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Topical review

Nontricyclic antidepressant analgesics and pain: Are serotonin norepinephrine reuptake inhibitors (SNRIs) any better?

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1. Introduction

Almost 50 years of clinical investigation has resulted in a large amount of literature regarding pain and antidepressants, one of the first categories of drugs found effective for chronic noncancer pain (CNCP) by randomized controlled trials (RCTs). These RCTs first examined tricyclic antidepressants (TCAs) based on published observational data and the rationale that their actions potentiated descending pain-inhibitory brainstem mechanisms involving serotonin and noradrenaline [5]. Attention turned to more selective antidepressants as they were developed because of limitations in efficacy and concern about adverse effects. These were initially the selective serotonin reuptake inhibitors (SSRIs) (fluoxetine and congeners) and the more noradrenergic agents (the tetracyclic antidepressant maprotiline and the TCAs nortriptyline and desipramine, which are the metabolites of amitriptyline and imipramine). The results of these investigations were generally disappointing regarding any superiority (except for nortriptyline) [54]. Recent pain treatment research has explored the dual serotonin noradrenaline reuptake inhibitor antidepressants (SNRIs), particularly venlafaxine, duloxetine, and milnacipran. Like the TCA amitriptyline, these have a more balanced effect on both serotonin and noradrenaline reuptake, but potentially have fewer adverse effects because of fewer receptor interactions. Recent RCTs have been primarily placebo-controlled trials of single agents, and there are few head-to-head trials comparing efficacy and side effects [54]. This review will focus on the SNRIs and RCTs in neuropathic pain (NP) and fibromyalgia (FM). There is a need to address whether these drugs represent an advance in efficacy and safety over older antidepressants and other analgesics. Of importance to the clinician are the following: (1) the clinical meaningfulness of the results of a reportedly positive RCT; (2) how antidepressants compare directly in head-to-head RCTs [54]; and (3) the role of indirect comparisons of SNRIs with each other and with other drugs (older TCAs, gabapentinoids, opioids, cannabinoids) using number needed to treat (NNT) and number needed to harm (NNH) as estimates of efficacy and tolerability [12]. Also critical for the practitioner is an appreciation of how generalizable RCT results are to clinical practice (external validity) [51] since patient populations seen in practice are more diverse than in RCTs. Finally, published guidelines for NP and FM, although not all agreeing as to the place of SNRIs, can be of some help in the choice of drug or drugs, but guidelines for NP may not be applicable to all painful conditions.

2. Mechanism of action

RCTs in NP have repeatedly and clearly demonstrated the separation of the analgesic and antidepressant effects [31,53]. The earliest concept of the mechanism of antidepressant analgesia was that this occurred via pain-inhibiting systems that descend from the brainstem onto the dorsal horn of the spinal cord [5]. In this early model, an endorphin-transmitting neural pathway from the periaqueductal gray area of the midbrain to the raphe nucleus lower in the brainstem was shown to make a serotonergic connection to the dorsal horn of the spinal cord. Another inhibitory system extends from the locus coeruleus in the lateral pons to the dorsal horn, which involves noradrenergic transmission. TCAs have several other putative actions [6,33,47]. Venlafaxine exerts more of a serotonergic effect at lower doses and has increasing noradrenergic activity with increasing doses [23]; it has a short half-life (5 hours) and is metabolized by cytochrome P450 isoenzymes to an active metabolite desvenlafaxine (t½: 11 hours) [29]. Duloxetine and milnacipran have a preferential noradrenergic action and a longer half-life (12 and 8 hours, respectively) and are without active metabolites [29].

Understanding the mechanisms of the action of antidepressants is important clinically because all of these drugs have a moderate effect at best and are often accompanied by adverse effects that limit dosing and therapy. Combinations of an antidepressant with drugs such as gabapentinoids acting on the alpha-2-delta subunit of the calcium channel [18] or with opioids [28] or, potentially, cannabinoids, may be required, with the hope of an additive or even synergistic effect on pain and without interacting side effects due to different mechanisms being recruited [19].

3. Literature review (complete methodology available on request from CPNW)

A search for high-quality RCTs, systematic reviews, and guidelines was carried out by the authors using PubMed, Medline, and

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the Cochrane Database of systematic reviews. The Food and Drug Administration website, www.fda.gov, was searched for unpublished trials. The main focus was on trials with adults, published in English, up to 2011. RCTs were evaluated according to quality [25].

