ALTERNATIVES IN PAIN MANAGEMENT

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Review of antidepressants in the treatment of neuropathic pain

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Abstract

Introduction: Neuropathy is a pathological pain disorder characterized by burning, stabbing, and cramping sensations. There are multiple etiologies for this pain such as diabetes, vascular disorders, and chemotherapy treatment. Neurotransmitters, such as norepinephrine and serotonin, are thought to play a part in the modulation of this pain. The objective of this review is to summarize the current literature to support the efficacy and impact of adverse events of the various classes of antidepressants utilized in the treatment of neuropathic pain.

Methods: A Medline/Pubmed search was conducted to identify randomized clinical trials within the last 12 years examining the efficacy and safety of antidepressants for the treatment of neuropathy. Systematic reviews and meta-analyses were also included.

Results: Antidepressants are commonly used in the treatment of neuropathy, with meta-analyses supporting the use of tricyclic antidepressants and selective norepinephrine serotonin reuptake inhibitors. Trials indicate that venlafaxine, duloxetine, and tricyclic antidepressants (TCAs) have comparable efficacy, but TCAs have a higher incidence of adverse effects. Other antidepressants, such as citalopram, paroxetine, and bupropion have limited evidence supporting their use in neuropathy.

Discussion: Based on the evidence reviewed, venlafaxine and duloxetine should be used as first-line agents. TCAs should be used as second-line agents, due to higher incidence of adverse effects. Other treatment options include citalopram, paroxetine, and bupropion, but data supporting their efficacy is limited.

Keywords: antidepressants, pain management, neuropathy, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs)

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Introduction

Neuropathy is a debilitating yet common and complex disorder. More than 2% of people in the general population and 15% of people older than 40 years have neuropathy. Diabetes is the most common cause, with a prevalence of 30%; up to 50% of patients with diabetes will eventually develop neuropathy.[1]

Neuropathic pain is a pathological pain, meaning it does not serve any physiologic or protective functioning.[2] There is a consensus that both peripheral and central nervous system processes have a role in chronic pain. There are 4 main categories of the pathological processes involved in neuropathy: (1) wallerian degeneration, (2) axonal degeneration or axonopathy, (3) primary neuronal degeneration or neuronopathy, and (4) segmental demyelination or myelinopathy.[1] *Wallerian degeneration* is any type of mechanical injury leading to interruption of axons. *Axonal degeneration* implies distal axonal breakdown and is thought to be caused by metabolic derangement within neurons or ischemia. It is the most common pathological reaction of the peripheral nerve. *Neuronopathy* is a loss of

nerve cell bodies that results in the degeneration of the peripheral and central axons. A sensory neuronopathy implies damage to the dorsal route ganglion neurons, which leads to sensory ataxia, sensory loss, and diffuse areflexia. Compounds such as high-dose pyridoxine and doxorubicin produce primary sensory neuronal degeneration.[1] Segmental demyelination is injury to either myelin sheaths or Schwann cells, which results in the breakdown of myelin while sparing of axons. This occurs mechanically by acute nerve compression or chronic nerve entrapment.[3]

Neuropathic pain is often described as burning, stabbing, or cramping. Other sensations include pins and needles, electric shocklike paroxysms, or pain that starts as dull but with repeated stimulation becomes unbearable.[4] Although diabetes is often the most common cause of neuropathic pain, a variety of other pathological processes that affect the central nervous system and periphery also contribute to the development of neuropathy.[1,4] These processes include but are not limited to trauma, vascular and metabolic disorders, bacterial/viral infections, inflammation, autoimmune disorders, and genetic abnormalities, as well as chemotherapy and environmental neurotoxins.[4]

Hyperglycemia, changes in insulin signaling, and hyperlipidemia are all major contributors to the development of diabetic neuropathy.[1] Hyperglycemia can overload the mitochondrial electron transport chain generating reactive oxygen species. It can also increase flux through the polyol pathway, increasing cellular osmolarity and decreasing nicotinamide adenine dinucleotide phosphate (NADPH) levels. This combination leads to oxidative stress. Hyperlipidemia is associated with diabetic neuropathy by a variety of mechanisms.[1] These include an excess of free fatty acids, modified low-density lipoproteins bound to extracellular receptors, as well as triggered signaling cascades, which activate NADPH oxidase and increase oxidative stress.[4] Insulin has neurotropic effects that promote neuronal growth and survival. In insulin deficiency or resistance, it is thought that decreased availability of insulin reduces neurotrophic signaling, thus contributing to the development of neuropathy.[1] Additionally, insulin resistance can further contribute to diabetic neuropathy via mitochondrial dysfunction and oxidative stress.[1] The above mechanisms occur within different cell types of nerves; including neurons, glial cells, and endothelial cells of the microvasculature. Ultimately, these forms of cellular stress cause neuronal dysfunction or death of the nerve. This dysfunction contributes to the manifestation of clinical neuropathy.[1]

Serotonin and norepinephrine are thought of as the main neurotransmitters involved in the modulation of endogenous pain mechanisms. By inhibiting serotonin and norepinephrine reuptake in presynaptic terminals, the neurotransmitters accumulate at the synaptic junction, thus enhancing pain suppression via multiple postsynaptic receptor-mediated mechanisms.[2] Although antidepressants have been shown to be efficacious in the treatment of neuropathic pain, not all antidepressants show similar efficacy.[2]

Secondary to the differences in efficacy among the antidepressants, the aim of this review article is to summarize the current literature to support the use of those agents in the treatment of neuropathic pain.

Methods

A Medline/PubMed (US National Library of Medicine, Bethesda, MD) search was conducted to identify clinical trials published within the past 12 years (2002-14) that studied the efficacy and associated adverse events of the antidepressants in the treatment of acute neuropathic pain. Maintenance of pain management trials were excluded in this review. If there were no published, randomized clinical trials, open-labeled trials, case series, and case reports using certain antidepressants were reported for completeness. All data had to be published in a peer review journal. Key search words included various combinations of the following, *antidepressants*, *neuropathy*, *neuropathic pain*, *painful diabetic neuropathy*, *spinal cord injury*, *polyneuropathy*, *multiple sclerosis neuropathy*, *monoamine oxidase enzyme inhibitors*, *tricyclic antidepressants*, *serotonin norepinephrine reuptake inhibitors*, *selective serotonin reuptake inhibitors*, *duloxetine*, *levomilnacipran*, *milnacipran*, *citalopram*, *paroxetine*, *escitalopram*, *fluoxetine*, *bupropion*, *mirtazapine*, *nefazodone*, *trazodone*, *atomoxetine*, *desipramine*, *nortriptyline*, *amitriptyline*, and *imipramine*. No limits were used in these searches. The Cochrane Database (Cochrane Collaboration, Oxford, United Kingdom) and other systematic reviews and meta-analysis are also evaluated and analyzed in this review article.

