Robinson C, Dalal S, Chitneni A, et al. A Look at Commonly Utilized Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) in Chronic Pain. *Health Psychology Research*. 2022;10(2). doi:10.52965/001c.32309

General

A Look at Commonly Utilized Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) in Chronic Pain

Christopher Robinson, MD[1], Suhani Dalal, DO[2], Ahish Chitneni, DO[3], Anand Patil, DO[4], Amnon A. Berger, MD, PhD[1], Syed Mahmood, MD[1], Vwaire Orhurhu, MD, MBA[5], Alan D. Kaye, MD, PhD[6], Jamal Hasoon, MD[7]

[1] Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, [2] Department of Internal Medicine, Loma Linda University, [3] Department of Physical Medicine & Rehabilitation, New York-Presbyterian (Columbia/Cornell), [4] Touro University California College of Medicine, [5] Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh Medical Center, [6] Department of Anesthesia and Pain Management, Louisiana State University Health Sciences Center, [7] Department of Anesthesiology and Pain Medicine, University of Texas Medical Branch

Keywords: Serotonin noradrenaline reuptake inhibitors, neuropathic pain, chronic pain, duloxetine, venlafaxine, milnacipran

https://doi.org/10.52965/001c.32309

Health Psychology Research

Vol. 10, Issue 2, 2022

Purpose of Review

Chronic pain continues to be one of the leading healthcare cost burdens in the United States and is typically defined as ongoing pain, lasting longer than six months. Various treatment options exist for chronic pain, including physical therapy, medical management, pain psychology, and interventional therapies. Pain medications have been the mainstay of treatment for chronic pain conditions with an increasing use of membrane stabilizers and antidepressants to treat neuropathic pain conditions. Specifically, serotonin noradrenaline reuptake inhibitors (SNRIs) have been used to treat a range of pain conditions expanding from everyday use for depressive disorders.

Recent Findings

SNRIs, including duloxetine, venlafaxine, and milnacipran, have demonstrated efficacy in reducing pain in musculoskeletal pain (chronic low back pain and osteoarthritis), fibromyalgia, and neuropathic pain conditions (peripheral diabetic neuropathy).

Summary

The article describes the function, role, and use of SNRIs to treat chronic and neuropathic pain by altering the noradrenergic descending inhibitory pathways.

INTRODUCTION

Chronic pain continues to be one of the leading healthcare cost burdens in the United States and affects roughly 30% of the US population.[1] It can be defined as ongoing pain lasting longer than six months. Furthermore, neuropathic pain is caused secondary to disease or a lesion of the somatosensory system, including peripheral fibers and central neurons.[2,3]

Typical conditions that may result in neuropathic pain include diabetes mellitus, alcoholism, infection, and significant nervous system disorders such as stroke, Parkinson's disease, and multiple sclerosis. Patients experiencing neuropathic pain report symptoms of shooting, burning, or stabbing pain and tingling, numbness, or a "pins and needles" sensations.

Generally, the treatment options for chronic and neuropathic pain include physical therapy, pain psychology, medical management, and interventional therapy, including surgical interventions. Various pain medications have been trialed with an increasing use of membrane stabilizers and antidepressants to treat neuropathic pain conditions. In recent years, antidepressants such as serotonin noradrenaline reuptake inhibitors (SNRIs) have been used to treat a wide range of pain conditions in addition to their use for depressive disorders but at lower doses for analgesia with analgesia a different risk profile and side effects at these doses.[4–6]

SNRIs function by inhibiting serotonin and noradrenaline reuptake in the pre-synaptic cleft of the neuron, with numerous studies showing their potential use for the treatment of musculoskeletal pain, low back pain, and neuropathic pain conditions.[2,3,7] Serotonin and norepinephrine are primarily involved in the modulation of pain via descending pain pathways in the brain and spinal cord[2,7] The descending pathways release the neurotransmitters above, and when there is dysfunction of these pathways, these antinociceptive pathways are likely to be involved.[3] When monoamine reuptake inhibition occurs, the activity of these descending inhibitory pathway are increased along with their antinociceptive effects.[3,8] Additionally, patients with chronic pain often develop concurrent depression as these pathways are intertwined, affecting both pain and mood.[3,9] Fortunately, treating pain and depression can often be combined with the use of SNRIs.[8]

