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Increasing the Degrees of Freedom for Treating Painful Diabetic Neuropathy

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Treatment guidelines nowadays seem to be less of a 'line to guide' for physicians on how to prescribe analgesics, but more of a directive or even a law. In the Netherlands hospital-based physicians are strict in following guidelines and do not deviate. This is partly driven by fear for being sued, partly by dogmatic insurers who stolidly refuse to reimburse anything that is not in a guideline. If patients do not respond to the usual step by step titration of analgesics from the various classes, according to the local treatment guidelines, doctors inform the patients: "apparently there is nothing we can do (by following the guidelines), you have to live with it." If I discuss the various co-analgesics we recommend in our clinic, either as a stand-alone therapy, or as co-analgesics, such as the neutraceuticals palmitoylethanolamide and alpha-lipoid acid, the reaction of colleagues in hospitals mostly is: "I cannot make use of such compounds, as they are no part of our treatment guidelines." And if I do so, many of my peers will see me as a quack doctor.

When I discussed this attitude recently with a German professor of orthopedics, he was stupefied by this simple line of thought resulting in following the guidelines only. It seems that strict adherence to guidelines is especially frequent in medical professionals of Anglo-Saxon orientated countries. However, as the orthopedic specialist pointed out, one needs to search and keep searching together with the patients into unknown territories, until one finds an adequate solution. There is no such thing as the average patient of the guidelines, every patient is unique and deserves an individual approach.

Adding compounds such as palmitoylethanolamide and alpha-lipoid acid to an analgesic regimen makes quite some sense. Firstly because the side effects of these neutraceuticals are mild and rare and secondly, because adding a new pharmacological mechanism of action to an analgesic combination often leads to a boost of the overall analgesic effect. Furthermore, there is quite a body of evidence supporting the use of these compounds, based on a great number of preclinical studies as well as on randomized clinical trials (RCT's). Mostly, in evaluating results of studies, one tends to forget that if the body of preclinical evidence is coherent in supporting the efficacy of a certain compound in disease-relevant animal models, such information needs to be added to the results of RCT's in the overall evaluation of an analgesic. Even when the level of clinical evidence for a certain compound is suboptimal, one should always consider the supportive evidence in animal pharmacology. In the case of palmitoylethanolamide data from pivotal trials supports its efficacy and safety, and the Numbers Needed to Treat for the compound, based on the key study, is 1.5 in sciatic pain [1]. In addition, around 40 clinical trials in some 5000 patients all point in the same direction. The compound has a clear analgesic and anti-inflammatory effect, as was already pointed out in 1993 by the Nobel laureate professor Rita Levi-Montalcini. She did a number of experiments using palmitoylethanolamide in her models [2,3]. Thus she was the first to discover one of the main mechanism of action of this natural compound. But as palmitoylethanolamide is a neutraceutical, all these data have difficulty diffusing into the community of pain specialists. Such a difficult diffusion of non-main stream ideas in pain treatment has been discussed in detail by the microbiologist Ludwig Fleck in his theory of thought styles [3]. Thought styles are ways scientists think and perceive. And what scientists call "scientific facts", are in reality social constructs everybody implicitly accepts to be true. Within the thought style of pain specialists, there is no place for neutraceuticals. We often hear "Oh, but that is a supplement, and thus it cannot have any real efficacy."

Pain clinicians also tend to forget that guidelines are based on a great number of clinical trials, conducted in a highly selective patient population, mostly devoid of comorbid disease states. A population which is quite artificial and does not overlap greatly with the n patients a pain clinician often sees in real life. Secondly, many physicians are not aware how big the impact of randomization procedures is on the weighting of clinical trial outcomes in a meta-analysis; it is very big. And thirdly, conducting a randomized, placebo-controlled multi-centre clinical trial nowadays is fraught with many administrative complexities and hurdles, and often obtaining ethics committee approval has become the major hurdle to take. If this indeed optimally protects the patient is not so sure. All these ethics committees did not lead to a reduction in scientific misconduct, nor to fewer issues with approved drugs.

This all leads to an extremely simplified field of consensus related to what analgesic to choose: a handful of antiepileptics, antidepressants and opioids. Most of these analgesics have quite cumbersome side effects and many patients cannot tolerate these drugs. They and prefer to stay in pain, rather than becoming a zombie. Therefore it is quite important for pain specialists and pain patients that we create increasing dimensions of freedom in selecting the appropriate analgesic cocktail for chronic pain patients.

Guidelines should be re-defined as guidelines only and not as straitjacket. Furthermore, the decision to select an appropriate pain-treatment should remain in the hands of the clinician, without influence of the medical insurance companies. This is of utmost importance, as in the Netherlands prescribing physicians increasingly receive letters from such insurance companies explaining that they do not reimburse treatment, because they think the treatment is "not rational". Rationality in the eyes of the insurance companies is 100% based on guidelines. Even in patients experiencing great relief in pain, administrators nowadays turn down reimbursement, by hiding behind guidelines. This clearly needs to be changed, for the benefit of the patient and for the benefit of the treating physician.

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