Results

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are considered one of the original classes of antidepressants discovered for the treatment of various types of neuropathic pain as evidenced by many placebo-controlled, randomized clinical trials. The TCAs are relatively inexpensive and most treatments are administered only once a day, potentially allowing for increased compliance. However, TCAs can cause orthostatic hypotension, dry mouth, constipation, and urinary retention, which limit clinical utility.

A double-blind, double-dummy, crossover trial by Gilron et al[5] assessed the efficacy and tolerability of combined

nortriptyline and gabapentin compared with each drug given alone in patients with diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN). Each treatment had a 3-period crossover design with 6 weeks per treatment period. Target daily doses were gabapentin 3600 mg and nortriptyline 100 mg, either monotherapy or in combination. Inclusion criteria for the study included daily pain of at least 4 on a 0 to 10 pain scale for at least 6 months before the start of the trial. Additionally, patients had to have an aspartate-alanine aminotransferase concentration of at or below 120% of the upper limit of reference range, a serum creatinine concentration of 150% or less of the reference range, and a hemoglobin A_{1c} ($HgbA_{1c}$) of less than 13%. Exclusion criteria included neuropathy caused by other medical conditions. Other exclusions included major organ system disease, cardiovascular autonomic neuropathy, baseline postural hypotension, sedation because of concomitant drugs or other cause, benign prostatic hypertrophy in male participants, psychiatric or substance abuse disorder, or a coexisting disorder that could cause pain as severe as neuropathic pain.[5]

Fifty-six patients with DPN (71%) or PHN (29%) were enrolled.[5] Baseline characteristics for the DPN group were of 61-year-old white males diagnosed with pain for about 5 years with an intensity of 5.5 on a 0 to 10 rating scale. Baseline characteristics for the PHN group were of 68-year-old white males diagnosed with pain for about 3 years with an intensity of 5 on a 0 to 10 scale. An equal majority of patients were also using acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). The mean maximum tolerated dose of gabapentin was 2433 mg as monotherapy versus 2180 mg in combination ($P = .0009$). The maximum tolerated dose of nortriptyline was 61.6 mg as monotherapy versus 50.1 mg in combination ($P = .0006$). For patients with DPN, pain with combination treatment was significantly lower than it was with gabapentin ($P = .018$) or nortriptyline alone ($P = .009$). In the PHN group, combination treatment was more effective at decreasing pain, but the overall effect was not significant ($P = .54$). This was attributed to the small sample size of patients with PHN. Moderate or severe dry mouth was more frequent with nortriptyline or combination treatment than it was with gabapentin alone. Limitations of the study included low power and the possibility of partial unmasking of research team members. The authors concluded a combination of the study medications seemed to be more efficacious than either drug given alone for neuropathic pain.[5]

A double-blind, randomized, parallel group investigation of diabetic patients with chronic DPN by Boyle and colleagues[6] compared the analgesic efficacy of pregabalin, amitriptyline, and duloxetine. The authors also investigated the effects of these medications on sleep, daytime functioning, and quality of life. Inclusion criteria consisted of patients with diabetes 18 years or older with diabetes-related neuropathic pain. Exclusion criteria included evidence of cognitive impairment, end-stage disease of a major system, recurrent and/or severe hypoglycemic events in the previous 3 years, or recent cardiac or cerebral ischemic events. Patients were also excluded if they were pregnant or breast feeding, had a history of substance abuse, or had been involved in another clinical trial recently. Patients were randomized into 1 of 3 treatment arms (pregabalin, amitriptyline, or duloxetine). Patients were permitted to continue taking opioids, NSAIDs, and up to 4 g/d of acetaminophen. Once an 8-day placebo run-in was completed, patients were titrated through 14 days of lower-dosed medication (amitriptyline, 25 mg twice daily [BID]; duloxetine, 60 mg every morning; pregabalin, 150 mg BID). Dosages were further titrated (amitriptyline, 25 mg every morning and 50 mg every evening; duloxetine, 60 mg BID; pregabalin, 300 mg BID) for 14 days. The primary outcome was to assess pain with the brief pain inventory (BPI). Secondary outcomes included quality of life assessed using the short-form 36-item general health survey (SF-36) at screening and on the last day of treatment.[6]

Baseline characteristics among treatment arms were similar.[6] Most patients were white, insulin-dependent males aged 65 years diagnosed with diabetes ($HgbA_{1c}$, about 7.9%) for approximately 14.2 years; 78% of patients completed the study. The primary outcome showed no significant difference among the treatment groups. All 3 treatment arms reduced BPI severity by approximately 50%. For secondary outcomes, pregabalin improved sleep continuity ($P < .001$), whereas duloxetine (60 and 120 mg) decreased sleep efficiency ($P < .001$ and $P < .05$, respectively), total sleep time ($P < .0001$ and $P < .05$), and increased waking after sleep onset ($P < .01$). Amitriptyline (50 and 75 mg) had no significant effect on sleep efficiency or total sleep time but did significantly reduce waking after sleep onset ($P < .05$). There were no other significant differences among the groups in all other outcomes. Pregabalin was noted to have a significantly more adverse events ($P < .001$), such as fatigue, dizziness, and somnolence. One limitation that the authors suggested was that the SF-36 tool may not have been a sensitive enough measure to assess changes in mood throughout a 4-week period. The authors concluded amitriptyline, duloxetine, and pregabalin were equally effective analgesic medications for patients with diabetic neuropathy.[6]

