CORRESPONDENCE

The Pharmacological Therapy of Chronic Neuropathic Pain

by PD Dr. med. Andreas Binder, and Prof. Dr. med. Ralf Baron
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Lack of Differentiation

In this review, a universal recommendation on the use and dosage of tricyclic antidepressants to treat neuropathic pain is provided without taking into account potential differences between the various agents in the group of antidepressant drugs in respect to their efficacy and tolerability for this indication (1). Of the 8 tricyclic antidepressants approved in Germany for the treatment of depressive disorders, only amitriptyline, clomipramine and imipramine are approved for long-term pain treatment as part of an overall therapeutic concept (2). However, in this paper it appears as if all tricyclic antidepressants were equally recommended for the treatment of neuropathic pain. Presumably, the available evidence does not support this view. Furthermore, manufactures' recommendations vary widely in respect to the recommended dosage (for example, tianeptine 12.5 mg t.i.d. versus amitriptyline 150 mg daily); thus, it is difficult to understand how there could be a uniform dosage recommendation for the indication "neuropathic pain".

Recommending duloxetine for the treatment of neuropathic pain under the heading "Selective Serotonin-Norepinephrine Reuptake Inhibitors (SSNRIs)" could create the impression that essentially all SSNRIs are effective in treating neuropathic pain. Even though the authors point out that in Germany venlafaxine is not approved for pain therapy, they do not comment on the third SSNRI approved in Germany for the treatment of depressive disorders, milnacipran. Furthermore, they do not mention that in Germany only Cymbalta and Ariclaim, but not Yentreve are approved for the treatment of pain in patients with diabetic polyneuropathy, even though the active ingredient in all of these products is the same (duloxetine). Prescribing Yentreve for pain therapy or Ariclaim and Cymbalta for the treatment of pain syndromes other than diabetic polyneuropathy is considered "off-label" use of these products.

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PD Dr. med. Maximilian Gahr, MA, Prof. Dr. med. Bernhard J. Connemann
Klinik für Psychiatrie und Psychotherapie III, Universitätsklinikum Ulm, Germany
maximilian.gahr@uni-ulm.de

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The authors declare that no conflict of interest exists.

Pregabalin: Risk of Addiction and Misuse

I would like to add that the risks of drug dependence, addiction and misuse are not limited to opiates/opioids, but must be taken into consideration with the first-line drug pregabalin as well. In parts of the drug scene, pregabalin is consumed in significant amounts and with severe negative consequences (behavioral changes in some cases similar to those seen with benzodiazepines and lethal [mixed] intoxications, among others).

While it may be acceptable to prescribe pregabalin to patients who are known to the physician for many years and have their diagnosis adequately confirmed, I think that pregabalin should not be prescribed to unknown patients ("recently moved to the area", "family physician cannot be contacted", "on holiday and pregabalin package accidentally left at home") without verification of the information provided by the patient. Unfortunately, the broad range of indications, extending beyond neuropathic pain, promotes doctor hopping for the purpose of acquiring pregabalin.

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Karlheinz Hoffmann
Leer, Germany
sumakaho@gmail.com

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Consider Ineffectiveness

The article presents an algorithm to facilitate treatment planning in patients with neuropathic pain (1). It is stated that this approach leads to realistic treatment goals with pain reduction of approximately >30–50%. In reality, however, this recommendation does not apply to the most common types of neuropathic pain in epidemiological studies, even though they are listed under the indication groups in the article: Anticonvulsants and antidepressants are ineffective in the treatment of radiculopathies (2). Adding local and regional back pain—summarized in the article under "mixed pain"—to this, this algorithm does not apply to an even greater group of pain patients (3).

To the contrary: These concepts—partly introduced with support of the pharmaceutical industry—have led to another drug misuse epidemic, on top of the misuse of opioids to treat non-tumor pain: the pregabalin epidemic. And this, despite the fact that more than half of the patients with neuropathies do not achieve significant pain alleviation (4). For the sake of honesty, such limitations should be mentioned in articles like this that serve educational purposes.

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Prof. Dr. med. Marcus Schiltenwolf
Sektion konservative Orthopädie, Klinik für Orthopädie und Unfallchirurgie, Universitätsklinikum Heidelberg, Germany
marcus.schiltenwolf@med.uni-heidelberg.de

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In Reply:

We would like to thank you for your interest in the treatment of chronic neuropathic pain. Due to limitations in text length, a CME article cannot provide comprehensive information about all details. Thus, suggestions of readers regarding topics relevant to clinical practice are even more important, and we are happy to discuss them.

The meta-analysis by Finnerup et al. published in Lancet Neurology mentions for the substance classes of tricyclic antidepressants (TCAs) 16 positive studies for the agents amitriptyline, clomipramine, desipramine, imipramine, maprotiline, and nortriptyline (1). Nevertheless, a general recommendation for the use of TCAs is made which is not based on the evidence supporting the efficacy of individual substances, but on the principle postulated for the treatment of neuropathic pain with TCAs which assumes the underlying mechanism of action is a modification of the functionality of descending noradrenergic (and serotonergic) systems (2). As this active principle is shared by all members of the TCA group, a general recommendation is made (1). The reason for not mentioning the SSNRI milnacipran is that for this substance—in contrast to duloxetine and venlafaxine—no studies evaluating its use in patients with neuropathic pain are available. Providing a detailed list of market approvals—and these can vary between products of different manufacturers even if the active ingredient is the same—is beyond the scope of a CME article of this type. For this reason, we explicitly highlighted this fact.

A proper diagnosis precedes the use of any medication in pain therapy. Therefore, the diagnostic evaluation is the first step of the treatment algorithm presented by us. Thus, we agree with Mr. Hoffmann that any uncritical prescription should be avoided, even though this was not stated by us in our article. Rather it is important to ensure that treatment is provided for one of the approved indications, e.g. neuropathic pain.

The concept of "mixed pain" represents a constellation in pain patients which is accepted by the European Medicines Agency in its guideline for the development of pain therapies (3). Radiculopathy is a pain syndrome which often does not respond sufficiently to treatment, as is the case with other conditions, for example chemotherapy-induced polyneuropathy (1). A neuropathic pain component is not present in all back pain patients. Rather, as we have highlighted, its prevalence lies in the range of 16 to 25%. Therefore, it is clear that not in every patient back pain can be alleviated with drugs targeting neuropathic pain. Furthermore, we have explicitly stated the efficacy of pregabalin for the treatment of neuropathic pain, using the number needed to treat (NNT). An NNT of 7.7 clearly shows that treatment with pregabalin (alone) cannot achieve adequate pain reduction in all patients with neuropathic pain. Thus, the aim of our CME article was to highlight the difficulties in the pharmacological therapy of chronic neuropathic pain and to educate about possible approaches to alleviating this pain (4).

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PD Dr. med. Andreas Binder, Prof. Dr. med. Ralf Baron
Sektion Neurologische Schmerzforschung und -therapie
Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany
andreas.binder@uksh.de

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