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REVIEW

Duloxetine: Its Role in the Management of Chronic Pain

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Abstract: Chronic pain represents one of the most important public health problems and, in addition to classical analgesics, antidepressants are an essential part of therapeutic management. This is due to the regulation of pain signals in the central nervous system and the spinal cord by serotonin and noradrenaline. As the role of serotonin and noradrenaline in the modulation of pain perception has become better understood, serotonin and noradrenaline reuptake inhibitors—including duloxetine—have been assessed in terms of their therapeutic values as analgesics. Several randomized, double-blind, controlled trials have led to duloxetine's approval in the treatment of diabetic peripheral neuropathic pain as well as in the management of fibromyalgia.
The superiority of duloxetine over placebo was shown, while comparison studies with other antidepressants showed only partly superiority. Duloxetine has been found to be safe and well tolerable, with mild-to-moderate adverse events, a favourable cardiovascular profile, and minor influence on weight gain. A beneficial influence on the quality of life and well-being could be widely shown. First results indicate that duloxetine might also be effective in other pain states such as lower back pain, osteoarthritis, migraine and also in the treatment of children with depression and pain.

Keywords: duloxetine, chronic pain, antidepressants

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Introduction

The International Association for the study of pain defined the state of chronic pain as a persisting "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] Pain is amongst the most common symptoms reported in both the general population as well as the general medical setting[2] posing as a major international health problem. Pain accounts for more than 40% of all symptom-related outpatient visits in the US alone each year. The management of pain disorders costs the US over 100 billion dollars anually in health care, workers compensation, and lost work productivity.[3] Besides, pain medications are the second most prescribed class of drugs (after cardiac-renal drugs).[4]

Different care approaches are available in the treatment of pain and in addition to classical analgesics, antidepressants are an essential part of therapeutic management. Antidepressants were found to be effective in pain treatment because monoamine neurotransmitters play a significant role in the modulation of painful states.[5] Serotonin and noradrenaline depletion probably results in an absence of the physiological inhibitory effect of these neurotransmitters on pain pathways, with the result that normally non-painful physical stimuli are perceived as painful.[6] This suggests that antidepressants with dual mechanism of action affecting both serotonin and noradrenaline may allow a very effective management of pain.[7]

Duloxetine is one of a newer type of antidepressant drugs with a relatively balanced and potent dual reuptake inhibition of both serotonin and noradrenaline, weak affinity to the dopamine transporter and insignificant affinity to more than 60 neurotransmitter receptors.[8]

Since its development as an antidepressant in the U.S. in 2004 duloxetine's efficacy on pain has long been hypothesized.[9] Today, several studies have been performed and confirmed experimental data that besides its antidepressant effects, duloxetine is an important treatment option in several pain states.

Mechanism of Action, Pharmacokinetics and Pharmacodynamic Profile

Pharmacology and chemical properties

Duloxetine is a thiophenepropylamine derivate with a secondary amino group to which naphtaline is linked via an ether bond, Figure 1. Its chemical name is (+)-(S)-N-methyl-gamma-(1-naphthyloxy)-2-thiophenepropylamine, its empirical formula is C18H19NOS and its molecular weight is 297.4. Duloxetine is available as a hydrochloride salt.[10]

The interaction of duloxetine with monoamine transporters and neuronal receptors has been characterized in vitro as well as in vivo.[11] Duloxetine inhibits the energy-dependent uptake process of serotonin, noradrenaline and dopamine into synaptosomes. Compared to other antidepressants, duloxetine exhibits the highest affinity for the serotonergic and noradrenergic re-uptake transporters in vitro.[12] Data from microdialysis studies in rats show that duloxetine increases the concentration of both serotonin and noradrenaline in the extracellular fluid.[13] Duloxetine has no clinically relevant binding affinity for muscarinergic, histaminergic or cholinergic receptors.[14]

Pharmacokinetics

Duloxetine is fairly well absorbed from the enteric-coated pellets following oral administration with the maximal plasma concentration measured 6 hours post dose. The mean elimination half-life after oral administration is 12 hours (8–17 hours).[15] Food administration delays the peak concentration from 6 to 10 hours.[15] The bioavailability is ≥70% and in