SNRIs often have better tolerability than selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepres-

sants (TCAs), making them an apt choice for pain reduction in those with chronic pain.[7,8] In addition, some studies have demonstrated that SSRIs have little efficacy in treating chronic pain when compared to placebo or tricyclic antidepressants, suggesting that norepinephrine uptake inhibition may play an essential role in the analgesic properties of SNRIs.[7,10–14] Another advantage to SNRIs over other membrane stabilizers is that this drug class is more specific and does not act on muscarinic or histamine receptors, thus circumventing potential side effects. Despite this, there are still side effects such as dry mouth, insomnia, constipation, and nausea with SNRIs and up to 8-14 weeks to find the optimal dose.[3] The three most commonly utilized SNRIs to treat chronic and neuropathic pain are duloxetine, venlafaxine, and milnacipran. Below we discuss these specific SNRIs in more detail.

DULOXETINE

Duloxetine is an SNRI commonly used to manage depression, generalized anxiety disorder, painful diabetic neuropathy, and chronic musculoskeletal pain conditions (osteoarthritis and low back pain).[15] Duloxetine's primary route of administration is orally due to its excellent oral availability with no effect if taken with food. Duloxetine is >90% bound to albumin, has an elimination half-life of 12 hours in adults, and is excreted mainly in the urine and with a minor amount in the feces.[16] Metabolism occurs via the hepatic system via CYP1A2 and CYP2D6 forming inactive metabolites.[16] Typical doses for chronic musculoskeletal and neuropathic pain are 30-60 mg once a day. Common side effects, which are similar for most SNRIs, include headache, drowsiness, insomnia, fatigue, nausea, weight loss, weakness, change in libido; serious, though rare, side effects include suicidality, hepatoxicity, serotonin syndrome, and hyponatremia.[17,18] A gradation effect with low dosages targeting serotonin and higher doses increasingly targeting norepinephrine with dose-independent effect on dopamine is also noted.[19]

The analgesic effects of duloxetine likely involve the descending noradrenergic inhibitory system.[20] When duloxetine was studied in rats with hindlimb paralysis via spinal nerve ligation (SNL), it was found that three daily injections of duloxetine attenuated the hyperalgesia caused by SNL, improved noxious stimulus-induced analgesia, and provided effective treatment.[20] Furthermore, the rats treated with duloxetine had higher noradrenaline levels in the dorsal spinal cord than the control group.[20] This effect was inhibited by intrathecal injections of alpha-2-adrenoreceptor antagonists, suggesting that analgesic effects of duloxetine, and other SNRIs, are dependent on the noradrenergic descending inhibitory system.[20,21] Though duloxetine provides antidepressant effects, the pain relief is mainly due to directly targeting pain modulation.[22]

Duloxetine can be used as a medication to treat one of the most common joint disorders in the USA, osteoarthritis.[3] Patients suffering from chronic knee osteoarthritis were administered a 60 mg/day dose. They demonstrated sustained improvement in their pain for up to 48 weeks in addition to improvement in overall physical, mental, and emotional health.[23] When combined with pregabalin, duloxetine had mild improvement in patients with hand osteoarthritis.[24] At doses of 60 mg/day, duloxetine was also effective for treating pain in patients suffering from chronic low back pain (CLBP) irrespective of age or sex.[25] Oddly, patients who experienced early side effects of duloxetine (nausea, constipation, and drowsiness) appeared to have a more significant reduction in pain as those who did not, suggesting that adherence despite early side effects can result in increased improvement in pain.[25]

Duloxetine can also be used to treat peripheral diabetic neuropathy (PDN). A randomized, double-blind placebo-controlled trial comparing duloxetine to placebo in patients with diabetic peripheral neuropathy revealed a statistically significant pain improvement ($p < 0.001$) on the 24-hour pain score compared to the placebo group.[11] Patients in the study were treated with duloxetine 60 mg once daily, duloxetine 60 mg twice daily, or placebo, and their 24-hour pain severity was measured on an 11-point Likert scale.[11] Another study found a similar reduction in the 24-hour pain score in patients with diabetic neuropathy treated with duloxetine compared to placebo but found no significant difference in duloxetine 60 mg once daily versus 60 mg twice daily.[21] These studies revealed that duloxetine is both effective and safe in the management of neuropathies.[11,20,21]

