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Ketamine for neuropathic pain: a tiger that won't bite?

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Editor—Neuropathic pain, a description associated with a defect in the somatosensory nervous system, is characterised by specific symptoms including burning, electric or shooting pain, hyperalgesia, and allodynia.[1] Hyperalgesia, allodynia, or both are signs of central sensitisation, a state in which there is an exaggerated response of nociceptive neurones to normal or subthreshold stimuli – that is a gain in function in relation to nociceptive stimuli.[2] Irrespective of aetiology, neuropathic pain is difficult to manage, and consequently has a large impact on patient quality of life and ability to participate in common daily activities. Owing to the limited efficacy of common pain treatments (including treatments considered specific for neuropathic pain such as antiepileptic drugs and antidepressants),[3,4] many physicians have adopted the *N*-methyl-D-aspartate receptor antagonist ketamine as treatment for therapy-resistant or refractory neuropathic pain.[5] This is not surprising given the role of this excitatory receptor in the chronification of pain (particularly neuropathic pain) and the ability of ketamine to reduce windup and temporal summation, surrogate measures of central sensitisation.[6–8] Still, proof for use ketamine in neuropathic pain from RCTs is limited.

We and others have recently performed narrative and systematic reviews of RCTs that examined the efficacy of ketamine in a variety of neuropathic pain conditions.[9–14] Jonkman and colleagues[10] summarised most recent systematic reviews on ketamine treatment in acute and chronic pain, noting the large heterogeneity of included randomised trials and the number of studies that were of lower quality and often underpowered. The general conclusion from these reviews is that efficacy of intravenous ketamine in neuropathic pain is small and lasts no longer than 1–2 days. Efficacy was even less for other administration routes (oral, intranasal, subcutaneous). These results are in contrast to open-label studies and retrospective case series that show efficacy of ketamine in pain (including neuropathic pain).[12,15] The results of these non-randomised observational and experimental studies support the practice of clinicians who treat patients with ketamine.

An important question is why is there such a large disconnect between RCTs on ketamine efficacy in neuropathic pain and the observation that ketamine is effective in clinical practice as reflected in the outcomes of open-label studies and case series. The answer is not easy, but we will share some of our ideas that may, to some extent, explain the disconnect.[10–12] First, we would like to emphasise a statement made by MacKintosh[15] regarding the use of ketamine for cancer and neuropathic pain: that lack of evidence on ketamine efficacy in cancer pain is not the same as lack of benefit, but a lack of evidence of benefit. We agree and argue that the lack of evidence may be related to the following issues. Apart from the ketamine dose, duration of treatment is particularly important. Single or short-term infusion regimens (<10 h) have little impact on the relief of neuropathic pain. Only when infusion duration exceeds 10 h can sustained pain relief be expected.[9] This probably relates to a ketamine-induced chemical reset of central pain pathways that requires sustained blockade of the *N*-methyl-D-aspartate receptor.[16] In most RCTs, the ketamine dose is fixed and often relatively low to limit psychomimetic side-effects. In clinical practice, ketamine dose is regularly titrated up or down to patient need and co-medications (e.g. benzodiazepines) or co-analgesics (e.g. α_2-agonists), all aimed to optimise pain relief while reducing side-effects.

Use of pain intensity scores as an outcome parameter may be unrealistic. Chronic pain patients have difficulty scoring their pain on the 11-point numerical rating scale or on visual analogue scales,[17] and it is questionable whether the beneficial effects of ketamine are captured within this pain discriminatory dimension. Ketamine may improve the mood state of the patient, causing improved physical and emotional capabilities without directly improving pain intensity.[11] A better approach would be to query patient satisfaction with treatment and adapt the dose using this endpoint.

Alternatively, quantitative sensory tests can guide the efficacy of pain treatment. Selection criteria in RCTs often preclude large portions of patients that could benefit from ketamine therapy, and consequently these studies may not be representative of the clinical population that might benefit most from ketamine treatment.

Finally, in RCTs, patients are often selected under the assumption that their pain mechanisms and presentations are homogenous. Despite the fact that we are studying a population with a single underlying disease, these patients often represent heterogeneous subgroups with different underlying pain mechanisms and consequently pain phenotypes.[4] We and other groups propose phenotyping patients based on quantitative sensory testing to identify the presence of central sensitisation or impaired endogenous pain modulation, together with (neuropathic) pain questionnaires.[4,11] This may enable more specific treatment options in patient subgroups. For example, the endogenous pain system might be used as biomarker in an individualised, mechanism-based treatment approach in patients with chronic low back pain.[18]

In summary, it could be that the population that would benefit most from ketamine treatment is not included in current RCTs with their rigid dosing schemes, strict inclusion criteria, and endpoints that are often not well understood by the patient. We propose to focus future RCTs of ketamine for neuropathic pain on patients with specific phenotypes, such as presence of central sensitisation, or to specific and well-defined symptoms such as opioid tolerance or opioid-induced hyperalgesia. These symptoms and phenotypes might be more susceptible to improvement by ketamine.[11] Given the items discussed above, future RCTs should use an adaptive dosing-design with well-defined, comprehensible, and practical endpoints.

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Declarations of interest

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