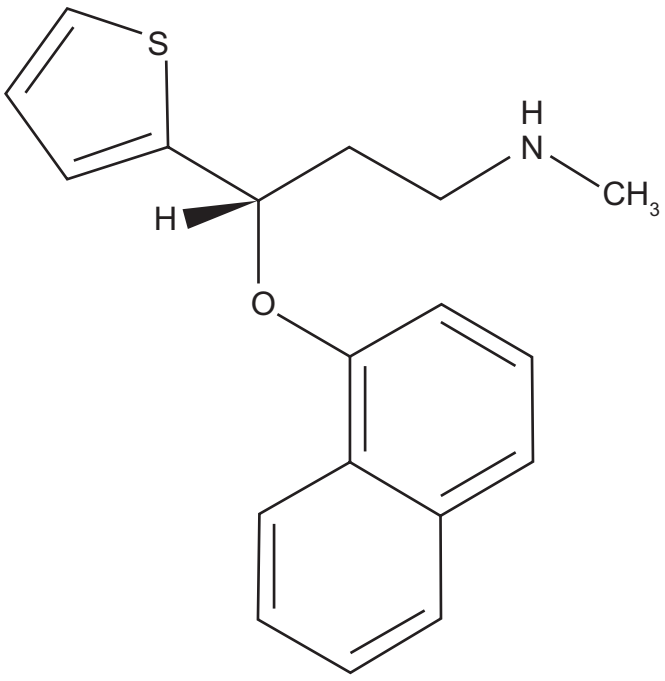

Figure 1. Chemical structure of duloxetine.

total ≥90% of duloxetine is bound to plasma protein[16] and it is 25% higher in the elderly and smokers show a decrease of 34% in the bioavailability.[16]

Clinically evident hepatic insufficiency yields decreased metabolism and elimination, so duloxetine should ordinarily not be administered to patients with any hepatic insufficiency. Duloxetine's half-life is about three times longer in cirrhotic patients. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, duloxetine should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.[17]

Pharmacodynamics

Duloxetine is extensively biotransformed by CYP 450 2D6 and 1A2 into numerous metabolites, including two inactive metabolites: 5-hydroxy-(major)-6-methoxy, duloxetine sulfate, and a 4-hydroxylated metabolite which is an inducer for CYP 450 1B and 1A.[18] Duloxetine is eliminated via hepatic CYP 2D6 and followed mainly renal metabolite excretion (~70%).[19] The oral clearance is 114 L/h (mean or total body) and an evening dose produces a 3-hour delay in absorption and 34% increase in clearance. Duloxetine's pharmacodynamics are inhibition of 5-HT > noradrenaline > dopamine.

Clinical Studies and Efficacy

General aspects

Pain can be produced spontaneously from damaged parts of nerves used to transmit pain information to the brain (called neuropathic pain).[20] On the other hand, nociceptive pain is defined as pain induced by an external (outside the nervous system) noxious stimulus to a structurally and functionally intact nervous system.[21] For some pain the origin is unclear as no damage to the nervous system or to the tissues to which the nerves connect can be identified. This article will focus on the two pain syndromes duloxetine is approved for: diabetic peripheral neuropathic pain and fibromyalgia.

Neuropathic pain

Neuropathic pain is reported in up to 3% of the general population and is characterized by continuous or intermittent spontaneous burning, aching or shooting pain.[4] It is most often associated with diabetic neuropathy, postherpetic neuralgia, spinal cord injury, trigeminal neuralgia as well as cancer-related pain to name the most common causes.[22] Neuropathic pain has a significant impact on quality of life.[23] Some patients suffering from neuropathic pain respond well to the treatment applied whereas others show no obvious response.[24] The incidence of neuropathic pain is growing, probably due to an increased number of older persons and diabetics, amongst whom about one in five develop painful neuropathy at some stage.[25]

Three approval multicenter, randomized, double-blind, placebo-controlled, parallel-group studies demonstrated efficacy of duloxetine in diabetic peripheral neuropathic pain (=DPNP), one of the most prevalent causes of neuropathic pain as mentioned before.[26] These studies enclosing 1139 patients were 12-week fixed-dose trials that examined Typ I and Typ II diabetics with painful diabetic neuropathy with a 6 months duration and at least moderate 24-hour pain severity.[27–29] All three trials excluded patients with major depressive disorder (MDD). Patients were randomized to treatment with 60 mg duloxetine QD (once daily), 120 mg duloxetine BID (twice daily) or placebo, the study performed by Goldstein et al also included a 20 mg treatment arm. However, the dose of 20 mg as part of a dose-response assessment was found to be ineffective in the management of DPNP.[30] Every study reported a significant ($p < 0.001$) improvement on the 24-hour average pain sore compared to placebo beginning at week 1 after randomization and continuing through the 12-week trial (see Fig. 2). In most secondary measures (including further pain questionnaires and data in quality of life) mean changes showed advantage of duloxetine over placebo, with no significant difference between 60 mg QD and 60 mg BDI.[30]