4. Published randomized controlled trials

4.1. Venlafaxine

Eight RCTs of venlafaxine were found, of which 7 reported positive pain-relieving effects. Venlafaxine has shown an effect in reducing several aspects of human experimental pain [15,58]. Venlafaxine was equal to gabapentin at reducing acute postoperative pain analgesic requirements and superior at reducing postmastectomy pain [1]. No significant effect from venlafaxine was noted on NP in breast cancer [49]. Venlafaxine was superior to placebo in an RCT in painful diabetic neuropathy (PDN) with an NNT for 50% + relief of 4.5 [40]. Both venlafaxine and imipramine relieved painful neuropathy vs placebo, with no significant difference overall between the 2 drugs, but a lower NNT for 50% relief or better for imipramine than venlafaxine (2.7 vs 5.2) [43]. Venlafaxine has also been shown to prevent migraine [36] and tension-type headache [59]. Regarding potential adverse effects, venlafaxine blocks neuronal reuptake of 5-HT and noradrenaline, but is relatively free of muscarinic cholinergic, histaminic, and alpha-adrenergic receptor effects. It has less potential for drug interactions than TCAs, although serotonin syndrome has been reported in cases of coadministration with SSRIs [21]. However, venlafaxine may increase hypertensive problems, exacerbate existing seizure disorders, and trigger mania. More common complaints include nausea, asthenia, sweating, anorexia, somnolence, dizziness, and dry mouth. For venlafaxine, the number needed to quit for major harm and withdrawal from a study was reported as 16.2 in NP [42].

4.2. Duloxetine

Of 12 identified RCTs of duloxetine, 10 reported positive pain-relieving effects. These were in knee osteoarthritis [9], FM [2,3,8,41], PDN [20,27,38,56], and low back pain [45]. Negative RCTs were in low back pain [46] and in pain from spinal cord injury and stroke [50]. A direct comparison of duloxetine and amitriptyline found no difference between these drugs in PDN [27].

A pooled review of 3 RCTs of duloxetine in PDN [26] found NNTs for 50% or more of 5.3 and 5.7 for 60 mg/d and 120 mg/d, respec-

Table 1
Number needed to treat (NNT) data for at least 50% relief in some neuropathic pain conditions. Caution should be used in interpreting these figures as they involve studies of differing experimental designs, numbers of patients and data analyses.

Drug	PHN	PDN	PN, NP	Central pain	FM	Comments
TCAs						
Collins et al. 2000 [11]	2.1	3.5				Review
Sindrup and Jensen 2000 [44]			2.6 (PN)			Review
Saarto and Wiffen 2010 [42]	2.7	1.3	3.6 (NP)			Review
Finnerup et al. 2010 [16]	2.8		2.1 (PN)	2.7		Review
Imipramine						
Sindrup et al. 2003 [43]			2.7 (PN)			RCT
Saarto and Wiffen 2010 [42]			2.2 (NP)			Review
SSRIs						
Sindrup and Jensen 2000 [44]			6.7 (PN)			Review
Finnerup et al. 2010 [16]			6.8 (PN)			Review
SNRIs (venlafaxine, duloxetine)						
Finnerup et al. 2010 [16]			5.0			Review
Venlafaxine						
Sindrup et al. 2003 [43]			5.2 (PN)			RCT
Rowbotham et al. 2004 [40]		4.5				RCT
Saarto and Wiffen 2010 [42]			3.1 (NP)			Review
Duloxetine						
Kajdasz et al. 2007 [26]						
60 mg/d		5.3				Review
120 mg/d		5.7				
Sultan et al. 2008 [48]						Review
60 mg/d		5.8			5.8	
120 mg/d		5.7			5.7	
Lunn et al. 2009 [30]						Review
60 mg/d		6			8	
Gabapentin						
Sindrup and Jensen 2000 [44]			4.1 (PN)			Review
Rice et al. 2001 [39]	5.0					RCT
Finnerup et al. 2010 [16]	4.3		6.4 (NP)			Review
Pregabalin						
Finnerup et al. 2010 [16]	4.2		4.5 (PN)	5.6		Review
Oxycodone						
Watson and Babul 1998 [52]	2.5					RCT
Watson et al. 2003 [55]		2.6				RCT
Tramadol						
Harati et al. 1998 [22]	4.3					RCT
Sindrup and Jensen 2000 [44]			3.4 (PN)			Review
Finnerup et al. 2010 [16]	4.8		4.9 (NP)			Review

