it does not affect further basal levels of these monoamines [72]. Even if the significant pain-relieving effect was found after 7 weeks of treatment [73], others showed that patients treated with DLX for OA knee pain or low lumbar pain who have <10% reduction in pain after 4 weeks treatment have low chance to reach moderate pain reduction by the end of 12 weeks [74]. DLX's recommended dose for the first week is 30 mg, raising the dose to 60 mg in the second week in order to avoid a high incidence of side effects.

Because of interfering with platelet function, it is indicated to stop its administration 4 days before surgery.

Data from animal pain models and clinical studies on DLX administration in perioperative setting (spine, knee, breast surgery) suggested its analgesic effects. Pre- and postoperative duloxetine reduced 24-h opioid consumption, delayed first analgesic requirement, and reduced incidence of chronic postoperative pain at 6 months, being of primary interest for patients with preoperative chronic pain and spine surgery [75–77]; results from ongoing studies will respond to questions remained unanswered. Duloxetine shows good tolerability with dizziness and nausea, dry mouth, and constipation, as more frequent side effects [78].

Study	Pathology	No trials	Number of patients	Findings
Lunn et al. [79] 60 mg	Diabetes fibromyalgia	14 8-DPN; 6-FM	6407	In both category showed efficacy DPN-NNT 5 FM-NNT 8
Quilici et al. [80]	Diabetes	11	679	Effective in DPN NNT = 5 Good toleration Superior to placebo Discontinuation due to AE
Wang et al. [81] 60/120 mg (QD)	Knee osteoarthritis	3	1011	Significant pain reduction Improved function Reported "acceptable" AE
Lee and Song [82]	Fibromyalgia	9	5140	Results showed equal efficacy and tolerability
Hauser et al. [83]	Fibromyalgia	10	6038	Small benefit over placebo

QD, quaque die; DLX, duloxetine; MLC, milnacipran; DPN, diabetes polyneuropathy; NNT, number needed to treat; FM, fibromyalgia; AE, adverse effect.

Table 5.
Meta-analysis for duloxetine in chronic pain management.

While duloxetine proved its efficacy in chronic nociceptive/neuropathic pain [79–83] (**Table 5**), it is yet unrevealed its possible impact on acute postoperative pain and chronic postoperative pain.

4.4 Milnacipran

Milnacipran (Savella™) described in 1998 by Briley as a potent SNRI that showed similar inhibition on both monoamine re-uptakes, in vitro and in vivo, was approved in Europe for the treatment of depression. It did not link to alpha adrenoreceptors, muscarinic cholinergic, and histaminic receptors and showed no effect on beta-adrenergic receptors sensitivity, thus having reduced side effects. The drug has an excellent bioavailability with a mean peak plasma concentration reached between 0.5 and 4 h after the oral administration. About 13% binds to plasma proteins and is wholly eliminated after 36 h [84]. Studies on the efficacy of milnacipran in psychiatric patients revealed its significant superiority when compared to SSRIs. Most frequent adverse effects were nausea, dry mouth, and headaches [85]. Milnacipran has FDA approval for the management of fibromyalgia.

In 2006, Obata et al. found that intrathecal administration of milnacipran reduced allodynia in a rat neuropathic pain model [86].

Other experimental data confirmed these findings regarding milnacipran's antiallodynic and antihyperalgesic effects [87] and showed its effectiveness in treating allodynia in vincristine-induced neuropathic pain [88].

In a Cochrane meta-analysis, Cording et al. analyzed six studies (4238 patients) that compared milnacipran 100/200 mg with placebo in fibromyalgia. By using a "conservative" method of analysis, they found 26% positive response with milnacipran as compared to 19% for placebo and an increased rate of side effects [89].

Despite the evidence that milnacipran (100 or 200 mg) was found to be useful in neuropathic pain, as compared with placebo, Derry et al.'s meta-analysis did not

obtain enough data to confirm former data and support its recommendation in chronic neuropathic pain [90]. Future trials are needed to establish milnacipran's possible favorable effects in pain management.

4.5 Levomilnacipran

Levomilnacipran (Fetzima™) is the enantiomer of milnacipran with the highest activity, and its primary indication is MDD. At usual doses, this drug is known to possess a higher potency for norepinephrine (twofold) reuptake inhibition, as compared with 5-HT [91]; but with higher doses, it showed equal efficacy in increasing 5-HT and NE levels [92].