In the meantime, follow-up long-term data have been published. Raskin et al analysed duloxetine's efficacy in patients receiving 60 mg BID or 120 mg QD for 6 months and found both doses to provide clinically significant pain relief.[31] Wernicke et al compared duloxetine with routine care and found significant therapy-group differences in favor of duloxetine in the SF-36 physical component summary score, a self-rating quality of life scale.[32] The authors concluded that their results supported the use of duloxetine in the long-term management of DPNP.[32]

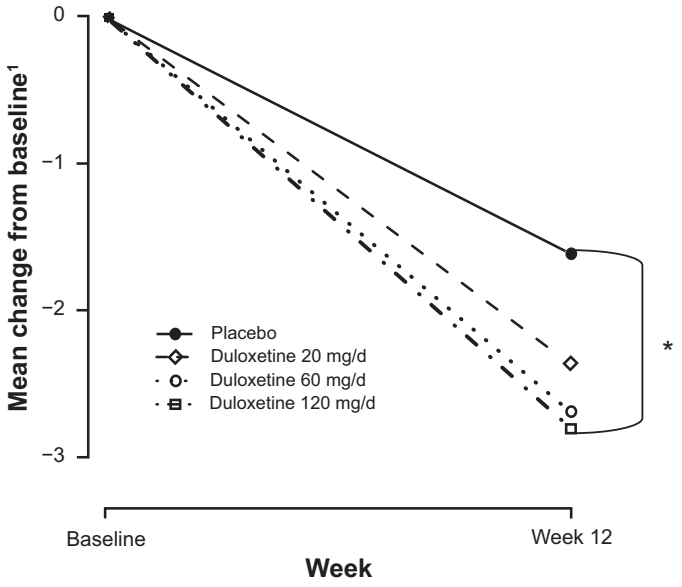

Figure 2. Pooled data from the 3 approval studies on duloxetine's efficacy in DPNP.[27–29]
¹Mean change in efficacy measured via the 24-h average pain score.
*Based on independent two sample t-tests all treatment groups differ highly significantly from placebo.

Only few direct head-to-head comparisons have been conducted comparing duloxetine to other approved or recommended drugs in the treatment of DPNP. In a meta-analysis Quilici et al examined duloxetine, pregabalin and gabapentin and found no statistically significant differences between duloxetine and gabapentin, but reported significant differences in the Patient Global Impression of Improvement/Change Scale favoring pregabalin and a significant difference in dizziness favoring duloxetine.[33] In a cost-utility comparison between desipramine, gabapentin, pregabalin and duloxetine performed by O'Connor et al desipramine and duloxetine were both more effective and less expensive than the other drugs.[34] In total, three studies have addressed cost effectiveness, two of which were performed by the company selling duloxetine somewhat questioning generalizability of the results.[35]

In recently published guidelines on the pharmacologic treatment of neuropathic pain by the European Federation of Neurological Societies Task Force tricyclic antidepressants, gabapentin, or pregabalin were recommended as first-line treatment of painful neuropathy, even though the efficacy of TCA's has not been clearly shown in large, well-controlled trials.[36] Dual-acting antidepressants, such as duloxetine, were recommended as second-line treatment based on their suggested modest efficacy.[36] But, in patients with cardiovascular conditions for which TCA's are contraindicated, duloxetine might be a more favorable treatment option given the beneficial cardiovascular safety profile.[36] Smith and Nicholson conclude their review on duloxetine in DPNP treatment stating that duloxetine consistently provides significantly more diabetic neuropathic pain relief than either placebo or routine care seen in pain measures as well as quality of life measures assessing the impact pain has on functioning.[37]

Fibromyalgia (FM)

Fibromyalgia is a controversial syndrome and is characterized by persistent widespread musculoskeletal pain, multiple tender points, abnormal pain sensitivity, and also symptoms such as fatigue, depressed mood, decreased volition, as well as sleep disturbance.[38] With a prevalence of around 2% in the general population, FM is ranked third most common diagnosis in rheumatology clinics.[39] The core diagnostic criteria of FM are defined as generalized pain that is both widespread and chronic, and include multiple tender points.[22] Dysfunction in pain perception is one of the proposed etiological factors in FM, even though the exact pathophysiological mechanism is still unknown.[40] TCA's have historically been the most widely used pharmacological treatment for FM. However, concern about potential side effects associated with TCA's has led to the prescription of modern antidepressants.[41] In June 2008, duloxetine became the second pharmacological treatment approved by the FDA in the USA for the management of FM besides pregabalin.