FM = fibromyalgia, PDN = painful diabetic neuropathy, PHN = postherpetic neuralgia, NP = neuropathic pain, PN=painful neuropathy, RCT = randomized controlled trial, TCA = tricyclic antidepressants.

tively. A systematic review of duloxetine in 6 RCTs (total of 1696 patients) – 3 in PDN and 3 in FM – concluded that it is equally effective for the 2 conditions [48], with NNT of 6 for 50% relief, NNH (adverse events) of 15, and a number needed to quit for lack of efficacy of 20. Another systematic review of RCTs of duloxetine concluded that there was moderately strong evidence for PDN and FM [30], with a 16% dropout rate. An NNT of 8 for 50% relief was noted for duloxetine in FM and 6 for PDN [30].

Regarding potential adverse effects, duloxetine is a potent SNRI with a generally similar side effect profile to venlafaxine, including nausea, hypertension, somnolence, dizziness, and dry mouth. Abrupt discontinuation emergent adverse events were reported in 6 short-term RCTs in major depression [37]; these adverse effects were reported in 44.3% (vs 22.9% placebo), with most described as mild to moderate in severity. Gradual withdrawal was recommended [37]. SNRIs with shorter half-lives (ie, venlafaxine and duloxetine) appear to present a greater risk of withdrawal symptoms. Serious withdrawal symptoms may include: agitation, anorexia, anxiety, confusion, impaired coordination, diarrhea, dizziness, dysphoric mood, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, and sensory disturbances (including shock-like electrical sensations). Combined NNH values for adverse effect dropouts for duloxetine and venlafaxine in NP were 13.1 [16], for duloxetine in PDN 17.5 (60 mg/d) and 8.8 (120 mg/d) [26].

4.3. Milnacipran

Of 4 RCTs of milnacipran in FM, all produced pain reductions [7,10,17,32]. Three of these RCTs used a composite responder primary outcome defined as at least 30% improvement. The value for 30% + improvement varied from 38.6–51% for 200 mg/d vs 27.9–32.9% for placebo. A moderate effect size of 0.5 was reported (0.48 pain diary, 0.52 visual analogue scale) [17]. Adverse effect dropouts for 200 mg/d ranged from 7.4% to 14.2% over placebo (3.6–19.6%). No comparative head-to-head RCTs or NNT/NNH figures are available for this drug. Milnacipran is the most recent SNRI approved in the United States for the treatment of FM. Unlike venlafaxine and duloxetine, milnacipran is not metabolized by hepatic cytochrome P450 enzymes, but is conjugated to the inactive glucuronide and renally excreted. Milnacipran appears to be generally well tolerated, with early nausea, headache, palpitations, hypertension, and hyperhidrosis occurring in $\geqslant$5%, and more than placebo [24].

4.4. Systematic reviews, meta-analyses, and treatment guidelines

Guidelines for the treatment of NP from Canada [34], the European Federation of Neurological Sciences Task Force [4], and the International Association for the Study of Pain (IASP) NeuP Special Interest Group (NeuP-SIG) [14] are in reasonable concordance and suggest TCAs as a first-choice treatment option along with gabapentinoids for postherpetic neuralgia, painful neuropathies, and central pain. The IASP NeuP-SIG [14] recommends SNRIs as first choices; European Federation of Neurological Sciences guidelines recommend SNRIs as a first choice for painful diabetic polyneuropathies [4], while Canadian guidelines rank SNRIs as a second-level choice. A comparison of the 3 guidelines [35] and an update of the IASP NeuP-SIG guidelines are now available [13], and these con-

Table 2
Number-needed-to-harm (NNH) data for drugs in some pain disorders. Caution should be used in interpreting these figures as they involve studies of differing experimental designs, numbers of patients and data analyses. NNQ is the number needed to quit for major harm and withdrawal from a study.