Regarding tolerability, the most frequently recorded adverse effects were nausea, constipation, and sweating, although a small proportion (3–6%) of patients recorded increased blood pressure and heart rate [93]. We have not found any data regarding its use in chronic pain patients.

5. Double function serotonin reuptake inhibitors

A particular category of drugs includes SRIs with double mechanism: 5-HT reuptake inhibition and interaction with 5-HT receptors. Animal studies have suggested that these receptors are included in the descending pain inhibitory systems [94, 95], and their activation is involved in reducing the acute nociceptive and neuropathic pain [96].

5.1 Trazodone

Trazodone (Desyrel™, Oleptro™) is the first non-tricyclic antidepressant approved for the treatment of MDD (1981), and it is also used to treat anxiety, alcohol dependence, insomnia, and chronic pain (off-label). It was developed for the treatment of "mental pain," which was recognized to occur in depression [97]. It acts as a SRI, antagonist of 5-HT_{A2} receptor, and a partial agonist for 5-HT_{A1} receptors. Secondary acts as an antagonist to α_1-adrenergic receptors and lacks any effect on cholinergic receptors. The drug shows a 65% oral bioavailability, 90% plasma protein binding capacity, and is metabolized in the liver (via CYP3A4) to an active metabolite—mCPP. The main excretion route is renal, and the biological half-time is 7 h. Side effects are not only shared with the other antidepressants but also list dry mouth, orthostatic hypotension, cardiac arrhythmias, and priapism.

Trazodone showed some efficacy in several chronic pain conditions represented in **Table 6**, but future studies are needed.

5.2 Nefazodone

Nefazodone (Serzone™) is related to trazodone but with fewer side effects. Doses of 300–600 mg are indicated for the treatment of MDD, panic disorders, and aggressive behavior. It acts as an antagonist of 5-HT_{A2} and 5-HT_{C2} receptors and serotonin, norepinephrine, and dopamine reuptake inhibitor. Its effects on the mentioned receptors enhance neurotransmission by an increased binding on the 5-HT_{A1} receptors. Nefazodone shows an affinity for α_1 and less for β-adrenoreceptors and does not interact with muscarinic cholinergic receptors. It has low bioavailability; it is metabolized in the liver (CYP3A4) and has four metabolites (mCPP active). Nefazodone has a biological half-time between 2 and 4 h and is excreted in urine. Frequent side effects are dry mouth, dizziness, and sleepiness, and rare, severe liver damage [98].

Murine studies yielded the capacity of nefazodone to potentiate opioid analgesia by acting through μ_1 and μ_2 receptors without affecting mortality [99]. Other results indicated that rats treated with nefazodone have shown an increased expression of μ-opioid receptors in the area of the central nervous system related to pain perception and modulation [100].

Even if it shows an excellent clinical profile, at this time we found only a two-center open-label study on the efficacy of nefazodone on preventing chronic daily headache. The study included 52 patients who received nefazodone between 100 and 450 mg (300 mg median) for 12 weeks. The results showed significantly lower incidence and intensity of daily headache and a good tolerance for nefazodone [101].

5.3 Vilazodone

Vilazodone (Viibryd™) approved by FDA (2011) for the treatment of MDD is a partial agonist to the 5-HT_{A1} receptor, GABA agonist, and SRI. Currently is presumed that it increases serotoninergic neurotransmission and it shows fast onset and good effect at daily doses between 10 and 40 mg. Vilazodone has 72% bioavailability when it is taken with food, is metabolized in the liver (via CYP3A4), and it did not possess active metabolites. It is excreted in urine and feces and has a biological half-time of 25 h [102]. Side effects include nausea, vomiting, diarrhea, and insomnia (>5%). Sexual adverse reactions and low influence on weight-gain were reported [103]. Even if it presumed that vilazodone should add value in the treatment of patients with the depression-pain syndrome, there are not yet available data on its efficacy in pain states.

Study	Chronic pain condition	Dose	Number of patients	Comparator	Efficiency
Wilson [103]	Diabetic neuropathy	50–100 mg	31	—	Effective
Ventafridda et al. [104]	Deafferentation pain	—	45	Amitriptyline	Equal efficacy
Goodkin et al. [105]	Chronic low back pain	201 mg (average)	42	Placebo	Similar effect
Morillas-Arques et al. [106]	Fibromyalgia	50–300 mg	66	—	Effective
Calandre et al. [107]	Fibromyalgia	50–300 mg trazodone + 75–450 mg pregabalin	41	—	Pregabalin enhanced the favorable effects of trazodone
Davidoff et al. [108]	Dysesthetic pain following spinal cord injury	150 mg	18	placebo	Similar effect
Battistella et al. [109]	Migraine (pediatric 7–18 years)	1 mg/kg	40	placebo	Effective
Frank et al. [110]	Rheumatoid arthritis	1.5 mg/kg	47	—	No effect

Table 6.
Trials for trazodone in chronic pain management.