Duloxetine's approval in the treatment of fibromyalgia was based on two randomized, double-blind, placebo-controlled trials.[42,43] Arnold et al reported a 12-week trial with 354 female fibromyalgia patients with or without major depressive disorder treating patients with 60 mg QD, 60 mg BID or placebo.[42] The study's primary outcome was the Brief Pain Inventory (BPI) average pain severity score and response was defined as a ≥30% reduction in this score. Both duloxetine groups improved significantly more compared to placebo on the BPI average pain severity score ($p < 0.001$).[42] A significantly higher percentage of patients treated with duloxetine had a

decrease of ≥30% in this rating scale and the treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. The second approval study examined efficacy and safety in women and men suffering from fibromyalgia again with or without major depressive disorder for 6 months. 520 patients were enrolled and were randomly assigned to duloxetine 20 mg/60 mg/120 mg per day or placebo.[43] Outcome measures were the BPI average pain severity score and the Patient Global Impressions of Improvement (PGI-I) score. Patients treated with 60 mg as well as 120 mg duloxetine improved significantly more on both outcome measures at 3 and at 6 months and similar to the first study also found duloxetine efficacious in patients both with and without major depressive disorder[43] (Fig. 3).

Recently published studies report of a positive risk/benefit profile in the long-term treatment of fibromyalgia.[41] Mease et al presented results on the long-term efficacy of duloxetine in the treatment of fibromyalgia deriving from 6-month placebo-controlled extension phases of 2 randomized, double-blind, placebo-controlled clinical trials having 6-month placebo controlled phases.[41] In the first study all patients were treated with duloxetine 120 mg after 28 weeks

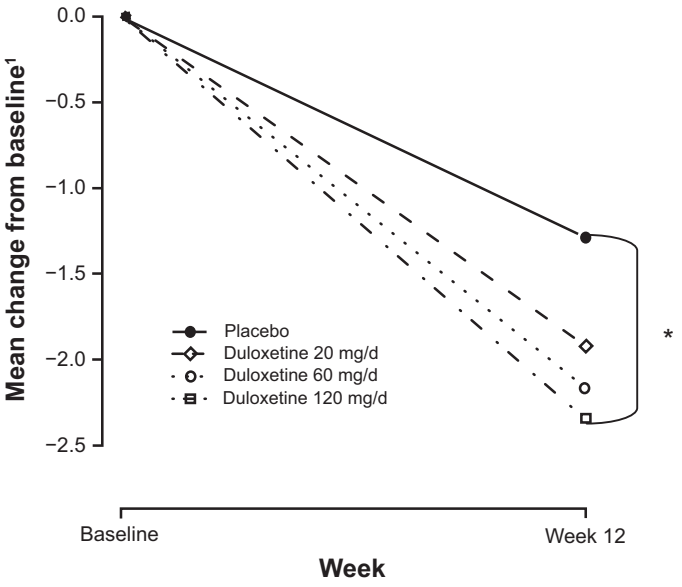

Figure 3. Pooled data from the 2 approval studies on duloxetine's efficacy in fibromyalgia.[42,43]
[1]Mean change in efficacy measured via the brief pain inventory.
*Based on independent two sample t-tests all treatment groups differ highly significantly from placebo.

on placebo or duloxetine 60 mg or 120 mg and in the second study patients taking placebo were titrated to duloxetine 60 mg after 27 weeks of treatment, while patients already receiving duloxetine remained on their dosages of 60 or 120 mg a day. The placebo/duloxetine groups in both studies showed significant improvement in the Brief Pain Inventory average pain severity score. In nearly all other efficacy and health outcome measures, including several quality of life measures, an improvement could also be observed.[41] Chappell et al conducted a phase 3, 60-week study, which included an 8-week open-label period followed by a 52-week, randomized, double-blind period enrolling 350 patients with moderate disease symptoms at study entry.[44] The authors examined a significant pain reduction in patients during the open-label study phase with continuing pain reduction during the 52-week study phase.[44]

