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Editorial comment

Why would studies on furry rodents concern us as clinicians?

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In the present issue of *Scand J Pain* Anna Folkesson and co-workers describe the effects of gabapentin and venlafaxine and a combination of the two drugs in the spared nerve injury model of neuropathic pain in the Sprague–Dawley rats [1]. In contrast to an earlier opposite finding with otherwise similar experimental setting, but different rat strain [2], venlafaxine potentiated the anti-hyperalgesic/allodynic effect of gabapentin. Nice. But why would a busy clinician devote any precious time to reading another paper from an experimental laboratory?

There are very few human studies on combinations of different drugs for neuropathic pain [3]. In a randomised, double blind trial [4] six painful diabetic neuropathy patients who had minimal or no benefit from gabapentin alone, combining venlafaxin to it improved pain control, mood and quality of life. From that very small study it is not possible to determine what venlafaxine would have done alone, and it would be more interesting to combine at least moderately effective drugs. The effect of co-administration of gabapentin and venlafaxin in the Folkesson experimental study was not produced by change in gabapentin pharmacokinetics, and as there are no known kinetic interactions produced by gabapentin, it is likely that also venlafaxin kinetics were unaffected. However, very little is known on possible drug interactions on the drug transporter systems in the central nervous system [5,6], which could change the actual effect-site concentrations.

Gabapentin binds to α_2-δ subunit of voltage sensitive Ca^{++}-channels in presynaptic sensory neurons and reduces release of synaptic neurotransmitters such as glutamate, noradrenaline, GABA, substance P, CGRP, acetylcholine and glycine [7]. Supraspinally gabapentin can activate the descending inhibitory noradrenergic tracts [8–10], possibly selectively in neuropathic pain states [11,12]. Thus, the antiallodynic or antihyperalgesic effect of gabapentin could be increased by drugs that reinforce the effect of noradrenaline in the dorsal horn of the spinal cord. In the Folkesson study, gabapentin was co-administered with the serotonin and noradrenaline reuptake inhibitor venlafaxine. Any direct extrapolation to human patients from an experimental animal study can be misleading, or even dangerous. However, both of these drugs are clinically available, and in practice often combined in treatment of individual patients with difficult neuropathic pain, and even in other types of chronic pain. More importantly, the principle of combining drugs with mechanisms of action that are likely to produce synergistic effect when used together, is something as valid in daily clinical practice as in the basic research laboratory.

The main limitations of the Folkesson et al. paper are that only one combination of doses, and only acute administration is studied. The "gold standard" for studying interactions between two active drugs is the isobolographic method, where dose–response curves for both drugs alone and in certain combinations are analysed [13]. However, when complex animal models, such as the spared nerve injury model of neuropathic pain are used, creating full dose–response curves for different drug combinations would necessitate sacrificing too many animals. The other issue is that merely acute effects of gabapentin, venlafaxin and the combination are studied. In some, but not all models of neuropathic pain the effect of antihyperalgesic medications, especially antidepressants such as amitriptyline can be assessed only after repeated administration [14,15]. This could also be the case with gabapentin, especially if some of its effects are mediated by blocking formation of excitatory synapses via the neuronal thrombospondin receptor [16].

It has been claimed that anything works in the laboratory, and (almost) nothing in the clinic. It has been difficult to assess the validity of the experimental animal models of neuropathic pain [17], in part because of the large number of different models used, and on the other hand, due to the relative shortage of reports on specific compounds that have been tested both in an given experimental model and in real human patients. The biggest dilemma in the evaluation of the validity of these models is the fact that efficacy of a given drug in clinical neuropathic pain varies from patient to patient, and in many cases adverse effects prevent using effective doses [18]. The spared nerve injury model, which is an anatomically clearly defined model of peripheral neuropathic pain, validated both in rats and mice [19,20] was used in the Folkesson study. Methodological quality and rigorous reporting practices [21] increase the value of any experimental study to both laboratory scientists as well as to clinicians. Although *Scand J Pain* has not – just not yet, I hope – decided to require all experimental studies to report experimental conditions and procedures according to the protocol proposed by Rice et al. [21], in the Folkesson paper we can already now learn, e.g. that only two (7%) of the rats were withdrawn from the study due to lack of predefined allodynic response after the nerve injury, and that gabapentin-induced ataxia was assessed to exclude bias on the pain measurements. This kind of information helps us to better understand what we know and what

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we still need to know, when putting together the pieces of the big puzzle.

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