

A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain

C Peter N Watson MD FRCPC¹, Ian Gilron MD FRCPC², Jana Sawynok PhD³

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BACKGROUND: Neuropathic pain (NP) encompasses many difficult-to-treat disorders. There are few head-to-head, comparative, randomized controlled trials (RCTs) of drugs for NP in different analgesic categories, or of different drugs within a category, despite many placebo-controlled RCTs for individual agents. Well-designed head-to-head comparative trials are an effective way to determine the relative efficacy and safety of a new drug.

OBJECTIVE: To perform a systematic review of head-to-head RCTs of oral analgesics in NP.

METHODS: A systematic review of RCTs involving NP patients was performed, of which head-to-head comparative trials were selected. Reference lists from published systematic reviews were searched. These studies were rated according to the Jadad scale for quality.

RESULTS AND CONCLUSIONS: Twenty-seven such trials were identified. Seventeen were comparisons of different analgesics, and 10 were of different drugs within an analgesic class. Important information was obtained about the relative efficacy and safety of drugs in different categories and within a category. Some significant differences between active treatments were reported. Trial inadequacies were identified. More and improved head-to-head RCTs are needed to inform clinical choices.

Key Words: *Head-to-head trials; Neuropathic pain; Randomized controlled trials; Systematic review*

Revue systématique qualitative des essais randomisés contrôlés comparant directement des analgésiques oraux dans la douleur neuropathique

HISTORIQUE : La douleur neuropathique (DN) englobe de nombreuses entités difficiles à traiter. Peu d'essais randomisés et contrôlés (ERC) ont comparé directement des analgésiques de différentes catégories ou d'une même catégorie dans la DN, malgré l'existence de nombreux ERC avec témoins sous placebo ayant porté sur certains agents individuels. Les essais de comparaison directe bien conçus permettent de déterminer clairement l'efficacité et l'innocuité relatives d'un nouveau médicament.

OBJECTIF : Réaliser une revue systématique des ERC de comparaison directe entre des analgésiques oraux dans la DN.

MÉTHODE : Les auteurs ont procédé à une revue systématique des ERC ayant regroupé des patients souffrant de DN et ont recensé les essais de comparaison directe. Ils ont aussi consulté les listes bibliographiques des revues systématiques publiées et ont classé les études selon l'échelle de qualité Jadad.

RÉSULTATS ET CONCLUSIONS : Les auteurs ont ainsi relevé 27 essais dont dix-sept comparaient des analgésiques différents et dix comparaient divers agents d'une même classe d'analgésiques. Ils en ont tiré une information importante sur l'efficacité et l'innocuité relatives des médicaments d'une même catégorie ou de catégories différentes. Certaines distinctions significatives entre les traitements actifs ont été observées. On a relevé des lacunes dans les essais. Pour faire des choix cliniques éclairés, il faudra procéder à d'autres ERC de comparaison directe plus rigoureusement conçus.

"Food and Drug Administration (FDA) regulations should require that new drugs be compared not just with placebos but with old drugs for the same conditions. Approval would depend on whether the new drug adds something useful in terms of greater effects, greater safety, fewer side effects or substantially greater convenience...If I could choose only one of the reforms I am suggesting it would be this one. There is an ethical issue here too. It is wrong to compare a new drug with a placebo if there is an effective drug already on the market." (Marcia Angell [1])

"Interpretation of the results of trials of treatments for neuropathic pain would be greatly facilitated by the inclusion of active comparators with well established efficacy." (Katz et al [2])

Head-to-head randomized controlled trials (RCTs) are critical in all areas of clinical medicine (1), and neuropathic pain

(NP) is no exception (2). NP has been defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (3). (An amended definition of NP has been proposed recently [4] but has not been accepted by the International Association for the Study of Pain.) When the lesion or dysfunction occurs in the peripheral nervous system, it is termed peripheral NP (PNP); when it occurs in the central nervous system, it is termed central pain. Central pain disorders may occur after stroke, spinal cord injury, traumatic brain injury, multiple sclerosis and syringomyelia. There are many PNP disorders (Table 1 and Figure 1 [5]). Most clinical research on drugs useful for NP has been performed in patients with post-herpetic neuralgia and painful diabetic neuropathy, but it is reasonable that a similar treatment approach may be applied to patients with other PNP disorders (except trigeminal neuralgia, which is a different and unique form of NP) and central disorders based on putative common mechanisms. Clinical experience indicates that some conditions, such as central pain and lumbar radiculopathies (the most common form of PNP)

¹University of Toronto, Toronto; ²Queen's University, Kingston, Ontario; ³Dalhousie University, Halifax, Nova Scotia
Correspondence and reprints: Dr C Peter N Watson, 1 Sir Williams Lane, Toronto, Ontario M9A 1T8. Telephone 416-239-3494, fax 416-239-6365, e-mail peter.watson@utoronto.ca

TABLE 1
Categories of peripheral and central neuropathic pain

Peripheral
Osteoarthritis/disc disease with nerve root pain (usually C5 and C6, and L5 and S1)
Postherpetic neuralgia (may have a central component)
Painful neuropathies (diabetes, alcohol/nutritional, HIV, etc)
Cancer-associated neuropathic pain
Phantom limb pain
Nerve trauma (causalgia)
Incisional neuralgias (post-thoracotomy, postmastectomy, etc)
Brachial plexus avulsion (likely a central component)
Neuropathic facial pain exclusive of trigeminal neuralgia
Trigeminal neuralgia*, glossopharyngeal neuralgia
Central
Central poststroke pain
Spinal cord injury pain
Traumatic brain injury
Multiple sclerosis
Syringomyelia

*Trigeminal neuralgia is a unique and common form of neuropathic pain with a differing medical and surgical approach from other forms of neuropathic pain (except the rare condition of glossopharyngeal neuralgia)

(Figure 1), are generally less responsive than others. Some peripherally generated problems can have a central component (postherpetic neuralgia and brachial plexus avulsion) and central sensitization may occur with other PNP disorders, making the distinction between peripheral and central pain states less clear. NP has different qualities, often in the same patient. Steady – often burning – pain, shock-like jabbing pain and pain from touch (allodynia) may all occur, indicating possible different pain mechanisms for such qualities and supporting a mechanism-based approach (6).