Interestingly, a pilot study has recently been performed analysing the usefulness of quantitative electroencephalographic (QEEG) changes to predict response of duloxetine in patients suffering from fibromyalgia.[45] This was based on data deriving from depressed patients were QEEG theta-band cordances were found to be an especially powerful predictor of clinical outcome in MDD.[46] Findings of the pilot study by Hunter et al suggest that the QEEG cordance biomarker may predict duloxetine response of painful symptoms in fibromyalgia with larger and more comprehensive studies standing out.[45]

Other pain syndromes

Besides its application in DPNP and fibromyalgia duloxetine has also been examined off-label in several other pain states. One randomized, placebo-controlled trial reports on duloxetine in the treatment of patients with osteoarthritis knee pain.[47] Chappell et al examined 231 patients in a 13-week trial applying 60–120 mg of duloxetine versus placebo.[47] Duloxetine was found to be superior to placebo on the weekly mean 24-h pain scores beginning at week 1 and continuing throughout the treatment period ($p < 0.05$).

Skljarevski et al recently published one of the first double-blind, randomized trials of duloxetine versus placebo in the management of chronic low back pain.[48] 404 patients were examined over 13 weeks comparing duloxetine 20/60/120 mg once daily with placebo

finding duloxetine 60 mg superior to placebo from weeks 3–11 in relieving pain, but not at weeks 12–13.[48] Examining 30 patients >60 years old with comorbid major depressive disorder and chronic low back pain Karp et al found 28 patients to have a significant pain response.[49] There were furthermore significant improvements in mental health-related quality of life, anxiety, sleep quality, somatic complaints, and both self-efficacy for pain management and for coping with symptoms. But physical health-related quality of life, back pain-related disability, and self-efficacy for physical functioning did not improve.[49]

Duloxetine has also been analysed in a case series as a migraine preventive medication.[50] A retrospective chart review was performed using the electronic medical records of a headache specialty practice in Greensboro, North Carolina. From January 2004 to December 2006, 65 patients were prescribed duloxetine for migraine prevention for at least 2 months with doses ranging from 30 mg to 90 mg daily, however, finding duloxetine only minimally effective as a migraine preventive medication.[50] In another 8-week, open-label trial of duloxetine on comorbid depressive disorder and chronic headache, Volpe reports significant improvements in both headache and depression after the first week.[51] Volpe concludes from this preliminary open trial that duloxetine 60 mg is effective and fast acting for the treatment of comorbid major depressive disorder and chronic headache.[51]

Pain and depression

The association between depression and pain is somewhat blurred. However, in depressed patients it is a frequent feature to report somatic symptoms, including pain.[52,53] Conversely, depression often accompanies and complicates chronic pain states and is considered one of the most common comorbid conditions. It is believed that the dysregulation of neurotransmitters common in depression as well as pain mediation underlies both entities.[6]

Depression in pain patients

Symptoms of depression can emerge as a reaction to the chronicity of the painful condition, the disability associated with the permanently present pain, and the loss of perceived self-efficacy arising from the pain and disability.[54] The presence of comorbid depression in chronic pain patients can complicate the individual's course of the illness and adaptation. Patients with acute or chronic pain concurrently suffering from depressive symptoms tend to rate their pain severity higher than those without depression which is called "pain scale augmentation".[55] While the goal of treatment of chronic pain states may sometimes not entirely involve cure, efforts are directed at mitigating pain in quality and quantity, improving adaptive functioning and pursuit of activities of daily living as well as relationships.[56] As a result, it has become common practice to invoke the use of antidepressants as part of the treatment for several chronic pain disorders.

