Beyond pain: can antidepressants improve depressive symptoms and quality of life in patients with neuropathic pain?

Background

Neuropathic pain, defined by the International Association for the Study of Pain (IASP) as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [42], is a complex and potentially disabling condition, considered as a separate nosological entity despite the large variety of etiologic factors implied [19].

Neuropathic pain secondary to medical conditions is a largely studied, yet difficult to treat phenomenon, affecting a large population of patients and burdened by both physical and psychosocial consequences. Recent studies have indeed pointed out that severe pain is one of the main predictors of depression, anxiety and low quality of life in patients with such chronic conditions, including for instance diabetes, spinal cord injuries, and cancer [57,76,84].

Neuropathic pain shares with depression and with other neuropsychiatric disorders a multiplicity of neurotransmitters potentially involved in its pathophysiology and phenomenology [6,49]. Indeed, recent studies suggest that chronic stress, including stress-related psychiatric disorders, exacerbates neuropathic pain via the integration of stress-affect-related information with nociceptive information in the amygdala [48,91]. This might partially explain the high levels of anxious and depressive symptoms occurring in this population of patients [10,12,13,14,26,65,68,93]; symptoms which in turn play a key role on the personal experience of pain and, in general, on quality of life, thus complicating and aggravating the burden associate with this illness [35].

Neuropathic pain and depression, furthermore, share some relevant principles of treatment, as conventional analgesics used in nociceptive pain are usually ineffective in alleviating neuropathic pain, while the use of antidepressants has been supported by evidence of efficacy. As a result, based on randomized clinical trials, certain

antidepressants have been recommended as first-line treatments [18,15,48,49]. Tricyclic agents, for instance, have been shown to be effective for different neuropathic pain conditions, with promising number needed to treat (NNT) values ranging from 2 to 3 [17,20]. Consequently, the updated therapeutic guidelines, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), include tricyclic agents (e.g. amitriptyline and imipramine) and serotonin and noradrenaline reuptake inhibitors duloxetine and venlafaxine among first line agents in neuropathic symptoms treatment [19].

Therefore, a prompt recognition of depression in patients with neuropathic pain, and other severe medical conditions, is particularly important to ensure optimal therapeutic approaches. Nonetheless, making an accurate psychiatric diagnosis can be extremely challenging, considering that depressive and anxious experiences may pertain to a continuum ranging from expected (though distressing) pain-related emotional reactions, to particularly severe depressive or anxiety symptoms, fulfilling strict diagnostic criteria for a psychiatric condition. As a result, clinicians approaching these conditions are on one hand concerned of over-medicalizing normal emotional reactions and, on the other, of overlooking relevant signals of depressive conditions, potentially overshadowed by the presence of intense pain, which may then become the only focus of treatment. In line with these considerations, current literature on antidepressants puts a strong emphasis on "pain control" as an outcome, while less attention is given to anxious-depressive outcomes, quality of life and to the psycho-social burden of pain [60,75].

To address this issue in 2009 under the auspices of IASP[42], a consensus process was used to develop evidence-based guidelines for the pharmacologic management of neuropathic pain that take into consideration not only clinical efficacy and adverse effects, but also impact on health-related quality of life, as well as costs[61].

Acknowledging that both affective and cognitive components play a crucial role in patients' experience and adaptation to neuropathic pain syndromes [51,56] the present systematic review and meta-analysis of randomised controlled trials (RCTs) aimed to

evaluate the efficacy of antidepressants on depressive symptoms, anxiety and quality of life in patients suffering from neuropathic pain.

Methods

Registration of review protocol

The protocol for this review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews. CRD42016043533).