6. Conclusions

SSRIs seem to be effective in most chronic pain conditions, and they are well tolerated [41]. The efficacy of SSRIs might be comparable to TADs and SNRIs, but their tolerability and safety are superior [30]. For some chronic pain conditions, valuable, while for others their utility is limited:

- For migraine, SSRIs are not better than placebo for reducing the number of attacks, and results of studies on migraine are conflicting [24, 111].
- Patients with chronic tension-type headache seem to benefit from SSRIs [24].
- There are conflicting results regarding the use of SSRIs for pelvic pain.
- Non-cardiac chest pain might benefit from SSRIs.
- Low back pain does not seem to respond well to SSRIs.
- The effects of SSRIs on fibromyalgia are uncertain [112].
- Diabetic neuropathy looks to improve from SSRIs treatment.
- Post stroke central pain might improve with fluvoxamine.
- Evidences support that antidepressants are useful for the treatment of irritable bowel syndrome [113].
- There is no evidence from randomized controlled trials to recommend antidepressants to treat chronic non-cancer pain in children and adolescents [114] or adults.

Even though several clinical trials were published, the results remain inconclusive. That happens because the sample sizes are quite modest rendering the studies slightly underpowered. Primary outcomes are variable: self-reported pain scores, effect on pain symptoms observed by the physician, complex pain questionnaires, and effects on quality of life and functionality. Current drug classes available for chronic pain treatment include anti-inflammatory drugs, opioids, gabapentinoids along with interventional or surgical management, and physical activity. Heterogeneity of the chronic pain syndromes, many currently available drugs and treatment modalities, and drug-drug and drug-interventional management associations should be considered when designing future larger scale trials.

In conclusion, compared to all other antidepressants in the management of chronic pain, for SSRIs, the data are still inconclusive, and studies are fewer in number. For depression, SSRIs are considered first-line agents due to a favorable side-effect profile and good tolerability. However, they have not yet entered first-line use for neuropathic pain conditions [12]. Probably, it would be advisable to restrict their use for those patients failing to respond to other medications or who do not tolerate side effects.

From SNRIs category, in particular duloxetine is already a first-line treatment for DPN and other chronic pain syndromes (fibromyalgia, musculoskeletal pain, and osteoarthritis), showing good results and an acceptable safety profile. It also showed favorable effects on chronic postoperative pain and life quality with the perioperative administration in surgery with a high incidence of chronic pain

(spine, breast). Venlafaxine is a drug of choice for the treatment of fibromyalgia. Milnacipran proved antiallodynic and antihyperalgesic effects and might show further positive results in chronic pain management; well-designed trials are still required.

SRIs seem to play their role through the spinal modulation pain pathways being less involved in reducing nociception, and that is probably why their effects are more evident in patients with chronic pain states.

Conflict of interest

Nothing to declare.

Author details

Adela Hilda Onuțu[1*], Dan Sebastian Dîrzu[2] and Cristina Petrișor[1,2]

1 Emergency Clinic County Hospital, Cluj-Napoca, Romania

2 Anaesthesia and Intensive Care II Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

*Address all correspondence to: adela_hilda@yahoo.com

References

[1] Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: Is chronic pain a disease? The Journal of Pain. 2009;**10**(11):1113-1120

[2] van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. British Journal of Anaesthesia. 2013;**111**(1):13-18

[3] Bingel U, Tracey I, Wiech K. Neuroimaging as a tool to investigate how cognitive factors influence analgesic drug outcomes. Neuroscience Letters. 2012;**520**(2):149-155

[4] Schreiber AK, Nones CFM, Reis RC, Chichorro J, Cunha JM. Diabetic neuropathic pain: Physiopathology and treatment. World Journal of Diabetes. 2015;**6**(3):432-444

[5] Waldfogel JM, Nesbit SA, Dy SM, Sharma R, Zhang A, Wilson LM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. Neurology. 2017;**88**(20):1958-1967

[6] Staud R. Peripheral pain mechanisms in chronic widespread pain. Best practice and research. Clinical Rheumatology. 2011;**25**(2):155-164