Thirty years ago, there was little science behind the few drugs used for NP conditions. Amitriptyline, phenothiazines and the combination of amitriptyline and fluphenazine were widely used based on uncontrolled and observational studies (7-10). With the evolution of trial methodology and clinical research, current data suggest that the major categories of drugs shown to be useful for NP by RCTs are antidepressants, anti-convulsants, opioids and the emerging field of cannabinoids. There are many such studies in NP (11); most are RCTs that show a moderate effect of a drug compared with placebo. The utility of these drugs in clinical practice based on these RCTs – that is, the external validity or generalizability of these findings – has been a neglected issue until recently (12). Thus, most RCTs do not provide measures of clinical meaningfulness, such as effect size, number needed to treat (NNT) (13) and number needed to harm (NNH), which makes comparisons between specific agents difficult (12). NNT and NNH values have been generated for some of these RCTs by others (11).

Since the first head-to-head RCT discussed here (published 20 years ago) (14), there have been few subsequent trials of this nature in NP comparing drugs in different analgesic classes or different drugs within an analgesic class. A recent review regarding algorithm development (11) identified only 13 head-to-head RCTs of 105 NP RCTs, but provided useful comparative data in their absence in the form of NNT and NNH values (Table 2). The advantage of head-to-head RCTs in NP is that they enable the clinician, struggling with the problem of the

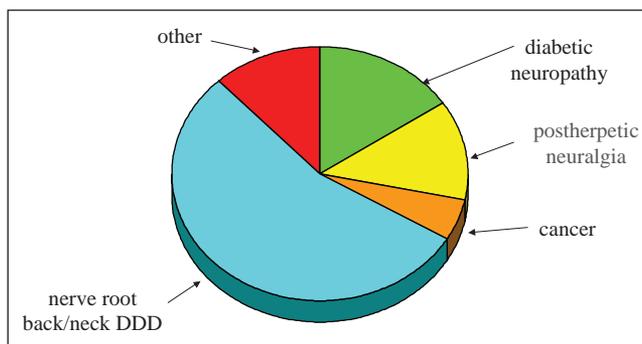


Figure 1 Prevalence of some forms of peripheral neuropathic pain. DDD Degenerative disc disease. Adapted from Irving (5)

TABLE 2
Number needed to treat for neuropathic pain randomized controlled trials of tricyclic antidepressants, selective serotonin/norepinephrine reuptake inhibitors (SNRIs), opioids, gabapentinoids and cannabinoids

Drug	Postherpetic neuralgia	Diabetic neuropathy	Other neuropathic pain
All tricyclics	2.3, 2.3, 2.1	3.0, 2.4, 3.4	2–5
Venlafaxine	4.5		5.2
Imipramine			2.7
Duloxetine		5.0, 4.1	
Gabapentin	3.2, 5.0	3.7	5.1, 3.8
Pregabalin	3.4		4.2
Oxycodone	2.5	2.6	
Cannabinoids			3.5, 3.7 for multiple sclerosis-related neuropathic pain
Tramadol	4.76	4.3	3.9

Data from reference 11

most appropriate drug selection, to know whether a new drug is equal to, noninferior to or better than a standard therapy (such as a tricyclic antidepressant [TCA]) and whether there are differences in adverse effects. The only other way to determine relative efficacy and safety is to compare measures such as NNT and NNH data from placebo-controlled trials. However, these measures usually compare studies with differences in experimental design, number of subjects, trial duration, inclusion criteria, pain intensity, outcome measures and data analyses; consequently, they can only be, at best, an approximate comparative measure.

Head-to-head trials may also reveal data about pain mechanisms, in that one drug may work in a particular subgroup. For example, it is possible that one of the drugs compared may relieve predominantly burning pain, electric shock-like pain or allodynia, revealing a mechanism-based difference in drug responsiveness (6). Therapeutically, this may be valuable in indicating drugs for combination therapy targeting different pain mechanisms. Further subgroups, such as age, sex, race and diagnostic categories, may also reveal differences between drugs.

The purpose of the present article is to review the data obtained from head-to-head RCTs of oral pharmacotherapeutic agents in chronic noncancer NP to determine whether there is clear evidence for drug selection choices.

METHODS

A qualitative systematic review of head-to-head RCTs was performed by the primary author (CPNW) using the following terms: (pain OR painful OR analgesia OR nociceptive OR antinociceptive OR antinociception) AND (neuropathic OR neuropathy OR neuralgia OR nerve OR radiculopathy OR radicular OR sciatica OR polyneuropathy) AND (Randomized Controlled Trial) searching PubMed, Medline and the Cochrane Databases for RCTs and systematic reviews of oral analgesics (antidepressants, anticonvulsants, opioids and cannabinoids) in chronic noncancer NP of three months duration or longer. The main focus was on trials in adults published in English from 1966 to 2009. In addition, the reference lists of retrieved articles and the FDA website (www.fda.gov) were searched.

Trials were evaluated according to the quality criteria of Jadad et al (15). To be included, trials were required to score at least 3/5 on this rating scale to ensure a standard of quality; this required randomization and double-blinded conditions, with a control group and accounting for withdrawals. A maximum score of 5 additionally indicated that the RCT described methods of blinding and randomization. Measures were sought in each trial, such as effect size, percentage of patients with 50% or greater improvement, NNT, NNH and number needed to quit (NNQ), as a means of determining clinical meaningfulness. The search excluded non-English publications, trials that compared topical agents, intravenous studies, acute NP conditions, NP with cancer, and the NP conditions of trigeminal neuralgia and complex regional pain syndrome.