Criteria for considering studies for this review

In this review RCTs with double-blind assessment (participants and observers), using placebo as unique comparator, with follow-ups of four weeks or longer, were included. Studies conducted in any language were included. Trials using quasi-random methods were excluded. Only studies assessing at least one among depressive symptoms, anxiety, and quality of life at study endpoint were included. Head-to-head studies comparing two active interventions were excluded. Adult participants aged 18 years and above were included. Participants could have one or more of a wide range of chronic neuropathic pain conditions (including HIV/AIDS, diabetes, alcoholism, autoimmune diseases, cancer, chemotherapy/radiotherapy, post-viral neuralgia, trigeminal neuralgia, phantom limb pain, postoperative or traumatic pain, regional pain syndromes, spinal cord injury, etc.). Conditions such as low back pain without radicular pain, fibromyalgia, complex regional pain syndrome type I were not included because they do not fulfill the current IASP [42] definition of neuropathic pain.

Any antidepressants according to the ATC/DDD system (see http://www.whocc.no/atc_ddd_index/?code=N06A) was included.

Primary outcome

The primary outcome of this study was the mean score at endpoint or mean change from baseline to endpoint on the Beck Depression Inventory (BDI) [4], Hamilton Depression Rating Scale (HDRS) [30], Montgomery-Asberg Depression Rating Scale (MADRS)[59], Clinical Global Impression Rating scale (CGI)[29], or on any other depression rating scale with evidence of adequate validity and reliability.

Secondary outcomes

The following secondary outcomes were assessed:

- Depression (dichotomous outcome): proportion of patients with clinically relevant improvement according to a pre-defined change in validated rating scales;

- Anxiety (continuous outcome): mean endpoint score or mean change from baseline to endpoint on Hamilton Anxiety rating Scale (HAMA) [30] or other scales with evidence of adequate validity and reliability;

- Anxiety (dichotomous outcome): proportion of patients with relevant improvement according to a pre-defined change in validated rating scales;

- Quality of life (continuous outcome): mean endpoint score or mean change from baseline to endpoint on validated scales, such as the SF-36 Health Survey[88] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [1]. If these scales were not available, a general health related QoL measure, as defined by each of the trials, was used only if there was evidence of validity and reliability;

- Pain response (continuous outcome): mean score at endpoint or mean change from baseline to endpoint on the VAS scale or any other rating scale with evidence of adequate validity and reliability;

- Dropouts due to any reason (dichotomous outcome);

- Dropouts due to inefficacy (dichotomous outcome);

- Dropouts due to adverse events (dichotomous outcome).

We performed subgroup analyses for the primary outcome grouping studies by: antidepressant class; individual antidepressant; psychiatric condition (studies enrolling patients with psychiatric symptoms or a formal diagnosis versus all other studies); and type of neuropathic pain. Further, we also performed a subgroup analysis to evaluate the tolerability (dropouts due to adverse events) of different antidepressant classes. Additional sensitivity analyses excluded studies at high risk of bias (having less than four items at low risk), studies with less than 100 patients, and studies that did not measure the primary outcome with the BDI [4].

Search methods for study identification

The following databases were searched: Medline, PubMed, Embase, PsycINFO, CINAHL, and Scopus up to February 2018 using the terms "antidepressants" "antidepressant agents", "antidepressant drugs", and "neuropathic pain" (details reported in the online supplemental material). Reference lists of relevant papers and previous review articles were hand searched for other relevant studies. The following electronic sources were also hand searched for published, unpublished and ongoing trials:

a. Medicine approving agencies: the Food and Drug Administration (FDA) in the United States; the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom; the European Medicines Agency (EMA) in the European Union; the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan; the Therapeutic Goods Administration (TGA) in Australia;

b. Online clinical trials repositories: clinicaltrials.gov (United States); ISRCTN and National Research Register (UK); UMIN-CTR (Japan); ANZ-CTR in Australia and New Zealand; The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP); The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Clinical Trials Portal; controlled-trials.com.

c. websites of the most relevant pharmaceutical companies producing antidepressants, such as GlaxoSmithKline, Sanofi, Janssen, Lundbeck, Pfizer, Abbott, Lilly, Merck.