A 14-week, randomized, double-blind, crossover, active-control, clinical trial of 51 patients aged 18 to 75 years, published in *Diabetic Medicine*, compared the efficacy and safety of pregabalin and amitriptyline in alleviating pain associated with DPN.[7] The primary endpoint was the median baseline reduction of pain using the visual analog

scale (VAS). Secondary outcomes included pain assessment using the short form McGill pain questionnaire, the 5-point Likert scale for pain, physician global assessment of efficacy for depression, change in sleep pattern, Hamilton rating scale for depression, patient self-evaluation of overall change on 7-point Patient Global Impression of Change scale, adverse events, and patient preference for treatment. Before the start of the study, a 1-week washout period of previous medications taken for DBP was required to establish baseline pain scores. Amitriptyline was given orally, at doses of 10, 25, and 50 mg nightly, and pregabalin was given orally at doses 75, 150, and 300 mg BID. Each treatment was for 5 weeks. A 3-week placebo washout period took place between the 2 drugs. [7]

Baseline characteristics reported patients were 54.5 years old with a body mass index of 24.9 and $HgbA_{1c}$ level of 7.97%.[7] Patients had been diagnosed with diabetes for 5 years and had experienced mostly foot pain for the past 12 months. Forty-four patients completed the study. Average doses of pregabalin and amitriptyline were 218 mg/d and 16 mg/d, respectively.[7] Patients were permitted to receive up to 3 g/d of acetaminophen. Compliance was assessed via self-report as well as tablet counting. Per the patient's global assessment of efficacy and safety, good, moderate, and mild pain relief were noted in 48%, 13%, and 15% of patients on pregabalin and 34%, 11%, and 27% of patients on amitriptyline. No significant differences were noted in both the primary and secondary outcomes for either medication. More patients receiving pregabalin showed good and moderate improvement in their pain compared with those receiving amitriptyline. Pregabalin also appeared to have less adverse events than amitriptyline. The most common side effects included increase in sleep duration and tiredness. One limitation noted within the study was the lack of a placebo arm, which could have improved the sensitivity for detecting change with each drug in DPN. The authors stated that both pregabalin and amitriptyline were safe and effective for the treatment of diabetic neuropathic pain.[7]

A 31-week, randomized, controlled, double-blind, triple-crossover study of 38 patients with neuropathic pain from spinal cord injury investigated the effectiveness of amitriptyline and gabapentin compared with diphenhydramine in relieving chronic neuropathic pain at or below the level of injury.[8] The main efficacy measure was the average VAS rating for pain during week 8 of each study period. Additionally, an 11-point numeric rating scale and the Center for Epidemiologic Studies Depression Scale-short form (CESD-SF; high $\geq$ 10, low $\leq$ 10) were assessed for each medication. There were 6 possible sequences of the 3 medications, and patients were randomized to 1 of the 6 sequences. The maximum doses in this study were amitriptyline 50 mg 3 times daily (TID), gabapentin 1200 mg TID, and diphenhydramine 25 mg TID.[8] Each study drug was administered for 9 weeks after a 1-week washout period. Patients were allowed to take up to 8 oxycodone/acetaminophen 5-325 mg tablets daily for breakthrough pain. [8]

Twenty-two patients completed all 3 phases of the study. Baseline VAS scores were 4.6 for participants with low CESD-SF scores and 7.41 for those with high baseline CESD-SF scores. In those with high baseline CESD-SF scores, amitriptyline (mean [SD], 4.21 [1.95]) was more effective than diphenhydramine (mean, [SD], 6.68 [1.88]; $P = .035$) at week 8. There was a trend showing amitriptyline may be more effective than gabapentin, but results were not significant ($t = 2.23$; $P = .061$). Gabapentin did not show superiority over diphenhydramine ($P = .97$). For those with lower CESD-SF scores, there were no significant differences among the medications. At least 50% of the participants who completed the study did not use the oxycodone/acetaminophen for breakthrough pain. Most common side effects included dry mouth, drowsiness, and constipation. Limitations included a high dropout rate, a short washout period, potential bias because of patient payment, and patient self-reported measures. The authors concluded the most effective of the 3 study drugs was amitriptyline because of its efficacy in pain relief as well as its low monthly cost.[8]

In its review of the TCA data, the European Federation of Neurological Societies task force classified TCAs as effective with level A evidence on the basis of 2 class I meta-analyses but does not recommend a specific drug within the TCA class. The American Academy of Neurology[1] states that amitriptyline (25-100 mg/d) is supported by level B evidence based on 1 class-I and 2 class-II studies. A 2014 Cochrane Review[9] of imipramine for neuropathic pain found little evidence to support its use to treat neuropathic pain.

Selective Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are becoming increasingly popular as treatment for neuropathic pain. These medications are thought to be better tolerated than the traditional TCAs and have solid data in different types of neuropathies demonstrating efficacy. The first agent to show efficacy in noncontrolled or open-label trials was venlafaxine. Since those publications, several other studies with stronger research designs have been conducted with venlafaxine and will be reviewed.[10-14]

Rowbotham and colleagues[11] evaluated the efficacy and safety of 6 weeks of venlafaxine extended-release in a multicenter, double-blind, randomized, placebo-controlled

trial of 244 patients with stable, type-1 or type-2 diabetes with painful DPN. Primary measures included the VAS-pain intensity (VAS-PI) and VAS-pain relief (VAS-PR) scales. The Clinical Global Impressions severity of illness (CGI-S) and the Clinical Global Impression-improvement (CGI-I) scales, the patient global rating of pain relief, and the percentage of patients receiving a 50% reduction in their pain intensities were also reported. Patients were divided equally into 3 groups, 80 patients received placebo, 80 patients received venlafaxine ER 75 mg, and 82 patients received venlafaxine ER 150 to 225 mg. Demographic and baseline characteristics were comparable among treatment groups. Most patients were 59-year-old males with neuropathic pain for 252 weeks. Average baseline VAS-PI and CGI-S scores were 68.8 mm and 4.6, respectively, which were considered moderately severe pain.[11]