The efficacy of duloxetine in the treatment of depressive disorders has been established in several randomized, double-blind, placebo-controlled studies.[57–61] Compared with placebo, symptoms of depression as measured by the Hamilton Depression Scale (HAM-D) improved significantly with duloxetine, dose ranging from 40 mg to 120 mg/d. While improvement of depression is important, the objective of antidepressant treatment is symptom remission. For remission is considered to be the elimination of all signs and symptoms of the depressive syndrome as well as the restoration of occupational and psychosocial function to that of the asymptomatic state. Therefore, remission rates under pharmacological treatment are of high interest. In placebo controlled-studies the estimated probabilities of remission (HAM-D17 $\leq$ 7) with a duloxetine standard dose of 60 mg/d were 44%. This was almost three times the placebo rate.[58]

Pain in depressed patients

Depression consists of both emotional and physical symptoms. Physical symptoms of a major depressive disorder according to the DSM-IV criteria include fatigue, sleep and appetite disturbances. In addition, patients complain about somatic symptoms such as headaches, joint or abdominal pain. In fact, there is support for the notion that physical symptoms are often the heading complaints of major depressive disorder.[62,63] Bair et al reported the prevalence of pain in depression ranged from 15% to 100% with a mean of 65%.[64] In several studies the duloxetine treatment group experienced a significant improvement of painful physical symptoms compared to placebo, measured by the Visual Analogue Scale of pain-related complaints and the Somatic Symptom Inventory.[59,65] On the one hand,

the improvement of painful physical symptoms under duloxetine therapy might be due to the improvement of the depression itself. Further analysis, however, showed that duloxetine not only has an indirect impact on pain relief, but exerts a direct analgesic effect. Overall pain reduction is independent from an improvement in HAM-D score in approximately 50% of cases.[66]

First case reports state that duloxetine might be effective in the treatment of children with depression and pain symptoms without producing any major adverse effects.[67,68]

Safety and Tolerability

Data deriving from approval studies

Data of the approval studies in DPNP and fibromyalgia regarding safety and tolerability are similar to those of the depression approval trials. Most adverse events were mild or moderate. The top 10 treatment-emergent adverse events in the studies by Wernicke et al, Raskin et al, and Goldberg et al were nausea, dizziness, headache, constipation, fatigue, somnolence, diarrhea, nasopharyngitis, insomnia and increased sweating (Fig. 4).[27–29] Serious adverse events occurred with no significant treatment group differences (Table 1). Although patients treated with duloxetine showed changes in chemistry laboratory assessments, these changes were of low magnitude and not considered clinically relevant.[27–29] No significant treatment group differences in mean change of systolic and diastolic blood pressure could be observed, but a slight and significant increase in heart rate was found in the 60 mg BID duloxetine group compared to the 60 mg QD treatment group. Duloxetine did not prolong Qt interval and led to a slight but significant decrease in weight.[27–29]

The most frequently reported treatment-emergent adverse events of the approval studies on fibromyalgia are in agreement with those mentioned for DPNP. The studies by Arnold et al and Ruskin et al found nausea, dry mouth, constipation, diarrhea, somnolence, decreased appetite, nasopharyngitis, hyperhidriosis, anorexia, feeling jittery, and nervousness to be the top treatment-emergent adverse events (Fig. 5).[42,43] Again, no significant treatment group differences in the percentage of serious adverse events were observed (Table 2). Russell et al reported a mean change in weight of less than 1 kg for all the treatment groups, whereas Arnold et al found a slight but significant decrease in weight

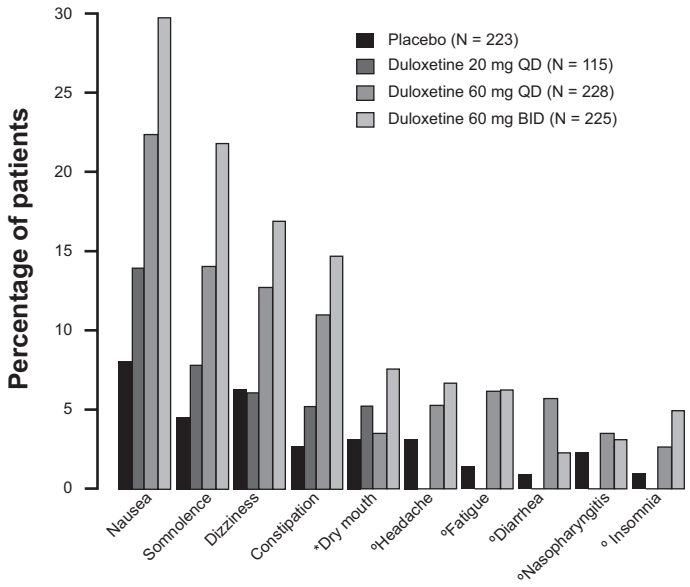

Figure 4. Pooled data from the 3 approval studies on duloxetine's safety in DPNP.
*Solely data of Goldstein et al available (reference 27); °Solely data of Wernicke et al available (reference 29).

