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Editorial comment

# The obligation to publishing negative outcome data from neuropathic pain clinical trials

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In this issue of the *Scandinavian Journal of Pain*, Jarkko Kalliomäki et al. report a negative trial of a chemochine receptor (CCR2) antagonist in painful diabetic neuropathy [1]. This was a relevant trial performed with appropriate methodology and of high quality.

## 1. The importance of publishing well done negative outcome trials

The researchers should be praised for having taken the initiative to publish the results, and it is even more praiseworthy that the initiative stems from a drug company. The journal deserves to be credited for taking up the responsibility to also publish negative results that may not attract so much attention as do positive trials. Publication of high quality negative trials is extremely important because it may have implications for clinical practice and for research strategies within the field, so the limited resources are used most cost-effectively.

Most clinicians will probably strive to pursue an evidence-based pharmacological treatment approach for their patients with neuropathic pain. To do so, it is obvious to consult resources such as guidelines and reviews [2–4]. These resources will typically have compiled all the relevant published trials within the field. Based on critical review of the trials, an evidence-based recommendation is given and information on the efficacy to be expected with each drug is often presented. A publication bias with mainly or solely publication of positive trials will have a major impact on the conclusion of the review. When there are a number of unpublished negative studies, the recommendations will be overly optimistic with respect to efficacy; or the recommendations may be directly wrong.

There are probably negative unpublished data on all the major drug classes used for neuropathic pain in clinical practice. One example is the comparative placebo-controlled trial of pregabalin versus amitriptyline in painful diabetic neuropathy that failed to find a better effect of pregabalin than of placebo, but the study did find that amitriptyline was superior to placebo (Pfizer protocol 1008-040. Unpublished data on FDA website: http://www.accessdata.fda.gov/scripts/cder/drugsatfda). We also know of other negative trials on pregabalin as well as some on gabapentin in neuropathic pain that were not published [3].

Negative data may also be hidden within published data, like the lack of statistically significant difference in pain-relieving effect between gabapentin and placebo in a trial on gabapentin plus morphine showing superiority of the combination treatment over monotherapy with each of the drugs in postherpetic neuralgia [5].

## 2. Negative clinical trials when animal-studies predicted efficacy of a drug for neuropathic pain

The overall negative result as judged by results for the primary efficacy variable with the CCR2 antagonist in the present clinical trial [1] highlights another important issue. The study was based on sound reasoning on theories on neuropathic pain mechanisms, which was supported by results with the CCR2 antagonist in well-established models of neuropathic pain in animals. This is not the first time positive data from experimental models of neuropathic pain are not translated into positive results in subsequent clinical trials; this was also the case for, e.g. topiramate, lamotrigine and levetiracetam [6–8]. This calls in question the relevance and the predictive value of the experimental animal pain models and the research strategy in the field. This issue deserves to be thoroughly scrutinized. It is thought-provoking that the current first-line treatments, i.e. antidepressants and gabapentinoids, were introduced in neuropathic pain treatment based on empiric observations.

## 3. Importance of stratifying subtypes of neuropathic pain in clinical drug trials

Although the current overall study result with the CCR2 antagonist is negative, interesting results are reported from analysis of secondary effect variables in the Kalliomäki et al. study [1]. Thus, the CCR2 antagonist reduced evoked pains and pressing pain subtypes of the neuropathic pain symptom inventory (NPSI). This may point at a selective effect of the drug on specific pain symptoms. It may have been more interesting to use this information to establish subgroups of the patients at baseline, e.g. according to pain symptoms, to see if a clear effect was present in any given subgroup.

Similar findings have recently been reported in other overall negative trials, e.g. for topical clonidine in painful diabetic

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neuropathy [9] and levetiracetam in central neuropathic pain in multiple sclerosis [10]. Thorough characterization of patients with respect to symptoms and signs at baseline have been lacking in large scale industry-sponsored trials in neuropathic pain, and these trials may have overlooked effects in relevant patient subpopulations [11]. Such knowledge could have helped us learn more about neuropathic pain mechanisms and give us the possibility to try to tailor the treatment to the single pain patient [12].

## 4. Increasing awareness of importance of publishing negative trials

Publication of negative trials has become more common within the last decade. We will probably see an increasing number of negative trials published in the future, since the importance of doing so has been acknowledged, and because of the establishment of clinical trial databases (e.g. http://www.clinicaltrials.gov), i.e. databases in which trials must be registered before the first patient is included. Some scientific journals will only accept manuscripts on trials that are registered in a trial database. This forces researchers and industry to register their trials and seek to publish the results no matter the outcome. Good clinical practice guidelines, that all trials must comply with, request that the responsible party publish the results. The trial databases also ensure that the results are reported according to the study protocol, especially preventing the frequent occurrence of changing primary and secondary outcome measures [13].

Considering the importance of negative trial data for evidence-based clinical practice and for prioritizing clinical research, the current trend towards more publication of negative trials, certainly is positive. And the *Scandinavian Journal of Pain* should be proud to be part of this highly important change in scientific publication practice [13,14].

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