The use of duloxetine is not limited to osteoarthritis, CLBP, and PDN but can be used in other neuropathies. One randomized, double-blind placebo-controlled trial evaluated duloxetine on taxane-induced sensory neuropathy in breast cancer patients revealing duloxetine's ability to provide effective neuropathic pain relief.[26] Moreover, duloxetine effectively decreased neuropathic pain and motor neuropathy in chemotherapy-related pain.[27] Cancer patients with chemotherapy-induced peripheral therapy were given a placebo, venlafaxine, or duloxetine. Their cranial, sensory, motor neuropathies, and neuropathic pain level were evaluated on day one, week 2, and week four after enrollment.[27] The study found that the level of cranial, motor, sensory, and neuropathic pain was significantly decreased in the venlafaxine and duloxetine groups compared to placebo, with the pain reduction being more significant in the duloxetine group compared to the venlafaxine group.[27] Another randomized, double-blind placebo-controlled trial was conducted on 70 patients experiencing neuropathic pain secondary to cancer refractory to opioid and gabapentinoid treatment.[28] Seventy patients with a Brief Pain Inventory - Short Form (BPI-SF) of 4 or higher were included to participate in the study to receive placebo or duloxetine treatment.[28] Domains such as continuous pain, intermittent pain, neuropathic pain, and effective descriptors were studied, and results revealed that neuropathic pain showed significant change in pain scores in the duloxetine group from day 0 to 10.[28]

Fibromyalgia is a somatic disorder that typically results in widespread musculoskeletal pain. Typically, patients experiencing fibromyalgia report myalgias, arthralgias, fatigue, and sleep disturbances.[29] In general, patients suffering from fibromyalgia have a decreased quality of life and high levels of disability. Treatment for fibromyalgia symptoms consists of physical therapy, analgesic medications such as non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, or nerve pain medications. In recent

years, the use of SNRIs such as duloxetine in the treatment of fibromyalgia pain has been studied. A randomized, double-blind, placebo-controlled trial of 393 patients received duloxetine or placebo treatment.[30] The primary assessment consisted of changes in pain scores, with secondary examinations consisting of quality of life improvement and safety outcomes.[30] The efficacy of duloxetine in controlling pain from fibromyalgia was limited, with no significant changes in pain scores reported 14 weeks post-treatment.[30] Despite no improvement in pain scores, secondary outcome measures such as quality of life and safety outcomes showed significant findings in the duloxetine group. It demonstrated that they might have potential use in the overall symptomatic improvement in patients receiving duloxetine.[30] Overall, compared to duloxetine in neuropathic pain, the use of SNRIs for fibromyalgia pain must be further studied. Although specific studies have shown improvement in secondary outcomes in patients experiencing fibromyalgia pain, the direct correlation between SNRIs and pain relief in chronic pain fibromyalgia patients is yet to be found. Other studies on the use of duloxetine for fibromyalgia have found that only a minority of patients experienced pain relief, and many patients experienced side effects that outweighed the benefits of treatment.[31]

VENLAFAXINE

Venlafaxine is another SNRI commonly used in the treatment of neuropathic pain. Similar to duloxetine, the route of administration is oral with typical doses ranging from 75-225 mg with a lower protein binding (27%), half-life elimination of 5 hours, hepatic metabolism via CYP2D6 to an active metabolite, O-desmethylvenlafaxine (ODV), and excretion mainly through the urine.[32–34] The side effect profile is similar to duloxetine.

A 2017 systematic review assessed the use of venlafaxine to treat neuropathic pain.[35] The review concluded that venlafaxine was well-tolerated and demonstrated significant pain relief for neuropathic pain compared to placebo.[35] However, venlafaxine was nonsuperior to other medications used for neuropathic pain.[35] Another review found similar results among 11 randomized clinical trials, citing the tolerability of venlafaxine with limited adverse effects.[36]