Included and excluded studies were reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [58].

Data extraction

Data extraction was developed in accordance with recommendations provided by the Cochrane Handbook for systematic Reviews of interventions [34]. Three investigators (GT, RC and GO) independently examined all titles and abstracts and obtained full texts of potentially relevant papers using an ad hoc form. Disagreement was resolved by consensus. Possible inconsistencies were discussed, and a fourth reviewer (CB or LG) was involved when necessary. Considerable care was taken to exclude duplicate publications. For all studies, we extracted information on study design, source of data, population characteristics, intervention details, and outcomes of interests.

Risk of bias (quality) assessment

To assess the methodological quality of included trials, two authors (ER and GT) independently applied the criteria for quality assessment recommended in the Cochrane Collaboration Handbook [34]]. This includes the following assessment: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (detection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting of outcomes (reporting bias) and other biases (e.g. sponsorship bias). To determine the risk of bias of a trial each study was given a quality rating such as "low risk of bias", "high risk of bias" or "unclear risk of bias", according to the presence of sufficient information and potential bias. Studies with a high risk of bias were included in the main analysis but we examined, in a sensitivity analysis, the effect of excluding them.

If disagreement occurred, this was resolved with the involvement of a third author (GO or CB). Results were summarized in the 'Risk of bias' graph and a 'Risk of bias' summary and were taken into due account when discussing the results of the meta-analysis.

Publication bias

For the primary outcome, the visual inspection of the funnel plot and the Egger's test [16] were employed to investigate the likelihood of publication bias.

Data synthesis

Results from the studies were pooled in meta-analyses. For continuous outcomes, we pooled standardized mean differences (SMDs). For dichotomous outcomes a Mantel–Haenszel risk ratio were calculated. Continuous and dichotomous outcomes were analysed using a random-effects model, with 95% confidence intervals (CI), as this takes into account any difference between studies even if there is no statistically significant heterogeneity. Subgroup and sensitivity analyses were interpreted with caution, as multiple analyses can lead to false positive conclusions. In order to perform the analyses we used Review Manager (RevMan version 5.3) [70].

Results

A total of 2919 articles were identified from electronic databases. In addition, 68 records were identified through hand-searching and additional sources. After removing duplicates, 2367 records were screened for eligibility. Of these, 2179 were excluded based on title and abstract screening, and the remaining 188 articles were retrieved for more detailed evaluation. A total of 39 individual studies fulfilled the criteria for eligibility and were included in the review (Figure 1) [2,5,7,18,21,24,25,27,28,31,33,36,41,44,45,46,47,50,53,54,55,64,66,67,71,72,73,77,78, 79,80,82,83,85,86,87,89,76]. Of these, 32 provided data suitable for re-analysis.

Characteristics of studies included in the meta-analysis

All included studies were double-blind and employed a placebo arm for comparison. Fifteen studies lasted between 4 and 8 weeks, thirteen studies lasted between 9 and 13 weeks, three studies lasted between 14 and 18 weeks, and one study lasted 26 weeks. In the majority of studies, the antidepressants evaluated were duloxetine (twelve studies) followed by amitriptyline (six studies) and venlafaxine (four studies) (Table 1). The total number of participants was 4418, while the mean number of participants per study was 138 (range 11-457). The mean age ranged between 39.9 and 72.9 years (three missing data). Eleven studies included patients with diabetic neuropathy; two post-herpetic neuralgia; three chemotherapy-induced neuropathies; five spinal cord injury or post-operative pain or amputation; two HIV-associated neuropathies; three chronic radicular back pain; one multiple sclerosis; one atypical facial pain; and one burning mouth syndrome. For three studies the aetiology and the site of pain was mixed or unclear.

