Central Sensitisation Causes, therapies and terminology - Authors' reply

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Central sensitisation in chronic pain conditions:

A plead for focussing on implementation potential in assessment and treatment

Authors' response:

We are pleased with the way our review addressing the latest discoveries regarding central sensitisation in patients with chronic pain and its potential for applying these discoveries to precision medicine approaches[1] has been received by the international community, including the 4 letters to the Editor. We thank all authors of the letters for their positive feedback and special interest in our review, and their willingness to discuss it further with a wider audience.

We fully support Minhas et al. in their claim for population based public health strategies to improve the prevention and surveillance/detection of central sensitisation in pain conditions. Within this view, we applaud their pioneering work showing potential links between domestic abuse and increased risks of developing syndromes indicating central sensitisation[2]. This is an important area for further research with massive implementation potential.

We agree with Mehta et al. that conditions such as osteoarthritis and rheumatoid arthritis are characterised by peripheral inflammation as well as features of central sensitisation, and that a balanced bottom-up and top-down approach seems rational. As explained in our review article, the possibility for precision pain medicine treatment according to pain phenotyping in rheumatology practice appears to be the logical next step[1]. Within this view, targeting peripheral inflammation together with strategies that attenuate central sensitisation seems appropriate for the subgroup of the rheumatoid arthritis population showing features of central sensitisation.

In addition, 2 letters addressed the issue of terminology. We agree with Weisman et al. that central sensitisation is not part of the definition of nociplastic pain, however, signs of sensitisation are

generally present in nociplastic pain conditions[3]. Given the clinical focus of the paper, central sensitisation was defined as an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity[4]. Earlier versions of the review included other definitions of central sensitization, but given the review's focus on human studies only, it was decided not to address them. Under the definition used for the purpose of our review, it is possible to study central (nervous system) sensitisation neurobiology in humans. This is not the case for other definitions such as "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[5], because in vivo measurements of nociceptive neuron responses in the central nervous system are not possible. While we are aware that the term central sensitisation is controversial and not optimal, our review focussed on human studies and intended to update clinicians as well as researchers. We are aware of the importance of appropriate terminology, but there is no agreement in the scientific community on terminology and this topic would be outside the scope of our review. Importantly, a key message for clinicians is that central sensitisation goes beyond the nociceptive system and pain experience[1]. This is key for clinicians to understand that non-pain symptoms can results from the same underlying mechanism (i.e. central sensitisation). Still, we agree that it's appropriate for clinicians to understand the preclinical neurophysiological experiments that led to the discovery of central sensitization[6], which were intended to improve understanding of chronic pain in humans[4]. We also agree that central sensitisation can be viewed as an umbrella term covering several, partly overlapping and highly related mechanisms.

Cayrol and van den Broeke argue against our use of precision medicine, but mixed up terminology: precision medicine is not the same as 'distinguish one patient from another', where they refer to the term of personalized medicine or individually tailored treatment. We adhere to the definition of precision medicine by The National Research Council's[7] which refers to classifying patients into different subgroups and tailor treatment accordingly, while personalized medicine literally means providing a treatment unique to each patient. Still, precision medicine and individually tailoring

treatment are certainly not mutually exclusive: when clinicians treat the subgroup of the chronic pain population showing features of central sensitisation with a 'central sensitisation-specific' treatment strategy. It also seems natural to adapt the treatment to the individual patients' characteristics (e.g. adapting the content of the physical activity program to the patient's self-defined functional goals, individually tailoring of insomnia-targeted cognitive behavioural therapy to the patient's current sleep habits, adapting drug dose to the patient's body mass index).

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