A double-blind placebo-controlled trial assessed the effects of venlafaxine extended-release on patients with diabetic neuropathy.[37] The study measured scores on the 100-mm Visual Analog Pain Intensity (VAS-PI) and the Pain Relief (VAS-PR) scales. For six weeks, patients were given a placebo, venlafaxine 75 mg, or venlafaxine 150-225mg.[37] They found that the pain VAS-PI scores decreased by 27% in the placebo group, 32% in the 75 mg group, and 50% in the 150-225 mg group.[37] Moreover, patients in the venlafaxine 150-225 mg group had statistically significant greater mean VAS-PR scores when compared to other groups.[37] The results suggest that a venlafaxine is an effective option for diabetic neuropathy.[37]

MILNACIPRAN

Milnacipran is an SNRI used to treat fibromyalgia and occasional off-label use to treat depression.[38] It effectively improves pain, fatigue, and function in patients with fibromyalgia.[39] Similar to duloxetine and venlafaxine, its route of administration is oral with typical doses ranging from 12.5-100 mg with a lower protein binding (13%), half-life elimination of 6-8 hours, and hepatic metabolism to inactive metabolites with excretion via the urine.[39] Milnacipran shares a similar side effect profile to the previous two SNRIs. It does, however, have a more significant effect on noradrenaline than serotonin compared to other SNRIs such as duloxetine, venlafaxine, and desvenlafaxine.[40]

A 2012 Cochrane review examined the use of milnacipran for fibromyalgia and neuropathic pain and found that milnacipran was associated with decreased pain but an increased incidence of side effects.[41] A meta-analysis of 19 studies involving 6,152 patients compared the efficacy of amitriptyline, duloxetine, and milnacipran to treat chronic pain.[42] Amitriptyline was more productive than duloxetine and milnacipran in reducing pain, sleep disturbances, and fatigue.[42] When compared to duloxetine, milnacipran was less effective in reducing pain but was superior in reducing fatigue in patients with fibromyalgia.[42]

A double-blind, placebo-controlled clinical trial comparing 100 mg of milnacipran to placebo for one month found no significant difference between milnacipran and placebo in conditioned pain modulation, allodynia, or global pain thresholds.[43] However, another study examined the effects of milnacipran on pressure-evoked pain and cerebral processing of pain in patients with fibromyalgia and found that patients taking milnacipran had increased cerebral activity in areas of the brain associated with pain inhibition, including the caudate nucleus, anterior insula, and the amygdala.[44] Unfortunately, there was no statistically significant decrease in pain sensitivity in patients taking milnacipran compared to the placebo.[44]

CONCLUSION

Chronic pain can be difficult to treat in patients and may be resistant to various medications and interventional options. Antidepressants and SNRIs offer a valuable therapeutic option for patients suffering from different neuropathic and chronic pain conditions. Duloxetine, venlafaxine, and milnacipran appear to have analgesic and some anti-inflammatory capabilities independent of their mood-stabilizing abilities. Additionally, these medications can be used at much lower dosages for their antinociceptive effects and have different side effects and safety profiles when used at these dosages. These medications may also provide opioid-free alternative pharmacologic options for patients struggling with debilitating pain, which is essential given the ongoing opioid crisis.[45–47] Further studies are still needed to establish better safety profiles and efficacy of antidepressant use in chronic pain. However, this article describes the safety and potential utility of SNRIs to treat a variety of chronic pain conditions.

REFERENCES

1. Dahlhamer J, Lucas J, Zelaya, C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(36):1001-1006. doi:10.15585/mmwr.mm6736a2

2. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017;3(1). doi:10.1038/nrdp.2017.2

3. Urits I, Peck J, Orhurhu MS, et al. Off-label Antidepressant Use for Treatment and Management of Chronic Pain: Evolving Understanding and Comprehensive Review. *Curr Pain Headache Rep*. 2019;23(9). doi:10.1007/s11916-019-0803-z

4. Riediger C, Schuster T, Barlinn K, Maier S, Weitz J, Siepmann T. Adverse Effects of Antidepressants for Chronic Pain: A Systematic Review and Meta-analysis. *Front Neurol*. 2017;8(JUL). doi:10.3389/fneur.2017.00307

5. Micó JA, Ardid D, Berrocoso E, Eschalier A. Antidepressants and pain. *Trends Pharmacol Sci*. 2006;27(7):348-354. doi:10.1016/j.tips.2006.05.004