[7] Okifuji A, Gao J, Bokat C, Hare BD. Management of fibromyalgia syndrome in 2016. Pain Management. 2016;**6**(4): 383-400

[8] Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendation for the management of fibromyalgia. Annals of the Rheumatic Diseases. 2017;**76**(2): 318-328

[9] Chowdhury D. Tension type headache. Annals of Indian Academy of Neurology. 2012;**15**:S83-S88

[10] Landa A, Peterson BS, Fallon BA. Somatoform pain: A developmental theory and translational research review. Psychosomatic Medicine. 2012; **74**(7):717-727

[11] Józefowicz RF, Smith JK. Diagnosis and treatment of somatoform disorders. Neurology: Clinical Practice. 2012;**2**(2): 94-102

[12] Janakiraman R, Hamilton L, Wan A. Unravelling the efficacy of antidepressants as analgesics. Australian Family Physician. 2016;**45**(3):113

[13] Brummett CM, Clauw DJ. Flipping the paradigmfrom surgery-specific to patient-driven perioperative analgesic algorithms. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2015;**122**(4):731-733

[14] Ciraulo DA, Shader RI, Greenblatt DJ. Clinical pharmacology and therapeutics of antidepressants. In: Pharmacotherapy of Depression. New York City: Humana Press; 2011. pp. 33-124

[15] Hieronymus F, Lisinski A, Nilsson S, Eriksson E. Efficacy of selective serotonin reuptake inhibitors in the absence of side effects: A mega-analysis of citalopram and paroxetine in adult depression. Molecular Psychiatry. 2017. DOI: 10.1038/mp.2017.147

[16] Walker FR. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: Do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? Neuropharmacology. 2013;**67**:304-317

[17] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology

of major depression. Biological Psychiatry. 2009;**65**(9):732-741

[18] Więdłocha M, Marcinowicz P, Krupa R, Janoska-Jaździk M, Janus M, Dębowska W, et al. Effect of antidepressant treatment on peripheral inflammation markers—A meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;**80**:217-226

[19] Gałecki P, Mossakowska-Wójcik J, Talarowska M. The anti-inflammatory mechanism of antidepressants—SSRIs, SNRIs. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;**80**:291-294

[20] Wattiez AS, Dupuis A, Privat AM, Chalus M, Chapuy E, Aissouni Y, et al. Disruption of 5-HT2A-PDZ protein interaction differently affects the analgesic efficacy of SSRI, SNRI and TCA in the treatment of traumatic neuropathic pain in rats. Neuropharmacology. 2017;**125**:308-318

[21] Lian YN, Chang JL, Lu Q, Wang Y, Zhang Y, Zhang FM. Effects of fluoxetine on changes of pain sensitivity in chronic stress model rats. Neuroscience Letters. 2017;**651**:16-20

[22] Chen M, Hoshino H, Saito S, Yang Y, Obata H. Spinal dopaminergic involvement in the antihyperalgesic effect of antidepressants in a rat model of neuropathic pain. Neuroscience Letters. 2017;**649**:116-123

[23] Dupuis A, Wattiez AS, Pinguet J, Richard D, Libert F, Chalus M, et al. Increasing spinal 5-HT 2A receptor responsiveness mediates anti-allodynic effect and potentiates fluoxetine efficacy in neuropathic rats. Evidence for GABA release. Pharmacological Research. 2017;**118**:93-103

[24] Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. Journal of General Internal Medicine. 1997;**12**(6):384-389

[25] Renoir T. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: A review of the clinical evidence and the possible mechanisms involved. Frontiers in Pharmacology. 2013;**4**:1-10

[26] Walker Z, Walker RW, Robertson MM, Stansfeld S. Antidepressant treatment of chronic tension-type headache: A comparison between fluoxetine and desipramine. Headache: The Journal of Head and Face Pain. 1998;**38**(7):523-528

[27] Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. The New England Journal of Medicine. 1992;**326**(19):1250-1256

[28] Luo YL, Zhang MY, Wu WY, Li CB, Lu Z, Li QW. A randomized double-blind clinical trial on analgesic efficacy of fluoxetine for persistent somatoform pain disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009;**33**(8):1522-1525. DOI: 10.1016/j.pnpbp.2009.08.013

[29] Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis and Rheumatology. 1996;**39**(11): 1852-1859

[30] Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. The American Journal of Medicine. 2002;**112**(3): 191-197

[31] Manna V, Bolino F, Cicco LD. Chronic tension-type headache, mood depression and serotonin: Therapeutic

effects of fluvoxamine and mianserine. Headache: The Journal of Head and Face Pain. 1994;**34**(1):44-49

