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Editorial comment

Biomarkers of pain – Zemblanity?

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Is it possible to develop a valid biomarker for "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"? Yes, definitely. We already use such a biomarker daily in clinical practice. Patient report is the gold standard of pain assessment and by the definition in the IASP taxonomy and especially the accompanying explanatory note, pretty much the only valid measure of pain (http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions#Pain). However, inability to communicate verbally does not negate the possibility that an individual is experiencing pain.

Other, more obvious biomarkers, such as a rise in the concentration of a neurotransmitter or a change in the plasma level of a hormone, activity of a certain neurone or a group of neurones (even a very large and opinionated group of neurones), or a behavioural pattern, such as withdrawal of limb from a noxious stimulus, all could be useful for research. But such changes should never be misunderstood as synonymous to pain.

A certain activation pattern in fMRI imaging of brain areas known to be important for pain processing (including thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, and the periaqueductal grey matter) has, in an experimental setting in healthy young adults, been shown to discriminate between painful heat and non-painful warmth applied to the skin [1]. This activation pattern could document a painful experience with very high sensitivity and specificity [1]. But what if a patient would report suffering from pain without showing this brain activation pattern? The editorial accompanying this fMRI-study in NEJM ends with wise words: we may ultimately have to acknowledge that "pain is pain" and can be reported only by the patient [2]. Pathophysiological changes typical to certain painful conditions, such as cartilage damage in arthrosis or MRI changes in low back pain have notoriously bad correlation to pain experienced by the individual. It is dangerous to create an idea that by measuring some simple–or complicated, for that matter – surrogate parameter or even a profile of such parameters we could judge if another person is in pain. Or even more importantly, that lack of such changes would always signal absence of pain. Magnitude of responses in the "pain matrix" in the CNS do not necessarily reflect pain intensity, are strongly influenced by the context, and they can be elicited also by non-nociceptive stimuli [3].

The review by Lars Arendt-Nielsen and Michele Curatolo in the present issue of the Scandinavian Journal of Pain, entitled "Mechanistic, translational, quantitative pain assessment tools in profiling of pain patients and for development of new analgesic compounds" is not in conflict with the above [4]. Emphasis should be placed on the word "tools" in the title of the paper. Finding better preclinical testing methods is critical for more effective development of novel analgesics. Until now, the track record of rational drug development in the field of analgesics [5] has not been very convincing. Most of the new analgesics have originally been developed for other indications, and it has been argued that none of the analgesic drugs in clinical use at present is a result of a truly rational development program. This will change in the future, as completely new analgesics, targeted against defined pain mechanisms for focused patient subgroups are in late preclinical and early clinical development; there are some fascinating examples in the review by Arendt-Nielsen and Curatolo [4]. Previously, important mechanistic findings were made by chance, combined with well-informed curiosity; discovery of acetylsalicylic acid as the best example [6]. In modern world, venturing back to "irrational drug development", or trusting solely in serendipity is not a research strategy that would convince scientists, investors, or patients.

Zemblanity is a word coined by the British novelist and screenwriter William Boyd: "it is the opposite of serendipity, the faculty of making unhappy, unlucky, and expected discoveries by design" [7]. Pain biomarkers could be zemblaneous for clinical practice, but useful and beneficial for research.

1. Conflict of interest

No conflict of interest declared.

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