Nineteen studies recruited patients with no psychiatric diagnosis; eight recruited patients irrespective of diagnosis, as an assessment of psychiatric symptoms at baseline was not performed; one study excluded patients with major depression; one study excluded patients with major depression or dysthymia; and three studies excluded patients with depressive or anxious symptoms irrespective of a formal diagnosis.

We found an overall moderate quality of included studies. A high risk of attrition bias was found for almost half of the included studies. For seven studies the risk of sponsorship bias was considered high.

Efficacy of antidepressants

The meta-analysis of the primary outcome, carried out on fourteen comparisons (2504 patients), showed that antidepressants were more effective than placebo in improving depressive symptoms (SMD -0.16; 95% CI -0.28 to -0.04; I^2 = 49%) (Figure 2).

Secondary outcomes

No sufficient data have been retrieved to perform analyses of depression and anxiety as dichotomous outcomes. No statistically significant difference emerged between antidepressants and placebo in reducing anxiety (6 comparisons; 713 patients; SMD -0.16; 95% CI -0.48 to 0.17; I^2 = 64%). Quality of life appeared to be significantly better in patients treated with antidepressants than in those on placebo (10 comparisons, 1742 patients; SMD 0.38; 95% CI 0.08 to 0.68; I^2 = 87%). Pain was significantly reduced in patients on antidepressants than in patients on placebo (20 comparisons, 3424 patients; SMD -0.23; 95% CI -0.33 to -0.13; I^2 = 40%). Acceptability and tolerability were significantly higher in patients on placebo (acceptability: 28 comparisons, 3739 patients; RR 1.31, 95% CI 1.13 to 1.52; I^2 = 0% (Figure 3); tolerability: 16 comparisons, 3549 patients; RR 2.69 95% CI 2.06 to 3.50; I^2 = 0%) (Figure 4). Results of secondary outcomes are summarized in Table 2.

Subgroups analyses

SNRIs showed a statistically significant advantage over placebo (12 comparisons, 2396 patients; SMD -0.12; 95% CI -0.23 to -0.01; I^2 = 35%) in reducing depression, while TCAs did not result significantly more effective than placebo (2 comparisons, 108 patients; SMD -0.77 95% CI -1.55 to 0.02; I^2 = 62%).

Single drug analysis did not show an advantage over placebo for duloxetine (8 comparisons, 1912 patients; SMD -0.09, 95% CI -0.20 to 0.03; I^2 = 32%), venlafaxine (3 comparisons, 462 patients; SMD -0.16, 95% CI -0.44 to 0.13; I^2 = 41%), and amitriptyline (2 comparisons, 108 patients; SMD -0.77, 95% CI 1.55 to 0.02; I^2 = 62%).

Depressive symptoms were significantly reduced by antidepressants as compared to placebo in patients with diabetes-related neuropathic pain (8 comparisons, 2160 patients; SMD -0.25 95% CI -0.40 to -0.10; I^2 = 18%). Conversely, analysis of patients with neuropathic pain secondary to injuries, post-surgery and post amputation, did not show

a significant difference between antidepressant and placebo (3 comparisons; 287 patients; SMD -1.03 95% CI -2.07 to 0.01; I² = 0%). Patients with any psychiatric diagnosis on antidepressants reported significantly higher improvements on depression than patients on placebo (10 comparisons, 2062 patients; SMD 0.14; 95% CI -0.28 to -0.00; I² = 50%). Conversely, no statistical difference emerged in patients without a psychiatric diagnosis (4 comparisons, 442 patients; SMD -0.25; 95% CI -0.57 to 0.07; I² = 57%).

The analysis of dropouts due to inefficacy showed significantly lower rates in patients taking antidepressants as compared to placebo (12 comparisons, 1764 patients; RR 0.46; 95% CI 0.25 to 0.84; I² = 0%) (Table 3 and online supplemental material).