[32] Shimodozono M, Kawahira K, Kamishita T, Ogata A, Tohgo SI, Tanaka N. Brief clinical report reduction of central poststroke pain with the selective serotonin reuptake inhibitor fluvoxamine. International Journal of Neuroscience. 2002;**112**(10):1173-1181

[33] Xiao Y, Liu J, Huang XE, Ca LH, Ma YM, Wei W, et al. Clinical study on fluvoxamine combined with oxycodone prolonged-release tablets in treating patients with moderate to severe cancer pain. Asian Pacific Journal of Cancer Prevention. 2014;**15**(23):10445-10449

[34] Riesner HJ, Zeitler C, Schreiber H, Wild A. Additional treatment in chronic pain syndrome due to hip and knee arthritis with the selective serotonin reuptake inhibitor fluvoxamine (Fevarin). Zeitschrift fur Orthopadie und Unfallchirurgie. 2008;**146**(6):742-746

[35] Kane CM, Mulvey MR, Wright S, Craigs C, Wright JM, Bennett MI. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. Palliative Medicine. 2018;**32**(1):276-286

[36] Keefe FJ, Shelby RA, Somers TJ, Varia I, Blazing M, Waters SJ, et al. Effects of coping skills training and sertraline in patients with non-cardiac chest pain: A randomized controlled study. Pain. 2011;**152**(4):730-741

[37] Lee RA, West RM, Wilson JD. The response to sertraline in men with chronic pelvic pain syndrome. Sexually Transmitted Infections. 2005;**81**(2): 147-149

[38] Engel CC, Walker EA, Engel AL, Bullis J, Armstrong A. A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. Journal of Psychosomatic Research. 1998;**44**(2):203-207

[39] Langemark M, Olesen J. Sulpiride and paroxetine in the treatment of chronic tension-type headache. An explanatory double-blind trial. Headache: The Journal of Head and Face Pain. 1994;**34**(1):20-24

[40] Holroyd K, Labus J, O'Donell J, Cordingley G. Treating chronic tension-type headache not responding to amitriptyline hydrochloride with paroxetine hydrochloride: A pilot evaluation. Headache. 2003;**43**:999-1004

[41] Foster CA, Bafaloukos J. Paroxetine in the treatment of chronic daily headache. Headache: The Journal of Head and Face Pain. 1994;**34**(10): 587-589

[42] Dickens C, Jayson M, Sutton C, Creed F. The relationship between pain and depression in a trial using paroxetine in sufferers of chronic low back pain. Psychosomatics. 2000;**41**(6): 490-499

[43] Atkinson JH, Slater MA, Wahlgren DR, Williams RA, Zisook S, Pruitt SD, et al. Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. Pain. 1999; **83**(2):137-145

[44] Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL, et al. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. The American Journal of Medicine. 2007;**120**(5):448-454

[45] Sindrup SH, Gram LF, Brøsen K, Eshøj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain. 1990; **42**(2):135-144

[46] Nørregaard J, Volkmann H, Danneskiold-Samstøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain. 1995; **61**(3):445-449

[47] Anderberg UM, Marteinsdottir I, Knorring L. Citalopram in patients with fibromyalgia—A randomized, double-blind, placebo-controlled study. European Journal of Pain. 2000;**4**(1): 27-35

[48] Aragona M, Bancheri L, Perinelli D, Tarsitani L, Pizzimenti A, Conte A, et al. Randomized double-blind comparison of serotonergic (Citalopram) versus noradrenergic (Reboxetine) reuptake inhibitors in outpatients with somatoform, DSM-IV-TR pain disorder. European Journal of Pain. 2005;**9**(1): 33-38

[49] Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. Journal of Neurology, Neurosurgery, and Psychiatry. 1996;**61**(3):285-290

[50] Viazis N, Katopodi K, Karamanolis G, Denaxas K, Varytimiadis L, Galanopoulos M, et al. Proton pump inhibitor and selective serotonin reuptake inhibitor therapy for the management of noncardiac chest pain. European Journal of Gastroenterology and Hepatology. 2017;**29**(9):1054-1058

[51] Roohafza H, Pourmoghaddas Z, Saneian H, Gholamrezaei A. Citalopram for pediatric functional abdominal pain: A randomized, placebo-controlled trial. Neurogastroenterology and Motility. 2014;**26**(11):1642-1650