6. Hirschfeld RMA, Mallinckrodt C, Lee TC, Detke MJ. Time course of depression-symptom improvement during treatment with duloxetine. *Depress Anxiety*. 2005;21(4):170-177. doi:10.1002/da.20071

7. Lee YC, Chen PP. A review of SSRIs and SNRIs in neuropathic pain. *Expert Opin Pharmacother*. 2010;11(17):2813-2825. doi:10.1517/14656566.2010.507192

8. Mika J, Zychowska M, Makuch W, Rojewska E, Przewlocka B. Neuronal and immunological basis of action of antidepressants in chronic pain – clinical and experimental studies. *Pharmacol Rep*. 2013;65(6):1611-1621. doi:10.1016/s1734-1140(13)71522-6

9. Morris DW, Trivedi MH, Fava M, et al. Diurnal mood variation in outpatients with major depressive disorder. *Depress Anxiety*. 2009;26(9):851-863. doi:10.1002/da.20557

10. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain*. 2005;116(1):109-118. doi:10.1016/j.pain.2005.03.029

11. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med (Malden, Mass)*. 2005;6(5):346-356. doi:10.1111/j.1526-4637.2005.00061.x

12. Goodnick P, Jimenez I, Kumar A. Sertraline in diabetic neuropathy: preliminary results. *Ann Clin Psychiatry*. 1997;9(4):255-257. doi:10.3109/10401239709147806

13. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med*. 1992;326(19):1250-1256. doi:10.1056/nejm199205073261904

14. 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. doi:10.1016/0304-3959(90)91157-e

15. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs*. 2012;26(1):39-67. doi:10.2165/11594710-000000000-00000

16. Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet*. 2011;50(5):281-294. doi:10.2165/11539240-000000000-00000

17. Cipriani A, Koesters M, Furukawa TA, et al. Duloxetine versus other anti-depressive agents for depression. Cochrane Common Mental Disorders Group, ed. *Cochrane Database of Systematic Reviews*. 2012;10. doi:10.1002/14651858.cd006533.pub2

18. Wohlreich MM, Mallinckrodt CH, Prakash A, Watkin JG, Carter WP. Duloxetine for the treatment of major depressive disorder: safety and tolerability associated with dose escalation. *Depress Anxiety*. 2007;24(1):41-52. doi:10.1002/da.20209

19. Lambert O, Bourin M. SNRIs: mechanism of action and clinical features. *Expert Rev Neurother*. 2002;2(6):849-858. doi:10.1586/14737175.2.6.849

20. Ito S, Suto T, Saito S, Obata H. Repeated Administration of Duloxetine Suppresses Neuropathic Pain by Accumulating Effects of Noradrenaline in the Spinal Cord. *Anesth Analg*. 2018;126(1):298-307. doi:10.1213/ane.0000000000002380

21. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology*. 2006;67(8):1411-1420. doi:10.1212/01.wnl.0000240225.04000.1a

22. Enomoto H, Fujikoshi S, Funai J, et al. Assessment of direct analgesic effect of duloxetine for chronic low back pain: post hoc path analysis of double-blind, placebo-controlled studies. *J Pain Res*. 2017;10:1357-1368. doi:10.2147/jpr.s133396

23. Uchio Y, Enomoto H, Ishida M, Tsuji T, Ochiai T, Konno S. Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open-label, long-term, Phase III extension study. *J Pain Res*. 2018;11:1391-1403. doi:10.2147/jpr.s171395

24. Sofat N, Harrison A, Russell M, et al. The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. *J Pain Res*. 2017;10:2437-2449. doi:10.2147/jpr.s147640

25. Alev L, Fujikoshi S, Yoshikawa A, et al. Duloxetine 60 mg for chronic low back pain: post hoc responder analysis of double-blind, placebo-controlled trials. *J Pain Res*. 2017;10:1723-1731. doi:10.2147/jpr.s138297

26. Salehifar E, Avan R, Janbabaei G, et al. The effect of pregabalin and duloxetine treatment on quality of life of breast cancer patients with taxane-induced sensory neuropathy: A randomized clinical trial. *J Res Med Sci*. 2018;23(1):52. doi:10.4103/jrms.jrms_1068_17