Drug	PHN	PDN	PHN + PDN	NP	FM	Comments
Minor harm (NNH)						
Antidepressants						
Collins et al. 2000 [11]						Review
all antidepressants			2.7			
tricyclics			3.2			
Sultan et al. 2008 [48]						Review
duloxetine		6.7			6.7	
Saarto and Wiffen 2010 [42]						Review
amitriptyline				6		
venlafaxine				9		
Anticonvulsants						
Wiffen et al. 2001 [57]						Review
carbamazepine				3.7		
gabapentin			2.5			
phenytoin				3.2		
Collins et al. 2001 [11]						Review
all anticonvulsants			2.7			
gabapentin			2.6			
Major harm (NNQ)						
Antidepressants						
Collins et al. 2000 [11]						Review
all			17.0			
tricyclics			14.0			
Kajdasz et al. 2007 [26]						Review
duloxetine		17.5 (60 mg/d) 8.8 (120 mg/d)				
Finnerup et al. 2010 [16]						Review combined NNH 15.9
tricyclics						
Sultan et al. 2008 [48]		15				Review
Saarto and Wiffen 2010 [42]						Review
amitriptyline				28		
venlafaxine				16		
Finnerup et al. 2010 [16]						Review combined NNH 13.1
SNRIs (venlafaxine, duloxetine)						

FM=fibromyalgia, PDN=painful diabetic neuropathy, PHN= postherpetic neuralgia, NP=neuropathic pain, PN=painful neuropathy, RCT= randomized controlled trial, TCA= tricyclic antidepressants.

tinue to suggest SNRIs as a first choice for these conditions. Finnerup et al. [16], in an updated review that considered NNT and NNH values, concluded that despite an increase of 66% in RCTs since their 2005 article, there was no reason to change their previous algorithm for NP, which documented superior NNTs for TCAs compared with SNRIs and SSRIs. A meta-analysis of antidepressants in FM identified a small effect size for pain reduction for SNRIs (duloxetine, milnacipran) and a large effect size for TCAs [24]. In light of more favourable efficacy results for TCAs, consistent placement of SNRIs as a first-line therapy could be due, in part, to apparently better tolerability profiles. Many of the TCA RCTs were performed many years ago and are of crossover design, which can produce different NNT values from parallel studies if not analyzed as intent to treat.

4.5. Future research directions

Further study of SNRIs is needed to evaluate their efficacy in other CNCP conditions, as well as SNRIs other than venlafaxine, duloxetine, and milnacipran. As for other analgesics for chronic pain, there is a striking lack of comparative effectiveness research such as head-to-head RCTs for SNRIs in CNCP [54]. Comparative studies are currently not required for drug approval by the Food and Drug Administration and therefore, clinical decisions must rely on placebo-controlled RCTs, which may lack measures of clinical meaningfulness. Thus, the relative lack of comparative data is a pragmatic and economic challenge for the clinician in making best therapeutic choices. More comparative studies are needed regarding SNRIs vs TCAs, and to determine how they compare with other agents such as gabapentin, pregabalin, opioids, and other treatments. A greater issue is the failure to find evidence that SNRIs, SSRIs, gabapentinoids (gabapentin, pregabalin), and cannabinoids provide superior or even noninferior or equivalent relief with fewer adverse effects than the older drug categories of TCAs and opioids.

4.6. Conclusions

Based on published evidence, multiple good-quality RCTs support the efficacy of SNRIs in certain chronic pain conditions, namely NP and FM and, in the case of duloxetine, chronic low back pain.

What are we to conclude about the relative efficacy and tolerability of the SNRIs as compared with other antidepressants and other analgesics? Consideration of a small number of head-to-head RCTs as well as NNT and NNH figures for venlafaxine and duloxetine (summarized in Tables 1 and 2) suggests trends toward less efficacy and better tolerability than older TCAs. However, small numbers of comparative trials and limitations in comparing NNT/NNH values across treatments diminish our confidence in making this assertion. Considering efficacy results from head-to-head RCTs and NNT figures, one might argue for the placement of SNRIs as second-line drugs for chronic pain. However, promotion of these agents to the first-line rung might be reasonable if overall safety benefits vs TCAs were more clearly demonstrated. It is hoped that future comparative RCTs will serve to better delineate the optimal role of newer SNRIs for pain relief.

Conflict of interest statement

Drs. Watson, Sawynok and Lynch report no current or recent conflicts of interest. Dr. Ian Gilron has consulted for Johnson & Johnson, Astra Zeneca, Pfizer, Eli Lilly and Wex Pharmaceuticals and has received Grant/Research Support from Apotex, Ethypharm, Novopharm, and Pfizer.

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