RESULTS

General

Table 3 lists excluded trials (n=10) (16-25) and summarizes reasons for their exclusion. The included RCTs are presented in Tables 4 and 5. Twenty-seven such trials were identified. Table 4 documents 17 head-to-head trials of different analgesics in NP (14,26-41). Table 5 lists 10 comparative trials involving different drugs within an analgesic class (42-51). Of this latter group, all were comparisons of antidepressants. Nineteen of the 27 trials (70%) were conducted in postherpetic neuralgia, painful diabetic neuropathy or a combination of both conditions. The minimum duration of pain in the trials was three months in all except two trials (28,37).

Twenty-one trials were of a crossover design (14,27,29,31-33,35-39,41-50) and six were of a parallel design (26,28,30,34,40,51). The median number of patients in the crossover trials was 37 (range 11 to 96) and the number of patients in each of the six parallel trials was n=49 (30), n=76 (34), n=145 (28), n=246 (26), n=338 (40) and n=47 (51). All except one (26) were nonindustry-sponsored trials. None of these comparative trials showed a newer drug (gabapentin, n=6; pregabalin, n=1; venlafaxine, n=2; and lamotrigine, n=1) to be superior in relieving pain to the older active comparator. Some measure of clinical meaningfulness was available from 18 trials, but NNT figures were only reported in three trials (32,39,50). Quality of life was not an outcome measure in many of these RCTs, but was included in a few studies (26,27,31-33,35,38,41). Nineteen trials included a placebo control (14,26-28,30-33,35,36,39-46,48,50).

TABLE 3
Excluded comparative head-to-head randomized controlled trials

Study	Reason for exclusion
Watson and Evans, 1985 (16); amitriptyline versus zimeclidine in postherpetic neuralgia	Nonblinded, nonrandomized
Gomez-Perez et al, 1985 (17); nortriptyline and fluphenazine in diabetic neuropathy	Not head-to-head, used combination of nortriptyline/fluphenazine versus placebo
Ventafriidda et al, 1988 (18); trazodone versus amitriptyline in deafferentation pain	NP with cancer
Harke et al, 2001 (19); carbamazepine versus morphine in NP pretreated with spinal stimulation	Series of two placebo-controlled trials (carbamazepine versus placebo and morphine versus placebo), possible order effect (population in phase 2 not same as phase 1)
Pandey et al, 2005 (20); gabapentin versus carbamazepine in Guillain-Barré syndrome	Acute pain, likely both inflammatory and neuropathic
Galer et al, 2005 (21); morphine versus morphine/dextromethorphan in chronic noncancer non-NP	Non-NP
Lynch et al, 2005 (22); amitriptyline versus ketamine in NP syndromes	Topical preparations
Keskinbora et al, 2007 (23); gabapentin versus opioids in neuropathic cancer pain	Neuropathic cancer pain
Rowbotham et al, 1991 (24); lidocaine versus morphine in postherpetic neuralgia	Intravenous study, short term
Kok-Yuen et al, 2008 (25); topical amitriptyline versus lidocaine in NP	Topical preparations

NP Neuropathic pain

Comparative trials of different analgesics for NP

Comparative trials of different analgesics for NP are summarized in Table 4. Most of the 17 comparative trials of different analgesics for NP compared a potential analgesic drug with a TCA, except for the comparisons of venlafaxine with gabapentin (31), gabapentin with morphine (33), nabilone with dihydrocodeine (38), morphine with mexiletine (39) and gabapentin with oxycodone (40).

The 1999 diabetic neuropathy study by Morello et al (29) comparing gabapentin with amitriptyline found no significant difference (NSD) in either pain relief or side effects between drugs. This study has been criticized because of the low dose of gabapentin used compared with the placebo-controlled trials in postherpetic neuralgia and painful diabetic neuropathy (52), and also the lack of placebo control. However, the degree of pain relief achieved (52% with gabapentin and 67% with amitriptyline) suggests that the statistically equal effect did not mean that both drugs were ineffective.

Results from an industry-sponsored trial comparing amitriptyline with pregabalin have been posted on the FDA website (26); however, complete details of this trial are not available for review. This unpublished Pfizer Protocol 1008-040 (www.accessdata.fda.gov/scripts/cder/drugsatfda) (26) apparently studied painful diabetic neuropathy and compared placebo, amitriptyline 75 mg and pregabalin 600 mg in a parallel design. An FDA review found that both drugs produced a 2.8-point reduction in pain intensity (versus 1.8 with placebo), but

TABLE 4
Comparative trials of different potential analgesics in neuropathic pain (n=17)