27. Farshchian N, Alavi A, Heydarheydari S, Moradian N. Comparative study of the effects of venlafaxine and duloxetine on chemotherapy-induced peripheral neuropathy. *Cancer Chemother Pharmacol*. 2018;82(5):787-793. doi:10.1007/s00280-018-3664-y

28. Matsuoka H, Iwase S, Miyaji T, et al. Predictors of duloxetine response in patients with neuropathic cancer pain: a secondary analysis of a randomized controlled trial—JORTC-PAL08 (DIRECT) study. *Support Care Cancer*. 2020;28(6):2931-2939. doi:10.1007/s00520-019-05138-9

29. Borchers AT, Gershwin ME. Fibromyalgia: A Critical and Comprehensive Review. *Clinic Rev Allerg Immunol*. 2015;49(2):100-151. doi:10.1007/s12016-015-8509-4

30. Murakami M, Osada K, Mizuno H, Ochiai T, Alev L, Nishioka K. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese fibromyalgia patients. *Arthritis Res Ther*. 2015;17(1). doi:10.1186/s13075-015-0718-y

31. Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Pain, Palliative and Supportive Care Group, ed. *Cochrane Database of Systematic Reviews*. 2018;2020(7). doi:10.1002/14651858.cd010292.pub2

32. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76(20):1758-1765. doi:10.1212/wnl.0b013e3182166ebe

33. Kadiroglu AK, Sit D, Kayabasi H, Kemal Tuzcu A, Tasdemir N, Yilmaz ME. The effect of venlafaxine HCl on painful peripheral diabetic neuropathy in patients with type 2 diabetes mellitus. *J Diabetes Complicat*. 2008;22(4):241-245. doi:10.1016/j.jdiacomp.2007.03.010

34. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain*. 2004;110(3):697-706. doi:10.1016/j.pain.2004.05.010

35. Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. Cochrane Pain, Palliative and Supportive Care Group, ed. *Cochrane Database of Systematic Reviews*. 2015;2017(6). doi:10.1002/14651858.cd011091.pub2

36. Trouvin AP, Perrot S, Lloret-Linares C. Efficacy of Venlafaxine in Neuropathic Pain: A Narrative Review of Optimized Treatment. *Clin Ther*. 2017;39(6):1104-1122. doi:10.1016/j.clinthera.2017.05.347

37. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain*. 2004;110(3):697-706. doi:10.1016/j.pain.2004.05.010

38. FDA. Savella (Milnacipran HCl) Tablets Label http://www.savellapregnancyregistry.com

39. Keks NA, Hope J, Keogh S, Copolov DL. Milnacipran: serotonin-noradrenaline reuptake inhibitor approved for fibromyalgia may be a useful antidepressant. *Australas Psychiatry*. 2018;26(5):537-540. doi:10.1177/1039856218794874

40. Mochizuki D, Tsujita R, Yamada S, et al. Neurochemical and behavioural characterization of milnacipran, a serotonin and noradrenaline reuptake inhibitor in rats. *Psychopharmacology*. 2002;162(3):323-332. doi:10.1007/s00213-002-1111-5

41. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. Cochrane Pain, Palliative and Supportive Care Group, ed. *Cochrane Database of Systematic Reviews*. 2015;2015(10). doi:10.1002/14651858.cd008244.pub3

42. Hauser W, Petzke F, Uceyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology (Oxford, England)*. 2011;50(3):532-543. doi:10.1093/rheumatology/keq354

43. Pickering G, Macian N, Delage N, et al. Milnacipran poorly modulates pain in patients suffering from fibromyalgia: a randomized double-blind controlled study. *Drug Des Devel Ther*. 2018;Volume 12:2485-2496. doi:10.2147/dddt.s162810

44. Petzke F, Jensen KB, Kosek E, et al. Using fMRI to evaluate the effects of milnacipran on central pain processing in patients with fibromyalgia. *Scandinavian journal of pain*. 2013;4(2):65-74. doi:10.1016/j.sjpain.2012.10.002

45. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States. In: *Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53)*. ; 2018.

46. Dalal S, Chitneni A, Berger AA, et al. Buprenorphine for Chronic Pain: A Safer Alternative to Traditional Opioids. *Health Psychology Research*. 2021;9(1). doi:10.52965/001c.27241

47. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: Controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16(5):405-416. doi:10.1037/a0013628