[52] Giannopoulos S, Kosmidou M, Sarmas I, Markoula S, Pelidou SH, Lagos G, et al. Patient compliance with SSRIs and gabapentin in painful diabetic neuropathy. The Clinical Journal of Pain. 2007;**23**(3):267-269

[53] Mazza M, Mazza O, Pazzaglia C, Padua L, Mazza S. Escitalopram 20 mg versus duloxetine 60 mg for the treatment of chronic low back pain. Expert Opinion on Pharmacotherapy. 2010;**11**(7):1049-1052

[54] Otto M, Bach FW, Jensen TS, Brøsen K, Sindrup SH. Escitalopram in painful polyneuropathy: A randomized, placebo-controlled, cross-over trial. Pain. 2008;**139**(2):275-283

[55] Muller JE, Wentzel I, Koen L, Niehaus DJ, Seedat S, Stein DJ. Escitalopram in the treatment of multisomatoform disorder: A double-blind, placebo-controlled trial. International Clinical Psychopharmacology. 2008;**23**(1):43-48

[56] Jaracz J, Gattner K, Moczko J, Hauser J. Comparison of the effects of escitalopram and nortriptyline on painful symptoms in patients with major depression. General Hospital Psychiatry. 2015;**37**(1):36-39

[57] Riediger C, Shuster T, Barlinn K, Maier S, Weitz J, Siepmann T. Adverse effects of antidepressants for chronic pain: A systematic review and meta-analysis. Frontiers in Neurology. 2017;**8**: 307

[58] Cegielska-Perun K, Bujalska-Zadrożny M, Tatarkiewicz J, Gąsińska E, Makulska-Nowak HE. Venlafaxine and neuropathic pain. Pharmacology. 2013;**91**(1–2):69-76

[59] Taylor K, Rowbotham MC. Venlafaxine hydrochloride and chronic pain. The Western Journal of Medicine. 1996;**165**:147-148

[60] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurology. 2015;**14**(2):162-173

[61] Rej S, Dew MA, Karp JF. Treating concurrent chronic low back pain and depression with low-dose venlafaxine: An initial identification of “easy-to-use”

clinical predictors of early response. Pain Medicine. 2014;**15**(7):1154-1162

[62] Richards JS, Bombardier CH, Wilson CS, Chiodo AE, Brooks L, Tate DG, et al. Efficacy of venlafaxine XR for the treatment of pain in patients with spinal cord injury and major depression: A randomized, controlled trial. Archives of Physical Medicine and Rehabilitation. 2015;**96**(4):680-689

[63] Fann JR, Bombardier CH, Richards JS, Wilson CS, Heinemann AW, Warren AM, et al. Venlafaxine extended-release for depression following spinal cord injury: A randomized clinical trial. JAMA Psychiatry. 2015;**72**(3):247-258

[64] Kus T, Aktas G, Alpak G, et al. Efficacy of venlafaxine for the relief of taxane and oxaliplatin-induced acute neurotoxicity: A single-center retrospective case-control study. Support Care Cancer. 2016;**24**(5): 2085-2091

[65] Zimmerman C, Atherton PJ, Pachman D, Seisler D, Wagner-Johnston N, Dakhil S, et al. MC11C4: A pilot randomized, placebo-controlled, double-blind study of venlafaxine to prevent oxaliplatin-induced neuropathy. Support Care Cancer. 2016; **24**(3):1071-1078

[66] Amr YM, Yousef AA. Evaluation of efficacy of the perioperative administration of venlafaxine or gabapentin on acute and chronic postmastectomy pain. The Clinical Journal of Pain. 2010;**26**(5):381-385

[67] Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. The Cochrane Database of Systematic Reviews. 2015;**23**(8):CD011091

[68] Trouvin AP, Perrot S, Lloret-Linares C. Efficacy of venlafaxine in neuropathic pain: A narrative review of optimized treatment. Clinical Therapeutics. 2017;**39**(6):1104-1122

[69] Aiyer R, Barkin RL, Bhatia A. Treatment of neuropathic pain with venlafaxine: A systematic review. Pain Medicine. 2017;**18**(10):1999-2012

[70] Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. Journal of Pain Research. 2014;7(23):339-351

[71] Wang CF, Russell G, Strichartz GR, Wang GK. The local and systemic actions of duloxetine in allodynia and hyperalgesia using a rat skin incision pain model. Anesthesia and Analgesia. 2015;**121**(2):532-544

[72] Stahl SM, Grady MM, Moret C, Briley M. SNRIs: Their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectrums. 2005; **10**(9):732-747