Study, condition, duration of pain	Jadad score	Drugs, daily dose	Completed/ randomized, n	Effect, yes/no	Comment	Clinical meaningfulness and quality of life
Max et al, 1988 (14), postherpetic neuralgia, 19 months (mean)	3	AT mean 65 mg/day, range 12.5–150 mg/day; lorazepam range 0.5–6 mg/day; placebo (lactose)	41/58	Yes (SSD) (AT); no (lorazepam)	Crossover design; AT effective but not as an antidepressant; lorazepam ineffective	47% moderate or greater relief with AT versus 15% with lorazepam and 16% with placebo
Leijon and Boivie, 1989 (27), central poststroke pain, 54 months or longer	4	AT 75 mg; CBZ 200–800 mg/day; placebo	14/15	Yes (SSD) (AT); no (NST) (CBZ)	Crossover – 3 phase; no AT antidepressant effect; CBZ not effective	67% improved on AT versus 36% with CBZ; NNQ = 0
Kieburtz et al, 1998 (28), HIV neuropathy, 2 weeks or longer	4	AT 25–100 mg/day; mexiletine 150–300 mg/day; active placebo	126/145 (total); 39 (AT); 44 (mexiletine); 43 (placebo)	No effect of any drug	Parallel design; no effect of either drug; pain durations as short as 2 weeks and mild pain all the time accepted for inclusion may have impacted result	A negative trial
Morello et al, 1999 (29), diabetic neuropathy, 3 months	4	AT mean 59 mg; GP mean 1565 mg	19/25 (AT); 19/25 (GP)	Yes (AT); yes (GP)	Crossover design; NSD between drugs in efficacy or adverse effects except weight gain with AT and different side effect profile; no placebo; lower dose GP	67% moderate or greater relief with AT; 52% moderate or greater relief with GP; NNQ = 2 for each drug
Graff-Radford et al, 2000 (30), postherpetic neuralgia, 6 months	5	AT 12.5–200 mg/day; fluphenazine 1–3 mg/day; AT 75 mg per day/ fluphenazine 1 mg 3 times per day; active placebo	49/49	Yes (SSD) (AT); no (NSD) (fluphenazine); yes (SSD) (AT/ fluphenazine)	Parallel design; fluphenazine ineffective and combination less effective than AT alone	No result reported
Simpson, 2001 (31), diabetic neuropathy, 3 months or longer	4	GP up to 3600 mg/day; venlafaxine up to 75 mg/day; placebo	11/11 in RCT phase; GP/ venlafaxine, n=5; GP/ placebo, n=6	Yes (SSD)	3 parts to study GP versus placebo, then nonresponders enter crossover RCT of 11 subjects comparing GP + venlafaxine with GP + placebo; final phase was an uncontrolled study with venlafaxine added to GP nonresponders; SSD for some SF-36 scales	In head-to-head RCT part of study, 3 subjects much/ moderately improved with GP/ venlafaxine versus 1 on GP/ placebo; SF-36 score improved with GP/venlafaxine
Raja et al, 2002 (32), postherpetic neuralgia, 3 months	5	NT mean 89 mg/day, range 40–140 mg/day; or DES mean 63 mg/day; morphine mean 91 mg/day, range 15–225 mg/day; or methadone mean 15 mg/day; placebo	44/76	Yes (SSD) (NT); yes (SSD) (DES); yes (SSD) (morphine); yes (SSD) (methadone); no (placebo)	Crossover design; both tricyclics and opioids effective; NST favoured opioids	NNT for opioids = 2.7 and NNT for tricyclics = 4.0; Multidimensional Pain Inventory showed no difference in overall activity or pain-related interference in daily activity
Gilron et al, 2005 (33), postherpetic neuralgia/diabetic neuropathy, 3 months	5	GP (up to 3200 mg/day); morphine (up to 120 mg/day); both GP (up to 2400 mg/day) and morphine (up to 60 mg/day); lorazepam placebo (1.6 mg/day)	41/57	No (NSD) (GP); yes (SSD) (morphine); yes (SSD) (GP/ morphine); no (placebo)	Crossover design; no difference between GP and placebo; GP adds 20% to morphine analgesia with lower doses of each	Moderate or greater relief in 31% placebo, 61% GP, 80% morphine and 78% GP/ morphine; SF-36 scores were higher for some measures on the combination than placebo or morphine alone
Chandra et al, 2006 (34); postherpetic neuralgia, longer than 8 weeks	5	GP up to 2700 mg/day versus NT up to 75 mg/day; no placebo	70/76	No (NSD)	Parallel design; NSD in pain; more dose-limiting side effects with NT; dose high to start with (in our view) – NT at 50 mg	47.5% and 42.8% reduction in pain score with NT and GP, respectively; 50% or greater relief with 25% on NT and 21% on GP (NSD)
Pfizer protocol 1008-040 (26), diabetic neuropathy (refer to FDA website), unpublished after one year	3	AT 75 mg/day fixed dose; pregabalin 600 mg/day; placebo	188/256	Yes (SSD) (AT); no (NSD) (pregabalin)	Parallel design; AT but not pregabalin superior to placebo	50% or greater relief in 46% with AT, 40% with pregabalin and 30% with placebo; AT significant for PPI of SF-MPQ, PGIC and CGIC; SF-36 results for both groups better than placebo

TABLE 4 – CONTINUED
Comparative trials of different potential analgesics in neuropathic pain (n=17)