Higher-dose venlafaxine ER (150-225 mg/d) was significantly more effective than placebo was for the primary outcome measure of reduction in weekly mean VAS-PI scores ($P < .001$). Higher-dose venlafaxine ER was also significantly more effective than venlafaxine ER 75 mg at week 6 ($P = .006$). At week 6, using last observation carried forward approach, the mean adjusted pain was reduced by 18.77 mm for placebo, 22.4 mm for venlafaxine ER 75 mg, and 33.8 mm for the venlafaxine ER 150 to 225 mg group. The number needed to treat to achieve a 50% or greater reduction from baseline in pain intensity was 4.5 after 6 weeks of treatment with venlafaxine ER 150 to 225 mg daily. The most commonly reported adverse events were nausea, dyspepsia, sweating, somnolence, and insomnia. Blood pressure and cardiac rhythm changes were more common in the venlafaxine group. The authors determined that higher dosages of venlafaxine reached statistical difference, compared with placebo and venlafaxine at lower dosages, on both primary outcomes and on all 4 of the secondary outcomes by week 6 of treatment.[11] The authors concluded that results of this study determined that treatment with venlafaxine ER resulted in dose-related clinically significant reductions in neuropathic pain.[11]

Kadiroglu and colleagues[12] evaluated the effect of venlafaxine on painful DPN in 60 patients with type 2 diabetes mellitus. The 8-week study was designed as a prospective, randomized, controlled trial consisting of 60 patients. To be included in the study, patients had to have a VAS score of at least 40 mm, have an $HgbA_{1c}$ less than 11%, and not have received prior treatment for peripheral diabetic neuropathy. Patients were randomized to receive venlafaxine XR 75 mg or a control with vitamin B1 and vitamin B6 tablets once a day. Outcome measures included severity of pain measured by the VAS, the short-form McGill pain questionnaire, and numeric analog scale scores at admission. Baseline characteristics between treatment groups were comparable; the average patient was a 53-year-old female who had diabetes for approximately 8.7 years and an $HgbA_{1c}$ of 8.65%. At the beginning of the study, the VAS score was 70.0 ± 13.0 mm, the short-form McGill pain questionnaire was 24.9 ± 6.2, and the numeric analog scale was 7.2 ± 1.1; scores were 73.0 ± 8.0 mm, 26.8 ± 6.2, and 7.4 ± 0.8, respectively, for the control group. The authors determined the severity of pain had better improvement in the treatment group than in the control groups for both the McGill pain questionnaire score ($P = .001$) and the numeric analog scale scores ($P = .001$). Severity of pain was markedly reduced after the second week in the treatment group compared with the control group. The most common adverse effect noted within the study was nausea. At the conclusion of the study, the severity of pain was reduced by 53% in the treatment group and 22% in the control group ($P < 0.05$). They concluded that venlafaxine was a safe and well-tolerated analgesic drug for the symptomatic treatment of DPN, and that it shows efficacy within the second week of therapy.[12]

Yucel and colleagues[13] investigated the effectiveness and safety of venlafaxine XR 75 and 150 mg on ongoing pain and on quantitative sensory tests for 8 weeks in 60 patients with neuropathic pain. To be included, patients were required to have symptoms of neuropathic pain for at least 6 months and a pain rating of at least 4 on a VAS pain scale from 0 to 10. Outcome measures included the VAS, patient satisfaction, side effects, global efficacy, and tolerance. Quantitative sensory measurements, taken from affected area before and after drug treatment, included pin-prick hyperalgesia, allodynia, detection and pain thresholds to electrical and heat stimuli, and temporal summation of repetitive electrical and heat stimuli. Baseline patient demographics were similar between the 2 groups. The VAS scores decreased significantly in all groups ($P < 0.009$ in placebo; $P \leq 0.001$ in both venlafaxine groups). Patient satisfaction increased significantly in all groups; however, satisfaction was significantly higher in the venlafaxine XR 75 mg group than it was in the placebo group ($P < 0.021$). There was no significant difference in side effects between the groups. The authors concluded that there was a more-pronounced decrease in ongoing pain intensity in the venlafaxine 75 and 150 mg groups than there was in the placebo group. However, there were no statistically significant differences among the groups.[13]

A 2003 study,[14] published in *Neurology*, compared the possible efficacy of venlafaxine versus imipramine in relieving painful polyneuropathy. It was a 12-week, randomized, double-blind, placebo-controlled, 3-way crossover study. Patients included were required to have polyneuropathy present for more than 6 months and a pain score of at least 4 on a 0 to 10 Likert scale after 1

week without taking pain medication. Forty patients were assigned to one of the treatment groups, and 29 completed all 3 study periods. Daily doses for venlafaxine and imipramine were 225 mg and 150 mg, respectively. Patients rated pain paroxysm, constant pain, and touch- and pressure-evoked pain using a 0- to 10-point numeric scale. Patients could also use up to 6 tablets of acetaminophen 500 mg as escape medication during all study phases. The sum of the individual pain scores was lower on venlafaxine ($P=.006$) and imipramine ($P=.001$) than it was on placebo. However, there was no statistical difference noted between venlafaxine and imipramine ($P=.44$).The numbers needed to treat to obtain one patient with moderate or better pain relief were 5.2 for venlafaxine and 2.7 for imipramine. Adverse effects between the treatment groups did not differ. Patients in the imipramine group reported a higher incidence of dry mouth and sweating, whereas those in the venlafaxine group reported increased tiredness. The authors concluded that venlafaxine was similar in efficacy and tolerability to imipramine.[14]

Another antidepressant with clinical trials supporting its use in neuropathy is duloxetine.[15] In one phase III, multicenter, double-blind, placebo-controlled trial, 348 patients with DPN were randomized to either placebo, duloxetine at 60 mg daily, or duloxetine at 60 mg BID for 12 weeks. Patients were required to score at least 3 on the Michigan Neuropathy Screening Instrument and 4 or higher on an 11-point Likert scale for 24-hour average pain severity. The primary efficacy measure was change in 24-hour average pain score on an 11-point Likert scale, recorded in a daily pain diary. Both duloxetine groups had significantly superior pain reduction compared with placebo for the primary outcome, with a mean change of −2.50 for duloxetine at 60 mg daily, −2.47 for duloxetine at 60 mg BID, and −1.60 for placebo. Duloxetine groups were also superior to placebo for secondary outcomes of 24-hour worst-pain score and night-pain score. There was no difference in efficacy between duloxetine groups. Adverse events seen more commonly in the duloxetine groups than with placebo included nausea, somnolence, hyperhidrosis, and anorexia, with vomiting and constipation occurring more frequently only in the duloxetine 60 mg BID group. Limitations included short treat duration because neuropathy requires a longer treatment duration, exclusion of serious illness, and a requirement for stable dosages of concomitant medications because the study may not be generalizable.[15]