from baseline to endpoint for both duloxetine groups compared to placebo.[42,43] The mean differences regarding laboratory results were within normal reference range and were not considered clinically relevant. No statistically significant treatment group differences occurred in mean change in the QTc interval or the incidence of treatment-emergent abnormal ECG values including heart rate, QTcB and QTcF. However, Arnold et al reported on a significant, but clinically not relevant difference of the systolic and diastolic blood pressure between the duloxetine 60 mg BID treatment group and placebo group ($p = 0.03$ for both measures), with a decrease in systolic and diastolic blood pressure for the placebo group, and an increase in systolic and diastolic blood pressure in the duloxetine 60 mg BID patient group.[42]

Data deriving from pooled trials and reviews

Smith et al evaluated three controlled trials as well as three long-term open label studies on duloxetine in DPNP finding 19.7% of the patients with study discontinuation.[37] Furthermore, a minor but statistically significant increase in blood glucose compared with placebo treated patients has been observed in controlled clinical trials.[37] Taken together, both controlled

Table 1. Serious adverse events (SAE) reported in DPNP approval studies.

Goldstein et al[27] [457 patients] 20 mg duloxetine QD: 115 patients 60 mg duloxetine QD: 114 patients	19 patients (4.2%) with at least 1 SAE[1] 1 patient with chest pain 1 patient with myocardial infarction
60 mg duloxetine BID: 113 patients	1 patient with hyperglycemia NOS 1 patient with myocardial infarction
Placebo: 115 patients	1 death due to accidental drowning 1 patient with chest pain 1 patient with hyperglycemia NOS
Raskin et al[28] [48 patients] 60 mg duloxetine QD: 116 patients	10 patients (2.9%) with 13 SAE 4 patients suffered: Atrial fibrillations Cholecystitis Diabetis mellitus Nephrolithiasis
60 mg duloxetine BID: 116 patients	2 patients suffered: urinary calculus ventricular extrasystoles
Placebo: 116 patients	4 patients suffered: Anemia Cerebrovascular accident Chest pain Chronic obstructive airways Dyspnea Melaena Pneumonia
Wernicke et al[29] [334 patients] 60 mg duloxetine QD: 114 patients	12 patients (3.6%) with SAE 5 patients suffered: Congestive Cardiac failure Coronary artery stenosis Hip fracture Prostate cancer Hypokalemia Hyponatremia
60 mg duloxetine BID: 112 patients	2 patients suffered: Blood calcium increase Concussion
Placebo: 108 patients	5 patients suffered: Atrioventricular block second degree Carcinoma Exacerbation of chronic obstructive Airways Diabetic ulcer Fatigue Hypertension

[1]Only SAE occurring in more than one patient were listed in the original publications.

and open-label clinical studies have demonstrated a high degree of safety and tolerability for the drug.

A Cochrane intervention review identified six double-blind randomised trials investigating the effects of duloxetine in chronic painful conditions with focus on DPNP.[35] Adverse events were very common in these trials, but were mild. Rates of any adverse event and adverse event leading to the discontinuation of the study were significantly greater with duloxetine than with placebo for the 60 mg and 120 mg doses. Withdrawals on the other hand were relatively few (all-doses-duloxetine 16.2% versus 8.7% for placebo).