Sensitivity analyses

Sensitivity analysis (reported in Table 3 and online supplemental material) conducted only on studies enrolling ≥ 100 patients, did not show a statistically significant difference (9 comparisons, 2293 patients; SMD -0.10; 95% CI -0.21 to 0.01; I² = 43%). Sensitivity analysis involving only studies using BDI [4], to measure depression did not indicate any statistical difference between the experimental and the control group (6 comparisons, 700 patients; SMD -0.89; 95% CI -1.93 to 0.15; I² = 44%).

Analysis conducted by excluding studies rated with a high risk of bias, indicated a statistically significant efficacy of antidepressant on placebo (7 comparisons; 678 patients; SMD -0.27; 95% CI -0.55 to 0.00; I² = 54%).

Publication bias

We were able to identify and include one unpublished trial. The visual inspection of the funnel plot suggested the occurrence of publication bias, and this was confirmed by Egger's test (slope = -0.148; p-value = 0.047) [16]. According to this finding, unpublished studies showing a lower effect for antidepressants might exist.

Discussion

To our knowledge, this is the first systematic review and meta-analysis specifically focusing on the effect of antidepressants on psychiatric symptoms and quality of life in patients suffering from neuropathic pain, which are largely overlooked by current scientific literature and clinical guidelines [37,38,39,40]. The results from this review can therefore contribute to clarify the place of antidepressants in the multidimensional treatment of patients with such distressing conditions.

Overall, antidepressants were more effective than placebo in reducing symptoms of depression. However, the magnitude of effect was small (Cohen's d 0.16) according to Cohen's criteria [11]. According to the approach proposed by Furukawa and Leucht [22], and assuming that a favorable outcome (i.e. response) is expected in about 35% of patients receiving placebo (as observed in the general population, according to Cipriani et al. 2018 [9], this effect can be translated into a number-needed-to-treat (NNT) of 16.

On the other hand, several secondary analyses fueled the uncertainty around the clinical relevance of this beneficial effect. All sensitivity analyses showed a similar effect size as compared to the primary analysis but did not reach statistical significance. Subgroup analysis by class of drug confirmed a marginally significant advantage for SNRIs over placebo, while TCAs did not reach a statistical significance, although only two small studies were included. In the subgroup analysis by individual antidepressant, no beneficial effect emerged for duloxetine, venlafaxine, and amitriptyline, which are among the most frequently prescribed drugs in these patients. Lastly, the subgroup analysis by psychiatric diagnosis showed a very small effect in patients without a formal psychiatric diagnosis, and a greater effect in those with a diagnosis of depression. This differential effect is in line with previous systematic reviews and meta-analysis assessing the efficacy of antidepressants in patients with severe medical conditions [62,69].

As for secondary outcomes, quality of life resulted significantly improved by antidepressants compared to placebo. The magnitude of the effect was relatively small (Cohen's d 0.38), however the NNT of 8 is consistent with the expected effect of antidepressants and other specialized palliative care interventions in severely ill

populations, such as cancer patients [43,63,69]. This quality of life improvement is likely to be primarily related to the analgesic action of antidepressants.

No advantage of antidepressants over placebo emerged in reducing anxiety, and, of the six studies included in our analysis, only one reached a statistical significance in favor of antidepressants46. Relatively few data contributed to this analysis, and this notably limits the generalizability of results, which are however consistent with some literature indications suggesting that neuropathic patients with anxiety would preferably benefit from an anticonvulsant rather than an antidepressant [74,81]. However, it is important to recognize that, despite some indications from pre-clinical [52] and observational studies [8,32,92] on the usefulness of antidepressants in reducing anxiety symptoms in neuropathic pain, very few quality randomized clinical trials have investigated this clinically burdening dimension.

Tolerability resulted in favor of placebo, with higher dropout rates for adverse events as compared to depressed patients treated with TCAs and SNRIs among the general population. This is in line with previous systematic reviews [23,62,69]. Also, acceptability (total dropouts), which can be considered as an index of the balance existing between efficacy and tolerability, favored placebo. These observations seem to suggest that these antidepressants, usually considered safe and well tolerated, could show a less manageable profile when used in a population with serious medical conditions, such as for instance diabetes, correlated with neuropathic pain.