In another phase-III, multicenter, double-blind, placebo-controlled trial, 334 patients with diabetic peripheral neuropathy were randomized to either placebo, duloxetine at 60 mg daily, or duloxetine at 60 mg BID for 12 weeks.[16] Patients included scored at least 3 on the MNSI and 4 or higher on an 11-point Likert scale for 24-hour average pain severity. The primary efficacy measure was reduction in 24-hour pain score as measured on an 11-point Likert scale, recorded in a daily pain diary. Pain reduction for both duloxetine groups was significantly superior to that of the placebo group for the primary outcome, with a mean change of −2.72 for duloxetine at 60 mg daily, −2.84 for duloxetine at 60 mg BID, and −1.39 for placebo. Both treatment groups had superior pain relief compared with placebo for secondary measures of 24-hour worst-pain score and night pain. There was no difference in efficacy between duloxetine groups. Adverse effects occurring more commonly in the duloxetine groups than in the placebo group included nausea, fatigue, somnolence, increased sweating, and dry mouth.[16]

Another double-blind, randomized trial included 457 patients with diabetic peripheral neuropathy randomized to either duloxetine at 20 mg daily, duloxetine at 60 mg daily, duloxetine at 60 mg BID, or placebo for 12 weeks.[17] Patients included were required to score at least 3 on the MNSI and to have a minimum score of 4 on an 11-point Likert scale for 24-hour average pain score. The primary efficacy endpoint was the mean change in 24-hour pain score on an 11-point Likert scale, as recorded in a pain diary. The duloxetine at 60 mg daily (−2.89) and duloxetine at 60 mg BID (−3.24) groups had significantly superior pain reduction compared with the placebo group (−1.91) in the primary endpoint, whereas the duloxetine at 20 mg daily (−2.36) group did not. All 3 treatment groups were superior to placebo for secondary outcomes of 24-hour worst-pain score. Duloxetine at 60 mg daily and duloxetine at 60 mg BID were superior to placebo for the secondary outcome of night pain. Somnolence and constipation occurred significantly more in duloxetine than with placebo, with back pain, arthralgia, and pruritus occurring significantly less in duloxetine; somnolence occurred more frequently in the 60-mg BID group. Limitations included short treatment duration and exclusion of comorbid conditions and medications than may have confounded study results, limiting generalizability.[17]

A randomized, double-blind crossover study compared duloxetine at 60 mg daily with placebo for 12 weeks in 231 patients with chemotherapy-induced peripheral neuropathy (CIPN).[18] Patients were required to have greater than grade-1 sensory CIPN, based on the National Cancer Institute's common toxicity criteria for adverse events and at least 4 on a 10-point for average CIPN pain for at least 3 months after chemotherapy completion. Grade-1 sensory CIPN was diagnosed by loss of deep tendon reflexes and/or the presence of symmetric "stocking-glove" numbness and/or paresthesias beginning after neurotoxic chemotherapy; grade 1 is the least severe of 5 grades. Patients in the duloxetine group initially received 30 mg daily for 1 week, which was then increased to 60 mg daily for an

additional 4 weeks before crossover. Pain was assessed using the BPI short form. The duloxetine group had a significantly greater reduction in average pain compared with placebo (−1.06 versus −0.34, $P = .003$). Adverse effects were similar between groups, with common adverse effects being fatigue, insomnia, and nausea. Some limitations include higher dropout rate in the duloxetine group (11% versus 1%), despite similar rates of adverse events, and lack of assessment of dosage changes in concurrent analgesic medications.[18]

Another randomized, double-blind crossover trial compared amitriptyline to duloxetine for 14 weeks in patients with painful diabetic neuropathy.[19] To be enrolled, patients were required to have a pain score greater than 50% on the VAS. The primary endpoint was reduction in the median pain score from baseline using a VAS (0-100). There was no significant difference between the 2 treatments regarding efficacy. Dosages were titrated to effect, with 48% of amitriptyline patients reaching a maximum dose of 50 mg and 65% of duloxetine patients reaching a maximum dose of 60 mg. Duloxetine had more mild adverse events, but amitriptyline had more severe adverse events. The most common adverse events with duloxetine were somnolence and constipation, whereas dry mouth was more common with amitriptyline. Limitations included the lack of placebo arm.[19]

An 8-week, double-blind, placebo-controlled trial compared duloxetine to placebo in patients with neuropathic pain caused by spinal cord injury or stroke.[20] Patients were required have severe neuropathic pain, rated 6 or higher on a VAS, caused by lesions or dysfunction in the central nervous system. Twenty-four patients were randomized to flexible-dose placebo, and 24 patients were randomized to flexible-dose duloxetine (60-120 mg/d). Pain was assessed using an average of 9 VAS scores, which were measured during the last 72 hours of treatment. Mean pain scores changed from 7.1 (± 0.8) at baseline to 5.0 (± 2.0) at endpoint, compared with 7.2 (± 0.8) at baseline and 6.1 (± 1.7) at endpoint in the placebo group ($P = 0.056$), which was a trend toward significance. There was no difference observed in response to duloxetine between patients with spinal cord injury and patients with stroke ($P = 0.61$). Somnolence was more common in the duloxetine group than it was in the placebo group ($P = 0.003$).[20]

There are currently no published clinical trials, to our knowledge, examining the use of milnacipran or levomilnacipran for the treatment of neuropathy. There is currently one ongoing study investigating the use of milnacipran in the treatment of idiopathic neuropathy pain. It is a randomized, placebo-controlled, double-blind trial projected to be completed in October 2014.[21]

The use of SNRIs, like venlafaxine and duloxetine, is supported by both the European Federation of Neurological Societies (level A evidence) and the American Academy of Neurology (level B evidence) guidelines.[1] The recommended dose for venlafaxine is 75 to 225 mg/d, with better pain control seen at higher dosages.[1,10] Duloxetine is also effective for neuropathy, but no increased pain control is seen with doses above 60 mg daily.[15,16] Both venlafaxine and duloxetine have comparable efficacy to TCAs.[14,18] To our knowledge, there is no data to support the use of milnacipran or levomilnacipran at this point in time.[21]