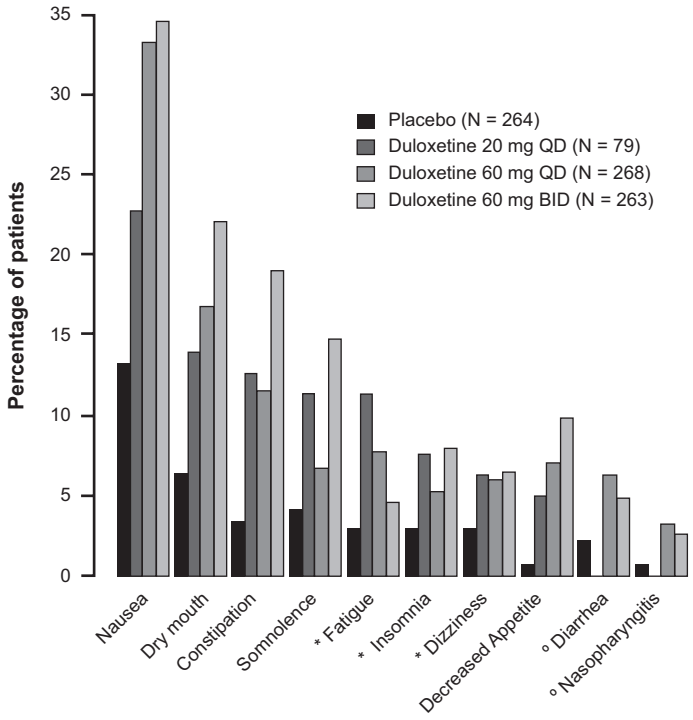

Figure 5. Pooled data from the 2 approval studies on duloxetine's safety in fibromyalgia.[42,43]
°Solely data of Arnold et al available (reference 42); *Solely data of Russel et al available (reference 43).

These numbers of events are in line with a retrospective analysis performed by Gahimer et al in 23,983 patients in duloxetine integrated exposure database.[69]

Choy et al pooled data from five clinical trials on the safety and tolerability of duloxetine in the short- as well as the long-term treatment on fibromyalgia.[70] The authors analysed data from four double-blind, randomized, placebo-controlled studies and a 1-year, open-label safety study. The most common treatment-emergent adverse events for the short-term treatment were nausea (29.3%), headache (20.0%), dry mouth (18.2%), insomnia (14.5%), fatigue (13.5%) constipation (14.5%), diarrhea (11.6%), and dizziness (11.0%) all occurring significantly more often compared to placebo ($p < 0.05$). Most of these treatment-emergent adverse events emerged early and were mild to moderate in severity. A similar adverse event profile was found for the long-term studies.[70] About 20% of patients discontinued due to adverse events. Serious adverse events were uncommon, and none of the serious adverse events occurred at a significantly higher frequency for duloxetine compared with placebo. Only mean changes could be observed regarding changes in vital signs and weight. In the 1-year study, 1% of the patients had suicide-related behavior. In conclusion, Choy et al stated that from 20 mg to 120 mg/day duloxetine demonstrated similar safety and tolerability in the treatment of fibromyalgia to that seen in other treatment indications. Most patients tolerated duloxetine without clinically meaningful effects.[70]

Conclusions and Place in Therapy

Duloxetine, a dual reuptake inhibitor, has been tested in randomised controlled trials treating two sorts of pain disorders: painful peripheral diabetic neuropathy and fibromyalgia. Duloxetine was found to be effective and safe in the management of these pain conditions and is approved for them. However, longer-term studies determining the durability of therapeutic response and overall tolerability, which are important issues due to the chronicity of pain disorders are warranted.[71] Also, studies indirectly comparing different

Table 2. Serious adverse events (SAE) reported in fibromyalgia approval studies.

Arnold et al[42] [354 patients]	
60 mg duloxetine QD: 118 patients	1 patient with blood creatine phosphokinase and hepatic enzyme increase
60 mg duloxetine BID: 116 patients	1 patient with appendicitis
Placebo: 120 patients	
Russell et al[43] [520 patients]	20 patients (3.8%) with at least 1 SAE[1]
20 mg duloxetine QD: 79 patients	
60 mg duloxetine QD: 150 patients	1 patient with asthma
120 mg duloxetine QD: 147 patients	1 patient with suicidal ideation
Placebo: 144 patients	1 patient with asthma
	1 patient with suicidal ideation

[1]Only SAE occurring in more than one patient were listed in the original publications.

medications may help elucidate the best medication for patients in chronic pain in term of overall risk and benefit profile. The treatment of chronic pain states should be comprehensible and should not be reduced to the core symptom pain. Especially in fibromyalgia or comorbid depression associated symptoms such as fatigue and insomnia should be relevant targets for pharmacotherapy and also psychotherapy.[71] Physical reconditioning is of benefit, and coping skills and level of functioning should be measured more intensely.

Duloxetine may provide a superior alternative to current therapeutic options in the treatment of chronic pain states. Fourteen trials using duloxetine to treat acute or chronic pain are in progress.[35] The encouraging results of duloxetine in the treatment of low back pain and ostheoarthritis as well as first treatment results in children with combined depression and pain syndromes promise additional fields of application. Since duloxetine is still a novel drug, long-term follow-up investigations and further research is needed.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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