[73] Chapell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarveski V, Belenkov Y, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Practice. 2011;**11**(1):33-41

[74] Williamson OD, Sagman D, Bruins RH, Boulay LJ, Schacht A. Antidepressants in the treatment for chronic low back pain: Questioning the validity of meta-analyses. Pain Practice. 2014;**14**(2):E33-E41

[75] Ho KY, Tay W, Yeo MC, Liu H, Yeo SJ, Chia SL, et al. Duloxetine reduces morphine requirements after knee replacement surgery. British Journal of Anaesthesia. 2010;**105**(3):371-376

[76] YaDeau JT, Brummett CM, Mayman DJ, Lin Y, Goytizolo EA, Padgett DE, et al. Duloxetine and subacute pain after

knee arthroplasty when added to a multimodal analgesic regimen: A randomized, placebo-controlled, triple-blinded trial. Anesthesiology. 2016; **125**(3):561-572

[77] Blikman T, Rienstra W, van Raaij TM, et al. Duloxetine in OsteoArthritis (DOA) study: Study protocol of a pragmatic open-label randomised controlled trial assessing the effect of preoperative pain treatment on postoperative outcome after total hip or knee arthroplasty. BMJ Open. 2016; **6**(3):e010343

[78] Dhillon S. Duloxetine: A review of its use in the management of major depressive disorder in older adults. Drugs and Aging. 2013;**30**(1):59-79

[79] Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. The Cochrane Database of Systematic Reviews. 2014;**3**(1): CD007115

[80] Quilici S, Chancellor J, Löthgren M, Simon D, Said G, Le TK, et al. Meta-analysis of duloxetine vs. pregabalin in the treatment of diabetic peripheral neuropathic pain. BMC Neurology. 2009;**10**(9):6

[81] Wang ZY, Shi SY, Li SJ, Chen F, Chen H, Lin HZ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: A meta-analysis of randomized controlled trials. Pain Medicine. 2015;**16**(7):1373-1385

[82] Lee YH, Song GG. Comparative efficacy and tolerability of duloxetine, pregabalin and milnacipran for the treatment of fibromyalgia: A Bayesian network meta-analysis of randomized trials. Rheumatology International. 2016;**36**(5):663-672

[83] Häuser W, Urrútia G, Tort S, Uceyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database of Systematic Reviews. 2013;**31**(1):CD010292

[84] Puozzo C, Panconi E, Deprez D. Pharmacology and pharmacokinetcs of milnacipran. International Clinical Psychopharmacology. 2002;**17**(Supp. 1): S25-S35

[85] Briley M. Milnacipran, a well-tolerated specific serotonin and norepinephrine reuptake inhibiting antidepressant. CNS Drug Reviews. 1998;**4**:137-148

[86] Obata H, Saito S, Koizuka S, Nishikawa K, Goto F. The monoamine-mediated antiallodynic effects of intrathecally administered milnacipran, a serotonin noradrenaline reuptake inhibitor, in a rat model of neuropathic pain. Anesthesia and Analgesia. 2005; **100**:1406-1410

[87] Li C, Ji BU, Kim Y, Lee JE, Kim NK, Kim ST, et al. Electroacupuncture enhance the antiallodynic and antihyperalgesic effects of milnacipran in neuropathic rats. Anesthesia and Analgesia. 2016;**122**:1654-1662

[88] Katsuyama S, Aso H, Otowa A, Yagi T, Kishikawa Y, Komatsu T, et al. Antinociceptive effects of the serotonin and noradrenaline reuptake inhibitors milnacipran and duloxetine on vincristine-induced neuropathic pain model in mice. ISRN Pain. 2014;**2014**: 915464

[89] Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. Cochrane Database of Systematic Reviews. 2015; **20**(10):CD008244

[90] Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2015;**6**(7): CD011789

[91] Auclaire AL, Martel JC, Assié MB, Bardin L, Heusler P, Cussac D, et al.