Other Antidepressants (SSRIs, Bupropion, Mirtazapine, Nefazodone, Trazodone, Atomoxetine)

Results from trials evaluating the efficacy of SSRIs for neuropathic pain have yielded conflicting results, with some medications (citalopram, escitalopram, fluoxetine, paroxetine) demonstrating relatively small effects on relieving pain associated with neuropathy. The SSRIs are generally better tolerated than the TCAs are but have consistently demonstrated less efficacy in relieving neuropathic pain, with the inclusion of depressed patients in some studies providing a confounding variable with the potential to inflate pain-relief results.[22-24]

Paroxetine was compared with imipramine and placebo in a small ($n = 20$), randomized, double-blind, crossover-design study to assess efficacy in painful diabetic neuropathy symptoms. Paroxetine at a 40-mg fixed dose was compared with imipramine adjusted to plasma levels of imipramine plus desipramine of 400 to 600 nM.[25] Self-rating showed no depressive symptoms for study patients at baseline. Paroxetine reduced symptoms of neuropathy, defined as a 50% reduction in pain as measured by observer and self-rating, but was less effective than imipramine. However, patients with a lesser response to paroxetine than they had to imipramine were found to have lower plasma concentrations of paroxetine than did those with responses to paroxetine similar to those observed in patients receiving imipramine. On imipramine, 5 patients dropped out because of intolerable adverse events, and 4 patients reported withdrawal symptoms following discontinuation of imipramine, whereas no patients dropped out because of adverse events and no patients reported withdrawal symptoms with paroxetine. In conclusion, paroxetine at 40 mg daily, in patients for whom that dose yielded a sufficient plasma level, appeared to reduce painful symptoms of diabetic neuropathy with similar efficacy and better tolerability compared with imipramine.[25]

Citalopram was compared with placebo in a small ($n = 15$), randomized, double-blind, crossover-design study to

assess efficacy in diabetic neuropathy symptoms. Citalopram at a fixed dose of 40 mg was compared with placebo.[26] Citalopram reduced symptoms of neuropathy, defined as a 50% reduction in pain as measured by observer and self-rating, compared with placebo (3 of 15 versus 1 of 15), results, which were interpreted by the investigators as indicative of less efficacy for citalopram compared with their previous findings in studies with imipramine. Side-effect ratings were higher during administration of citalopram than they were during administration of placebo, with 2 patients who received citalopram discontinuing because of intolerable side effects. However, citalopram was generally well tolerated. In conclusion, the investigators interpreted the findings of this study as suggesting that citalopram was less efficacious, but better tolerated, than imipramine for painful diabetic neuropathy.[26]

Max et al[27] conducted 2 randomized, double-blind, crossover studies in patients with painful diabetic neuropathy. Inclusion criteria required patients to have stable glycemic control and painful diabetic neuropathy of at least moderate severity for a minimum of 3 months. Eligible patients were assigned to one of the following 2 randomized, 2-period (6 weeks separated by a 2-week washout) crossover studies: a comparison of amitriptyline and desipramine or a comparison of fluoxetine and placebo. Following completion of one study and a 3-week washout period, eligible patients could be enrolled in the other study arm.[27]

Fifty-seven patients were randomly assigned to a study arm ($n = 29$ to amitriptyline-desipramine and $n = 28$ to fluoxetine-placebo).[27] An additional 17 patients were nonrandomly assigned to fluoxetine-placebo because of contraindications to amitriptyline-desipramine, and 5 additional patients were added to amitriptyline-desipramine after the fluoxetine-placebo study had filled. Twenty patients who completed the fluoxetine-placebo study were then enrolled in amitriptyline-desipramine, and 9 who completed amitriptyline-desipramine were enrolled in fluoxetine-placebo. Because of adverse effects or voluntary withdrawal, 16 patients did not complete the amitriptyline-desipramine study, and 8 did not complete the fluoxetine-placebo study.[27]

Thirty-eight patients completed the amitriptyline-desipramine study (mean daily dose of 105 mg for amitriptyline and 111 mg for desipramine) and 46 completed the fluoxetine-placebo (mean daily dose of 40 mg for fluoxetine).[27] Assessment of treatment efficacy was based on improvement in pain-rating scores taken at week 6 of treatment. Patients rated pain relief at the end of the treatment period as *complete*, *a lot*, *moderate*, *slight*, *none*, or *worse*. Percentages of patients rating pain relief as complete, a lot, or moderate were 74% for amitriptyline, 61% for desipramine, 48% for fluoxetine, and 41% for placebo. Although amitriptyline and desipramine were more efficacious than placebo in patients with and without depression, fluoxetine was more efficacious than placebo only in patients with depression. Hamilton depression scores improved significantly in patients receiving fluoxetine or amitriptyline but not in those desipramine or placebo. In conclusion, fluoxetine was not found to be superior to placebo in the treatment of pain in diabetic neuropathy, independent of improvement in depressive symptoms.[27]

Most recently, escitalopram was evaluated for efficacy in painful polyneuropathy in a randomized, placebo-controlled, crossover trial.[28] Inclusion criteria required patients to have symptoms consistent with polyneuropathy for at least 6 months, as well as confirmation of polyneuropathy by electrophysiologic testing or quantitative sensory testing. Patients were slowly tapered off any medications for neuropathic pain, with a 1-week washout, before receiving escitalopram or placebo. Patients then entered the crossover treatment sequence for 6 plus 6 weeks separated by a 2-week washout period. The study drug was titrated to 20 mg daily after 1 week and was maintained at that target dose for 4 weeks before tapering off. After the fifth week of treatment patients rated their pain relief using a verbal rating scale (complete, good, moderate, slight, none, or worse).[28]