Study, condition, duration of pain	Jadad score	Drugs, daily dose	Completed/ randomized, n	Effect, yes/no	Comment	Clinical meaningfulness and quality of life
Khoromi et al, 2007 (35), lumbar root pain and chronic sciatica, 3 months	5	Morphine mean 62 mg/day, range 15–90 mg/day; NT mean 84 mg/day, range 25–100 mg/day; combination, 49 mg/day morphine + 55 mg/day NT (means); placebo	28/55	No (NSD) (morphine); no (NSD) (NT); no (NSD) (combination)	Crossover design ×4 phases; no effect; high dropout rate “suggests resistant problem”	Moderate or greater relief for morphine 42%, NT 40%, combination 67% and placebo 37%; NNH for morphine = 10, NT = 30 and combination = 11; SF-36 showed carryover and period effects. No difference in phase I analysis
Rintala et al, 2007 (36), spinal cord injury, 6 months or longer	5	AT 150 mg/day (max); GP 3600 mg/day (max); diphenhydramine (active placebo) 75 mg/day	22/38	Yes (SSD)	Crossover design ×3 phases with high scores for depression; AT more effective than diphenhydramine and GP = diphenhydramine	In high depression score group, 30% relief in 62.5% on AT, 12.5% on GP and 25% on diphenhydramine; no quality of life assessment
Jose et al, 2007 (37), diabetic neuropathy, 1 month	4	Lamotrigine 50–200 mg/day; AT 10–50 mg/day; no placebo arm	46/75	No (NSD)	Crossover design; pain duration only 1 month; may have underdosed patients on AT	Few differences in efficacy, fewer side effects with lamotrigine; 50% improvement in 41% on lamotrigine and in 28% on AT
Frank et al, 2008 (38), chronic neuropathic pain, 79.8 months (mean)	4	Nabilone 2 mg/day versus dihydrocodeine 240 mg/day	64/96	Yes (SSD)	Crossover design and heterogeneous population with 22 having NP “after injury or surgery”, the rest in 13 different diagnostic categories including trigeminal neuralgia; dihydrocodeine superior to nabilone in pain relief and side effects (SSD)	Quality of life (SF-36) better with dihydrocodeine; 10 mm or greater improvement in visual analogue scale in 3/64 on nabilone and in 12/64 on dihydrocodeine; 49/64 had no change in pain score on either drug
Wu et al, 2008 (39), postamputation pain, 6 months or longer	5	Morphine mean 112 mg/day, range 15–180 mg/day; mexiletine mean 933 mg/day, range 300–1200 mg/day; placebo	56/60	Yes (SSD) (morphine); no (NSD) (mexiletine)	Crossover design	NNT morphine = 5.6 (50% or more); NNT morphine = 4.5 (30% or more)
Hanna et al, 2008 (40), diabetic neuropathy, 3 months or longer	5	Subjects on maximum dose of GP tolerated (48% on <1200 mg/day) then randomly assigned to controlled-release oxycodone up to 80 mg/day (60% on 40 mg/day) versus placebo	249/338	Yes (SSD)	Parallel design 33% reduction in pain from baseline to final with addition of oxycodone to maximally tolerated GP	–
Gilron et al, 2009 (41), neuropathic pain (diabetic neuropathy and postherpetic neuralgia), 6 months or longer	5	GP (target 3600 mg/day, mean max 2433 mg/day in monotherapy versus 2180 mg/day in combination); NT (target 100 mg per day, max tolerated 61.6 mg in monotherapy versus 51.1 mg in combination)	45/56	Combination therapy more effective than monotherapy	Crossover design; not clear whether effect is additive or synergistic; no serious adverse effects; no difference in adverse effects except less dry mouth with GP alone and less inability to concentrate with NT	At least moderate relief: 65% on GP, 76% on NT and 84% on combination (NSD). SF-36: Higher vitality score with combination and GP versus NT; weak evidence (P=0.057) that combination better than monotherapy

AT Amitriptyline; CBZ Carbamazepine; CGIC Clinician's global indication of change; DES Desipramine; FDA Food and Drug Administration; GP Gabapentin; max Maximum; NNH Number needed to harm; NNQ Number needed to quit; NNT Number needed to treat; NSD No significant difference; NST Nonsignificant trend; NT Nortriptyline; PGIC Patient's global indication of change; PPI Present pain index; RCT Randomized controlled trial; SF-36 Short-Form 36 Health Survey; SF-MPG Short-Form McGill Pain Questionnaire; SSD Statistically significant difference

the reduction with pregabalin was not significantly different (the starting pain intensity in the pregabalin group was 0.5 points higher than in the amitriptyline group). In this trial, amitriptyline, but not pregabalin, was superior to placebo. The FDA review goes on to say that the above results came from a less conservative ‘last observation carried forward’ analysis but, with the more conservative ‘baseline observation carried

forward’ analysis, neither pregabalin nor amitriptyline differed statistically from placebo with respect to mean pain intensity at the end point.

The 2000 placebo-controlled RCT by Graff-Radford et al (30) for postherpetic neuralgia compared amitriptyline with the phenothiazine fluphenazine, and the combination of the two drugs, and found NSD in pain with fluphenazine used

TABLE 5
Comparative trials of different antidepressants in neuropathic pain (n=10)