Finally, antidepressants appeared superior to placebo in reducing the intensity of pain, which is generally in line with results from existing literature [19]. The generalizability of this analysis is notably limited by the fact that many trials assessing this outcome were excluded from our review, as they did not measure any psychiatric outcome.

The study presents some limitations that need to be acknowledged. First, a moderate degree of heterogeneity (I^2 = 49%) was detected for the primary outcome (depression), which did not sensibly change after sensitivity and subgroup analysis, except for the analysis by type of pain. This might suggest that the physiopathology underpinning depressive symptoms, along with the responsiveness to antidepressants, can relevantly

differ between different neuropathy phenotypes. The heterogeneity was high (I^2 = 87%) for the outcome quality of life, which is possibly related to the fact that most included studies had a large sample size and precise estimates, providing narrow and hardly overlapping confidence intervals. Second, meta-analysis for the outcome depression, as well as quality of life, frequently included per protocol analysis results, rather than intention-to-treat analysis, and this could have magnified the effect of the intervention. Third, we included only trials measuring at least one among depression, anxiety and quality of life. However, most of these trials were designed with the primary aim of detecting an effect on neuropathic pain and might therefore be underpowered for these secondary outcomes.

Conclusions

We believe that our findings offer implications both for clinical practice and future research. Overall, while the analgesic efficacy of SNRIs and TCAs remains a cornerstone in the treatment of patients with neuropathic pain, their use for targeting psychiatric comorbid symptoms remains uncertain. The small-to-negligible beneficial effect observed, along with possible tolerability issues, prevents from recommending their routine use in clinical practice, particularly when depressive and anxiety symptoms are sub-threshold. On the other hand, further research is needed to ascertain their magnitude of benefit in formally diagnosed psychiatric conditions. Still, antidepressants carry a potentiality for improving emotional distressing symptoms in individuals with neuropathic pain, but current data does not allow to detect who can benefit from these medications. Therefore, the appropriateness of their use should be evaluated at an individual level using a case-by-case clinical approach, taking into due account that TCAs and SNRIs may result less tolerable and acceptable in such fragile population.

In conclusion, our findings suggest to carefully prescribe antidepressants in selected patients with neuropathic pain, and warrant at the same time further research to explore how a correct use of these drugs can help patients with neuropathic pain to cope better with their chronic disorder and to address the consequences on their psychosocial

health and quality of life. Future randomized trials on antidepressants and other interventions for neuropathic pain should take into account not only the intensity of pain, but also the relevant dimensions of anxiety, depression, and, ultimately, quality of life.

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Table Legend

Table 1

RATING SCALES: CGIC = Clinical Global Impression of Change; CGI-S Clinical Global impression of Severity; HDRS = Hamilton

Depression Rating Scale; CESD: Center for Epidemiologic Studies-Depression Scale; BDI = Beck Depression Inventory; MDI =

Major Depression Index; POMS = Profile of Mood State; CPRS = Comprehensive Psychopathological Rating Scale

PSYCHIATRIC DIAGNOSIS: 0=psychiatric diagnosis excluded; 1=irrespective of diagnosis (mixed, check baseline); 2=major
depression; 3=major depression and dysthymic; 4=depressive/anxiety symptoms without a formal diagnosis; 5=unclear.

Table 2

SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs:Tricyclic Antidepressants; BDI: Beck Depression Inventory; SMD:
Standardized Minimal Difference; CI: Confidence Interval; pts: patients

Table 3

SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs:Tricyclic Antidepressants; SNRI: Selectine Noradrenaline InHibitorsBDI: Beck
Depression Inventory; SMD: Standardized Minimal Difference; CI: Confidence Interval; pts: patients