Forty-one of the 48 patients entering the study were included in the data set. Four patients withdrew for an adverse event experienced while receiving escitalopram, whereas one patient withdrew because of an adverse event experienced while receiving placebo.[28] Pain relief with escitalopram at 20 mg daily was statistically greater than that observed with placebo, with more patients ($n = 11$ versus $n = 3$) reporting moderate to good pain relief ($P < 0.05$), and no patients reporting complete relief. These results were seen in patients independent of antidepressant effects of escitalopram. However, clinically relevant effects were observed in only a few patients, with more than half (13 of 24) of those reporting relief with escitalopram reporting only "slight" relief. In conclusion, the lack of robust improvement with escitalopram suggests that it cannot currently be recommended as a standard treatment for neuropathic pain.[28]

Bupropion demonstrated efficacy for peripheral neuropathic pain in a small ($n = 41$), randomized, placebo-controlled study of nondepressed patients.[29] Patients were randomized to either placebo or bupropion SR 150 mg daily for 1 week, followed by bupropion SR at 150 mg BID for 5 weeks. Pain was assessed using the Wisconsin Brief Pain Inventory. Patients also rated daily pain on a VAS of 0 to 10. Average weekly pain score, as rated by patients, was significantly lower for bupropion

($P < 0.001$). Pain significantly decreased from baseline to endpoint for patients taking bupropion, as rated by the Wisconsin Brief Pain Inventory ($P < 0.001$), whereas there was essentially no decrease in pain for placebo. The most common adverse effects for bupropion were dry mouth, insomnia, headache, gastrointestinal upset, tremor, constipation, and dizziness. Limitations included the few patients studied and the short duration of treatment.[29]

Mirtazapine has been assessed for relief of psychiatric symptoms (eg, anxiety, depression, insomnia) in patients with cancer and pain but has not, to our knowledge, been assessed for relief of neuropathic pain.[22] To our knowledge, nefazodone and trazodone lack human studies assessing their efficacy for neuropathic pain,[22] and although the norepinephrine reuptake inhibition action of atomoxetine suggests potential efficacy for neuropathic pain, it too has yet to be assessed for this indication.

Guidelines and Meta-analyses

As noted above, several clinical trials have been conducted investigating the use of antidepressants in the treatment of neuropathies. Unfortunately, few trials had an active comparator group, thus, a couple of meta-analyses have been conducted to determine whether one agent was more effective. The first comprehensive meta-analysis of the literature was conducted by the Cochrane Pain, Palliative and Supportive Care Group.[23] In that 2007 review, 61 clinical trials were included in the meta-analysis. The primary results of the study showed that TCAs were effective in treating moderate neuropathic pain. The number needed to treat was 3.6 (95% confidence interval [CI], 3-4.5). The SSRIs had limited data to support their use. Venlafaxine had 3 trials showing efficacy in DPN with a number needed to treat of 3.1 (95% CI 2.2-5.1). Nutraceuticals were not found to be effective (St John's wort and L-tryptophan) and TCAs were not effective in treating neuropathies related to human immunodeficiency virus. The primary limitations of this publication were that newer agents have been studied since the release date of publication (2007).[23]

In a second and more recent meta-analysis, Rudroju and colleagues[30] reviewed 21 trials of various agents (anticonvulsants and antidepressants) in the treatment of painful diabetic neuropathy. Their findings suggested that duloxetine, gabapentin, pregabalin, and venlafaxine were all efficacious when compared with placebo; however, no drug was found to be superior when comparing the 4 agents to each other. As far as tolerability, each agent reported more adverse events than did placebo. However, amitriptyline and duloxetine were found to have more patients drop out from lack of tolerability than gabapentin. The authors concluded that each of the agents had similar efficacy, but amitriptyline was less tolerated.[30]

Finally, the American Academy of Neurology conducted an extensive review of the literature to develop a practice guideline for the treatment of painful diabetic neuropathy.[31] The panel identified 79 clinical trials to be included in the analysis of the literature. In their findings, amitriptyline, venlafaxine, and duloxetine were probably effective in treating painful diabetic neuropathy (level B), but venlafaxine and duloxetine were both effective in improving quality of life. Venlafaxine was also found to be beneficial if gabapentin monotherapy was ineffective. Finally, there was a lack of data to support the use of desipramine, imipramine, and fluoxetine in the treatment of painful diabetic neuropathy. This practice guideline investigated only efficacy and did not consider the adverse event profile of these agents. For completeness, it should be noted this treatment guideline recommended pregabalin (level A) over all other agents, including antidepressants, for the treatment of painful diabetic neuropathy.[31]

Discussion

As noted above, multiple trials and reviews support the efficacy of antidepressants in the treatment of neuropathic pain. The TCAs have been found to be efficacious in the relief of multiple types of neuropathic pain; however, this class of medications has a higher incidence of adverse effects than do other agents that have been studied.[5-8] These side effects include increased sleep duration, tiredness, constipation, and dry mouth.[5,7,8] Imipramine, desipramine, and nortriptyline do not have superior efficacy compared with their study counterparts.[5-7,9,31] Higher dosages of venlafaxine were generally more effective in relieving neuropathic pain.[11] Additionally, venlafaxine has shown effectiveness as both monotherapy and adjuvant therapy to gabapentin in the treatment of neuropathic pain.[10-14] The most common side effects associated with venlafaxine are nausea, dizziness, lightheadedness, and fatigue.[10-12] Duloxetine therapy once daily was shown to be as effective as duloxetine therapy twice daily with less associated side effects.[15,16] Those side effects included nausea, somnolence, hyperhidrosis, and anorexia.[15] When the duloxetine dosage was increased, vomiting and constipation were more prevalent.[15] Both venlafaxine and duloxetine were shown to have comparable efficacy to TCAs.[14,19] There is no data to support the use of milnacipran or levomilnacipran at this point in time. For SSRIs, paroxetine had similar efficacy as imipramine, whereas citalopram was found to be less efficacious but better tolerated.[25,26] Fluoxetine was only efficacious if patients had preexisting depression.[27] Escitalopram was not shown to offer robust improvement in the treatment of neuropathic pain.[28] Bupropion has demonstrated efficacy compared with placebo.[29] Mirtazapine, nefazodone, trazodone, and atomoxetine lacked

data to support their use. In conclusion, there is significant evidence to support the use of antidepressants in the treatment of neuropathic pain.