Study, condition, duration of pain	Jadad score	Drugs, daily dose	Completed/ randomized, n	Effect, yes/no	Comment	Clinical meaningfulness and quality of life
Panerai et al, 1990 (42), central pain: postherpetic neuralgia, phantom limb and causalgia, 20.6 months (mean)	3	Clomipramine 25–100 mg/day; NT 25–100 mg/day; placebo	24/39	Yes (SSD) (clomipramine); yes (SSD) (NT)	Crossover design; clomipramine more effective (SSD) than NT; no antidepressant effect; conditions studied actually of peripheral origin	Not stated
Sindrup et al, 1990 (43), diabetic neuropathy, 1 year	4	Paroxetine 40 mg (fixed dose); imipramine 50–75 mg; placebo	19/29	Yes (SSD) (paroxetine); yes (SSD) (imipramine)	Crossover design; effect of S drug (paroxetine) but imipramine (serotonin/noradrenaline) more effective (SSD); no antidepressant effect; fewer adverse effects with paroxetine	Not stated
Sindrup et al, 1990 (44), diabetic neuropathy symptoms for 1–20 years	3	Clomipramine 50–75 mg; DES 50–100 mg; placebo	19/26	Yes (SSD) (clomipramine); no (NSD) (DES); no (placebo)	Crossover design; clomipramine (S) but not DES (N) effect on pain	Not stated
Sindrup et al, 1992 (45), diabetic neuropathy symptoms for 1–11 years	4	Mianserin 60 mg/day (fixed dose); imipramine 50–75 mg/day; placebo	18/22	No (mianserin); yes (SSD) (imipramine)	Crossover design, 3 phases; imipramine (noradrenaline + serotonin) effect but no mianserin effect (weakly N, serotonin blockade)	Not stated
Max et al, 1992 (46), diabetic neuropathy 3 months	3	AT mean 105 mg, range 12.5–150 mg; DES mean 111 mg, range 12.5–150 mg; fluoxetine mean 40 mg; placebo (benztropine 0.5–1.5 mg/day)	38/54 (AT); 38/54 (DES); 46/54 (fluoxetine); 46/54 (placebo)	Yes (SSD) (AT); yes (SSD) (DES); no (NSD) (fluoxetine)	2 RCTs with 2 period crossover studies; fluoxetine (S) not effective; AT (S+N) = DES (N); suggested N mechanism of action	74% moderate or greater relief with AT versus 61% with DES and versus placebo 40%; NSD between DES and AT
Watson et al, 1992 (47), postherpetic neuralgia, 3 months	4	AT 100 mg (37.5–150 mg/day); M 100 mg (50–150 mg/day); no placebo	32/35	Yes (SSD) (AT); Yes (SSD) (M)	Crossover design; M (N) less effective than AT (S+N) (SSD); no antidepressant effect; some responded better to M, some to AT	47% had mild/no pain on AT and 38% had mild/no pain on M; good/excellent (50% or more), AT = 50%, M=18%. No difference in disability ratings
Vrethem et al, 1997 (48), painful neuropathy, 6 months	4	AT 75 mg/day; M 75 mg/day; placebo	33/37; 19 = diabetic neuropathy, 14 = other neuropathy	Yes (SSD) (AT); yes (SSD) (M); no (placebo)	Crossover, 3 phase; AT (S+N) more effective than M (S) (SSD) but both better than placebo; no antidepressant effect; all pain qualities relieved; some had better pain relief on AT, some with M	20% per reduction in 63% AT, 50% M and 22% placebo
Watson et al, 1998 (49), postherpetic neuralgia, 3 months	4	AT 58 mg; NT 75 mg; no placebo	31/33	Yes (SSD) (AT); yes (SSD) (NT)	Crossover design; equal effects; less severe side effects with NT (SSD)	50% improved substantially on both drugs. No difference in disability ratings
Sindrup et al, 2003 (50), painful neuropathy, 6 months	5	Venlafaxine 225 mg/day; imipramine 150 mg/day; placebo	29/40	Yes (SSD) (venlafaxine); yes (SSD) (imipramine)	Crossover, 3 ways; no difference in primary end point but more had complete, good or moderate relief with imipramine (SSD); number of adverse effects same except for type	NNT for the TCA imipramine was 2.7 and for the SNRI venlafaxine was 5.2; complete, good or moderate relief more common with imipramine
Rowbotham et al, 2005 (51), TCA-naive postherpetic neuralgia, 3 months	–	DES 150 mg; AT 150 mg; fluoxetine 60 mg; no placebo	38/47; 13/15 (DES); 15/17 (AT); 10/15 (fluoxetine)	Yes (SSD) (DES); yes (SSD) (AT); yes (SSD) (fluoxetine)	Parallel design; TCA-naive patients; intent to treat showed NSD in daily pain intensity or pain relief with all 3 drugs	No difference in daily pain intensity or relief (NSD) but moderate or greater relief in 9/17 (53%) with AT, 12/17 (80%) with DES and 5/15 (30%) with fluoxetine (SSD); best clinically meaningful relief with N drug (DES)

AT Amitriptyline; CBZ Carbamazepine; DES Desipramine; M Maprotiline; N Noradrenergic; NNT Number needed to treat; NSD No significant difference; NST Nonsignificant trend; NT Nortriptyline; RCT Randomized controlled trial; S Serotonergic; SNRI Selective serotonin/norepinephrine reuptake inhibitor; SSD Statistically significant difference; TCA Tricyclic antidepressant

alone or in combination with amitriptyline; however, it found a statistically significant difference in pain with amitriptyline. This was an important trial because this drug combination was one of the original treatments for NP (9,10) and the combination of fluphenazine and nortriptyline was previously shown to be more effective than placebo (17). It is apparent from this RCT that amitriptyline is the analgesic component and, furthermore, that adding fluphenazine increased sedation without adding any analgesic benefit.

In 2007, Khoromi et al (35) studied chronic sciatic pain with placebo, morphine, nortriptyline and a combination of these two drugs, and found NSD with any of the treatments. This trial used between 15 mg and 90 mg of morphine per day with flexible dosing to maximal tolerable dose. Our own experience (53,54) indicates that this may be an inadequate dose of morphine to alleviate this type of refractory NP, which may explain the lack of efficacy of opioids in sciatic pain in this RCT.

Gilron et al compared gabapentin, morphine and the two drugs in combination in one trial (33) and then compared nortriptyline, gabapentin and the two drugs in combination in a subsequent trial (41). In both of these trials, the two-drug combination demonstrated superior efficacy to each single agent. However, NSDs were observed between either of the single agents.

Comparative trials of different drugs within an analgesic class used for NP

Table 5 summarizes comparative RCTs of different drugs within an analgesic class. The 10 studies (42-51) listed in Table 5 are all head-to-head RCTs of different antidepressants conducted usually with the aims of discovering the most effective drugs in this class, and potentially to inform their mechanism of action. No trials of different drugs within other classes of analgesics for NP such as opioids, gabapentinoids (gabapentin and pregabalin) or cannabinoids met our criteria.

General summary

Several general observations can be made on the basis of these head-to-head studies. Of the RCTs comparing different potential analgesics, there is no evidence supporting the efficacy of the benzodiazepine lorazepam (14), the phenothiazine fluphenazine (30) or the sodium channel-blocking agents mexiletine (39) and carbamazepine (27) for NP (trigeminal neuralgia was excluded). There is no evidence for the superiority of gabapentinoids over TCAs either regarding pain or adverse effects, although the nature of the latter differs with the two agents (26,29,36). There are nonsignificant trends suggesting the superiority of opioids over TCAs and gabapentinoids (32,33).

With regard to antidepressant comparisons, the TCAs amitriptyline, nortriptyline, desipramine and imipramine do not appear to differ in analgesic efficacy. The noradrenergic TCA desipramine is at least as effective as amitriptyline in treating diabetic neuropathy and postherpetic neuralgia (46,51). There is some indication that the noradrenergic antidepressant maprotiline, which has a tetracyclic structure, is less effective than amitriptyline. This has been shown by two studies (47,48) that were similar in design and covered two different conditions – postherpetic neuralgia and painful neuropathy. Unlike

imipramine, the nontricyclic agent mianserin was not efficacious (45). There is some evidence that the serotonergic drug clomipramine may be more effective than imipramine and desipramine (42,44) and that the selective serotonin reuptake inhibitor (SSRI) paroxetine may be effective (43); however, these studies were small, may have been inadequately powered, did not state clinical meaningfulness and could have been vulnerable to type 1 error. There is no good evidence for the effectiveness of the SSRI fluoxetine in treating NP (46,51). The preponderance of evidence from these RCTs is supportive of the greater efficacy of noradrenergic and noradrenergic/serotonergic TCAs in NP. The selective serotonin/norepinephrine reuptake inhibitor venlafaxine appears inferior to imipramine for meaningful relief (50). There is some evidence of individual variability in responsiveness when individual antidepressants are compared using head-to-head RCTs (47-49), arguing for sequential trials of different antidepressants in individuals.