Levomilnacipran (F2695), a norepinephrine-preferring SNRIs : Profile in vitro and in models of depression and anxiety. Neuropharmacology. 2013;**70**:338-347

[92] Bruno A, Morabito P, Spina E, Muscatello MR. The role of levomilnacipran in the management of major depressive disorder: A comprehensive review. Current Neurpharmacology. 2016;**14**(2):191-199

[93] Montgomery SA, Mansuy L, Ruth A, Bose A, Li H, Li D. 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. 2013;**74**(4):363-369

[94] Jeong H-J, Mitchell VA, Vaughan CW. Role of 5-HT1 receptor subtypes in the modulation of pain and synaptic transmission in rat spinal superficial dorsal horn. British Journal of Pharmacology. 2012;**165**(6):1956-1965

[95] Choi IS, Cho JH, Jang IS. 5-Hydroxytryptamine 1A receptors inhibit glutamate release in rat medullary dorsal horn neurons. NeuroReport. 2013;**24**(8):339-403

[96] Sałat K, Kołaczkowski M, Furgała A, Rojek A, Śniecikowska J, Varney MA, et al. Antinociceptive, antiallodynic and antihyperalgesic effects of the 5-HT1A receptor selective agonist, NLX-112 in mouse models of pain. Neuropharmacology. 2017;**125**:181-188

[97] Silvestrini B. Trazodone and the mental pain hypothesis of depression. Neuropsychobiology. 1986;**15**(Suppl 1): 2-9

[98] Mattia C, Paoletti F, Coluzzi F, Boanelli A. New antidepressants in the treatment of neuropathic pain. A review. Minerva Anestesiologica. 2002; **68**(3):105-114

[99] Pick CG, Paul D, Eison MS, Pasternak GW. Potentiation of opioid analgesia by the antidepressant nefazodone. European Journal of Pharmacology. 1992;**211**(3):375-381

[100] Ortega-Alvaro A, Acebes I, Saracíbar G, Echevarría E, Casis L, Micó JA. Effect of the antidepressant nefazodone on the density of cells expressing mu-opioid receptors in discrete brain areas processing sensory and affective dimensions of pain. Psychopharmacology. 2004;**176**(3–4): 305-311

[101] Saper JR, Lake AE, Tepper SJ. Nefazodone for chronic daily headache prophilaxis: An open-label study. Headache. 2001;**41**(5):465-474

[102] Schwartz TL, Siddiqui UA, Stahl SM. Vilazodone: A brief pharmacological and clinical review of the novel serotonin partial agonist and reuptake inhibitor. Therapeutic Advances in Psychopharmacology. 2011;**1**(3):81-87

[103] Wilson RC. The use of low-dose trazodone in the treatment of painful diabetic neuropathy. Journal of the American Podiatric Medical Association. 1999;**89**(9):468-471

[104] Ventafridda V, Caraceni A, Saita L, Bonezzi C, De Conno F, Guarise G, et al. Trazodone for deafferentation pain. Comparison with amitriptyline. Psychopharmacology. 1988;**95**(Suppl): S44-S49

[105] Goodkin K, Gullion CM, Agras WS. A randomized, double-blind, placebo-controlled trial of trazodone hydrochloride in chronic low back pain syndrome. The Journal of Clinical Psychopharmacology. 1990;**10**(4): 269-278

[106] Morillas-Arques P, Rodriguez-Lopez CM, Molina-Barea R, Rico-Villademoros F, Calandre EP. Trazodone for the treatment of

fibromyalgia: An open-label, 12-week study. BMC Musculoskeletal Disorders. 2010;**11**:204

[107] Calandre EP, Morillas-Arques P, Molina-Barea R, Rodriguez-Lopez CM, Rico-Villademoros F. Trazodone plus pregabalin combination in the treatment of fibromyalgia: A two-phase, 24-week, open-label uncontrolled study. BMC Musculoskeletal Disorders. 2011;**12**:95

[108] Davidoff G, Guarracini M, Roth E, Sliwa J, Yarkony G. Trazodone hydrochloride in the treatment of dysesthetic pain in traumatic myelopathy: A randomized, double-blind, placebo-controlled study. Pain. 1987;**29**(2):151-161

[109] Battistella PA, Ruffilli R, Cernetti R, Pettenazzo A, Baldin L, Bertoli S, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache. 1993;**33**(1):36-39

[110] Frank RG, Kashani JH, Parker JC, Beck NC, Brownlee-Duffeck M, Elliott TR, et al. Antidepressant analgesia in rheumatoid arthritis. The Journal of Rheumatology. 1988;**15**(11):1632-1638

[111] Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. Cochrane Database of Systematic Reviews. 2015;(5): CD011681

[112] Walitt B, Urrútia G, Nishishinya MB, Cantrell SE, Häuser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. Sao Paulo Medical Journal. 2015;**133**(5):454

[113] Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database of Systematic Reviews. 2011; (8):CD003460

[114] Cooper TE, Wiffen PJ, Heathcote LC, Clinch J, Howard R, Krane E, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. The Cochrane Library. 2017;**8**:CD012536