Based on the antidepressant data presented in this review, we concluded venlafaxine and duloxetine should be considered as first-line antidepressant agents for the treatment of neuropathy. Both agents showed efficacy in improving neuropathic pain, with lower incidence of adverse effects than TCAs. The TCAs are appropriate as second-line agents. These medications have efficacy in reducing neuropathic pain but have a higher incidence of adverse effects than do SNRIs. Should other agents not be effective, appropriate third-line agents include paroxetine, citalopram, and bupropion. These agents have been shown to be efficacious when compared to a TCA or placebo, but do not have as much data to support their use. Fluoxetine may be used as a third-line agent only in patients with concomitant depression. We would not recommend using escitalopram for the treatment of neuropathic pain because it did not show significant efficacy. We do not currently recommend the use of other antidepressants, including levomilnacipran, milnacipran, mirtazapine, nefazodone, trazodone, and atomoxetine because of the lack of data at this time.

References

1. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2012;11(6):521-34. DOI: 10.1016/S1474-4422(12)70065-0. PubMed PMID: 22608666.
2. Lee YC, Chen PP. A review of SSRIs and SNRIs in neuropathic pain. Expert Opin. Pharmacother. 2010;11(17):2813-25. DOI: 10.1517/14656566.2010.507192. PubMed PMID: 20642317.
3. Katirji B, Koontz D. Disorders of peripheral nerves. In: Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors. Bradley's neurology in clinical practice. Philadelphia: Elsevier/Saunders; 2012. p. 1915-2015.
4. Devor M. Neuropathic pain: pathophysiological response of nerves to injury. In: McMahon SB, Koltzenburg M, Tracey I, Turk DC, editors. Wall & Melzack's textbook of pain expert consult. 6th ed. London: Elsevier Health Sciences UK; 2013:861-88. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780702040597000619 (cited 2015 Feb 19).
5. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled cross-over trial. Lancet. 2009;374(9697):1252-61. DOI: 10.1016/S0140-6736(09)61081-3. PubMed PMID: 19796802.
6. Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini DV, Kerr D. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 2012;35(12):2451-8. DOI: 10.2337/dc12-0656. PubMed PMID: 22991449.
7. Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. Diabet Med. 2009;26(10): 1019-26. DOI: 10.1111/j.1464-5491.2009.02806.x. PubMed PMID: 19900234.
8. Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Arch Phys Med Rehabil. 2007;88(12):1547-60. Erratum in Arch Phys Med Rehabil. 2008;89(6):1206. DOI: 10.1016/j.apmr.2007.07.038.
9. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014;5: CD010769. DOI: 10.1002/14651858.CD010769.pub2. PubMed PMID: 24838845.
10. Eardley W, Toth C. An open-label, non-randomized comparison of venlafaxine and gabapentin as monotherapy or adjuvant therapy in the management of neuropathic pain in patients with peripheral neuropathy. J Pain Res. 2010;3:33-49. PubMed PMID: 21197308.
11. 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. PubMed PMID: 15288411.
12. Kadiroglu AK, Sit D, Kayabasi H, Tuzcu AK, 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):241-5. DOI: 10.1016/j.jdiacomp.2007.03.010. PubMed PMID: 18413214.
13. Yucel A, Ozyalcin S, Koknel Talu G, Kiziltan E, Yucel B, Andersen OK, Arendt-Nielsen L, Disci R. The effect of venlafaxine on ongoing and experimentally induced pain in neuropathic pain patients: a double blind, placebo controlled study. Eur J Pain. 2005;9(4):407-16. DOI: 10.1016/j.ejpain.2004.09.009. PubMed PMID: 15979021.
14. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003;60(8):1284-9. PubMed PMID: 12707430.
15. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005;6(5):346-56. DOI: 10.1111/j.1526-4637.2005.00061.x. PubMed PMID: 16266355.
16. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006;67(8): 1411-20. DOI: 10.1212/01.wnl.0000240225.04000.1a.
17. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005; 116(1-2):109-18. DOI: 10.1016/j.pain.2005.03.029. PubMed PMID: 15927394.
18. Smith EML, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309(13):1359-67. DOI: 10.1001/jama.2013.2813. PubMed PMID: 23549581.
19. Kaur H, Hota D, Bhansali A, Dutta P, Bansal D, Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. Diabetes Care. 2011;34(4):818-22. DOI: 10.2337/dc10-1793. PubMed PMID: 21355098.
20. Vranken JH, Hollmann MW, van der Vegt MH, Kruis MR, Heesen M, Vos K, Pijl AJ, Dijkgraaf MG. Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: a randomized, double-blind, placebo-controlled trial. Pain. 2011;

152(2):267-73. DOI: 10.1016/j.pain.2010.09.005. PubMed PMID: 21078545.
21. Columbia University; Forrest Laboratories. A placebo controlled, randomized, double blind trial of milnacipran for the treatment of idiopathic neuropathy pain. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). c2000 [updated 2013 Dec 13; cited 2014 Jul 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT01288937 NLM Identifier: NCT01288937
22. Mikav 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):1161-21.
23. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007;(4):CD005454. DOI: 10.1002/14651858.CD005454.pub2. PubMed PMID: 17943857.
24. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005;96(6):399-409. DOI: 10.1111/j.1742-7843.2005.pto_96696601.x.
25. 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):135-44. PubMed PMID: 2147235.
26. Sindrup SH, Bjerre U, Dejgaard A, Brøsen K, Aaes-Jørgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharmacol Ther. 1992;52(5):547-52. PubMed PMID: 1424428.
27. 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):1250-6. DOI: 10.1056/NEJM199205073261904. PubMed PMID: 1560801.
28. Otto M, Bach FW, Troels SJ, Brosen K, Sindrup SH. Escitalopram in painful neuropathy: a randomized, placebo-controlled, cross-over trial. Pain. 2009;139:275-283.
29. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Neurology. 2001;57(9):1583-8. PubMed PMID: 11706096.
30. Rudroju N, Bansal D, Talakokkula ST, Gudala K, Hota D, Bhansali A, Ghai B. Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. Pain Physician. 2013;16(6):E705-14. PubMed PMID: 24284851.
31. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy. PM R. 2011; 3(4):345-52, 352e21. DOI: 10.1016/j.pmrj.2011.03.008.