DISCUSSION

There are a limited number of head-to-head comparative RCTs of analgesics in NP published between 1988 and 2009. Some of those reviewed here were quite small and may have inadequate statistical power. Within our search criteria there were 17 studies of drugs in different analgesic categories and 10 of analgesics within a category, which were comparisons of different antidepressant drugs. There were seven RCTs using a gabapentin comparator, one using pregabalin, two using a selective serotonin/norepinephrine reuptake inhibitor antidepressant (venlafaxine) and one using the anticonvulsant lamotrigine. No consistent superiority of the latter drugs was found. There were no studies comparing different opioids, gabapentinoids or cannabinoids. All published RCTs were nonindustry funded. One industry-funded study submitted to the FDA (26) has not been published. Most head-to-head RCTs used a crossover design. Most NP RCTs were performed in postherpetic neuralgia patients, painful diabetic neuropathy patients or both, and this may limit their external validity (generalizability) to other NP conditions (12). There are limited data regarding clinical meaningfulness in many of these comparative trials, which is also problematic for determining their external validity (12).

Comparative RCTs of different analgesics

From the limited data in these head-to-head RCTs of different analgesics in NP, there is no evidence supporting the utility of the benzodiazepine lorazepam (14), the anticonvulsants carbamazepine (27) and lamotrigine (37), or the phenothiazine fluphenazine (in contrast to the favourable effect of the TCA amitriptyline [30]). Also, the sodium channel blocker mexiletine was ineffective compared with morphine for chronic post-amputation pain (39). Two studies showed no effect of mexiletine or the comparator drug amitriptyline in HIV neuropathy (28), and no effect of nortriptyline or morphine in sciatica (35). These latter two results raise questions about the generalizability of research in NP, in which 80% of the studies are performed in postherpetic neuralgia and diabetic neuropathy (12). There appears to be no good evidence supporting the analgesic superiority of the gabapentinoids (gabapentin and pregabalin) over TCAs (29,34) in these RCTs; amitriptyline was found to be superior in two studies (26,36). Combinations of gabapentin added to morphine (33) and

TABLE 6
Potential mechanisms of the analgesic action of antidepressants

Serotonin potentiation by inhibition of reuptake
Noradrenaline potentiation by inhibition of reuptake
Combined noradrenaline/serotonin potentiation
Dopamine potentiation
Opioid-mediated actions
Na ⁺ channel blockade
K ⁺ channel activation
Ca ²⁺ channel inhibition
Adenosine release
N-methyl-D-aspartate receptor blockade
GABA _B potentiation
Substance P reduction
Prostaglandin reduction

Data from reference 59. GABA Gamma-aminobutyric acid

oxycodone added to gabapentin (40) resulted in a 20% and 33% increase in analgesia, respectively.

These comparative RCTs of different analgesics indicate efficacy within three broad classes of agents for NP – antidepressants, opioids and gabapentinoids. The structures of these agents are diverse. The receptors for opioids, and their location and mechanisms of action, have received considerable attention and are reasonably well characterized (55). The pharmacodynamics of gabapentinoids (gabapentin and pregabalin), a more recently available class of drugs, focus on the alpha-2-delta subunit of Ca²⁺ channels and interactions with descending noradrenergic monoamine systems (56,57). Ironically, despite being the oldest and most-studied drugs for NP, the analgesic antidepressants are incompletely understood from a pharmacodynamic perspective. Antidepressants have been well characterized in terms of their ability to inhibit noradrenaline and serotonin reuptake (58), but antidepressants as a class of drugs have a multiplicity of pharmacological actions that potentially contribute to pain modulation (Table 6) (59). The focus on amine mechanisms for explaining analgesia by antidepressants reflects their actions in relieving depression (the biogenic amine hypothesis of depression), as well as the involvement of noradrenergic and serotonergic systems descending from the brain stem into the dorsal horn of the spinal cord, in regulating pain signals as they enter the central nervous system. It is important to recognize that, while depression is common in patients with chronic pain (60), and while depression and chronic pain share mechanisms (61), pain relief with antidepressants is independent of antidepressant actions (14,62); this dissociation has been recognized since the efficacy of antidepressants for NP pain was clearly established (63). Several lines of investigation, including the use of amine receptor antagonists and gene deletion approaches, indicate the requirement of noradrenergic and serotonergic systems for antinociception by antidepressants in several preclinical models (59,64). However, several experimental lines of evidence indicate that antidepressants also interact with other mechanisms that contribute to their ability to modulate pain signalling (59).

Comparative RCTs of antidepressants

Comparative RCTs of different antidepressant agents generally indicate that drugs that potentiate noradrenaline and serotonin, or predominantly noradrenergic mechanisms, are more

effective than serotonergic agents (such as the SSRIs), which are less or even not effective. The presence of both facilitatory and inhibitory descending serotonergic systems could be an important reason for this (64). There is some evidence that the more noradrenergic, weaker serotonergic TCAs nortriptyline (49) and desipramine (46,51) are equal to or more effective than the dual noradrenergic/serotonergic agent amitriptyline. Other data from two RCTs using the tetracyclic comparator antidepressant maprotiline, which is more noradrenergic than nortriptyline and desipramine, showed it to be less effective than amitriptyline (47,48). Thus, some serotonin augmentation appears to be important but the optimal proportion may not have been found yet. In keeping with this, the strongly serotonergic/weakly noradrenergic reuptake inhibitor venlafaxine appears to provide less clinically meaningful relief than the noradrenergic/serotonergic TCA imipramine (50). However, some comparative trials have also produced data that differs from these general observations because the serotonergic TCA clomipramine and the SSRI paroxetine have been shown to be effective in some instances (42-44). One trial showing clomipramine to be superior to nortriptyline in central pain (42) actually investigated the peripherally generated pain disorders of postherpetic neuralgia, phantom pain and causalgia; this profile of indications differs from many other trials. These RCTs involved small numbers of patients and the clinical meaningfulness of the results was not clear.

There may be more than one pain mechanism in an individual and between individuals, and multiple mechanisms may contribute to analgesia. Both TCAs (and opioids) are indiscriminate in relieving steady pain, jabbing pain and allodynia (47,49). To date, clear mechanism-based treatments have been elusive, except perhaps for carbamazepine and the shock-like pain of trigeminal neuralgia. There is some evidence, in three crossover studies (47-49), that different subjects may respond to one antidepressant and not the other, making the trial-and-error use of different drugs within this class a reasonable clinical practice.

It appears that a tricyclic structure is important for antidepressant analgesia, given the lack of effect of the non-TCA mianserin and the lesser effect of the tetracyclic noradrenergic antidepressant maprotiline, compared with the noradrenergic TCAs desipramine and nortriptyline, which appear equal to amitriptyline in efficacy for pain relief. Structure-activity considerations may not necessarily assist in identifying more effective agents. Demethylation of the side chain seems to be important in reducing side effects, as seen with amitriptyline and its demethylated metabolite nortriptyline (49). It is of interest that the tricyclic-based structure carbamazepine, although very effective for the shock-like NP of trigeminal neuralgia, is not very effective or not useful at all for other types of NP. From a structural perspective at the molecular level, the planar structure of TCAs may have some flexibility, allowing the molecule to assume multiple conformations and thereby engage several different pharmacological actions (ie, interact with several transporters, receptors and ion channels). Tetracyclic structures may have more structural rigidity and a lesser ability to interact with several molecular sites. While this may be beneficial for the side effect profile, it might sacrifice actions that actually contribute to efficacy. Furthermore, it may be that a drug that exhibits a multiplicity of actions that affect several aspects of perturbed pain pathways can result in

synergistic or additive effects, and these are lost with the more specific agents. The concept of polypharmacy or combination therapy using different agents for NP has been addressed directly (65). It may be that the more one strives for a highly selective agent, the more one may sacrifice some of the actions that are contributing to efficacy. We have no way of knowing how individual opioids and anticonvulsants compare because there are no head-to-head trials that compare them. There are some long-term observational data that suggest oxycodone is 'most used' and 'most preferred' over other opioids (53,54).

Why is there partial efficacy with all drugs to date?

It is not clear why all drugs proven by RCT to exhibit significant pain-relieving effects on NP are only moderately effective, but there are several relevant considerations. One potential reason for limited responses is that damage to or perturbation of the nervous system (peripheral or central) may be so well established in these conditions that the system is only amenable to partial restoration of function (66). A second potential reason is that not enough aspects of the mechanisms that drive the pain are being affected by the drugs used. Multiple mechanisms (both peripheral and central) are implicated in chronic NP, both within an individual and between individuals, and this complexity may be prominently involved in generating and maintaining the pain. Perhaps more attention should be paid to quieting the peripheral input to settle the resultant secondary sensitization that occurs in the central nervous system, as recent cases suggest (67-69). In this regard, existing and improved topical analgesics (70) might be considered as adjuvant therapies along with systemically active agents. A third reason to consider is the multidimensional nature of the chronic pain experience. Thus, pain is a complex experience and has well-recognized sensory, affective and cognitive aspects. In this context, any approach using drugs that target only sensory aspects of chronic pain may only be capable of eliciting a partial response. The developing literature on fibromyalgia may be useful to consider in this regard. While this condition is not necessarily regarded as NP (it lacks an explanation of how 'damage' to the peripheral or central nervous system occurs), it functionally exhibits peripheral and central sensitization in common with other forms of NP and, importantly, responds to drug classes that are used to treat NP (71). Current treatment guidelines recommend multimodal approaches to treatment such as pharmacotherapy, exercise, education, counselling and other psychological approaches, thus combining medical management as well as self-management strategies (72,73). Perhaps the therapy of more classic NP conditions, in which damage to

the central and peripheral nervous system is known to be involved, needs to consider multimodal treatment strategies as well as combinations of drugs with different pharmacodynamics for more effective management. Because of the inadequacies of monotherapy for many patients with severe NP, and because no magic bullet seems imminent, head-to-head RCTs of combinations of drugs useful for NP appear to be important. Head-to-head trials have limitations regarding the evaluation of efficacy if a placebo is not used and the drugs are equal; this type of trial may require more statistical power to show a difference. Limitations of the present review are listed in trial exclusion criteria (see the Methods section) in that the focus is on oral drugs and some NP conditions were excluded. Because of the dearth of head-to-head RCTs in NP and the inadequacies of some of those described here, we clearly need more and improved studies of this nature so that clinicians, grappling with these difficult problems, will know whether newer and more expensive drugs are superior to or comparable with a standard therapy in terms of efficacy, and whether they have fewer significant and intolerable side effects. Investigators designing RCTs of any sort in NP would be wise to follow the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials guidelines for chronic pain trials (73). Regulatory bodies such as the FDA and Health Canada should require comparative data to be part of the drug approval process. In any trial, principal investigators should have a major role in study design, data analysis and writing the article, and should insist on submission for publication. In the future, clinical trial registries will help to track the course of an RCT and whether it is published. Access to trials submitted for new drug approval are available on the FDA website (www.fda.gov) if submitted for drug approval and unpublished.

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