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EDITORIAL OPEN ACCESS

Management of chronic pain: Still a challenge for clinicians

Gergely Feher, Marietta Pohl, Gyula Bank, Kornel Mak, Antal Tibold, Gabriella Pusch

Chronic pain is a devastating disease and has recently been highlighted as one of the most prominent causes of disability worldwide. For example, lower back and neck pain were the leading global cause of disability in 2015 in most countries [1] Chronic pain syndromes significantly affect both the individual and the society and their management is a challenge for clinicians.

Chronic pain is usually defined as any pain lasting more than three months (apart from its origin) and affects about one-fifth of the total population. One out of ten people suffer from chronic widespread pain, especially in the elderly [2]. Although the clinical phenotypes of different pain syndromes are variable, they are linked through neuropsyhiatric complications that include mood disorders, persistent fatigue, coginitive dysfunction, headache, irritable bowel syndrome, and insomnia.

The key pathophysiological process behind each of these syndromes is central sensitization [3, 4]. Imaging studies have confirmed altered activity of afferent and descending pain pathways, as well as atrophy of different pain perception regions of the brain, which can result in psychiatric symptoms such as increased activation in areas involved in somatosensory-discriminative, affective, and coginitive processing of pain-primary/secondary somatosensory cortex, anterior and posterior cingulate, insula, prefrontal cortices and thalamus also known as "pain matrix" [3, 4]. One key brain area involved in the pain (neuro) matrix is the amygdala, often referred to as the fear-memory centre of the brain, which has an important role in the process of negative emotions (in parallel with the anterior cingulate cortex so called the fear network of the brain) [4].

These significant activation changes can powerfully modulate spinal cord synaptic transmission leading to increased excitability of dorsal horn neurons, that is, central sensitization, partly via suppressing inhibitory synaptic transmission [5]. Further potent inhibitory neurons, such as descending pathways originating in the brainstem, contribute to modulation of pain processing. Lesions that affect opioidergic and monoaminergic systems lead to exacerbation of the pain disinhibition [5].

Based on the above mentioned findings, chronic pain requires multidisciplinary team management. Chronic pain can also lead to pain personality (which may have genetic background) and manifests in higher harm avoidance (fearful, pessimistic, sensitive to criticism, and requiring high levels of re-assurance) and lower self-directedness (difficulty with defining and setting meaningful goals, low motivation, and problems with adaptive coping) may be the most distinguishing personality features of chronic pain sufferers and can lead to insufficient treatment response. This personality profile is evident in a wide variety of chronic pain conditions such as fibromyalgia, headache and migraine, temporomandibular disorder, trigeminal neuropathy, musculo-skeletal disorders and heterogeneous pain groups [6].

First of all, we have to find appropiate time for our patients taking the pain personality and other neuropsychiatric complications into account. Physicians commonly redirect and focus on clinical interviews before giving patients the opportunity to complete their statement of concerns, which can be associated with treatment failure [7].

Acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used/prescribed analgesics to treat any kind of pain, however, they are only effective for pain of nociceptive origin and not for chronic/neuropathic pain. They are widely available and their chronic use can be associated with significant adverse events such as gatric ulcers, renal failure or myocardial infarction [8]. Medication overuse headache is also a well-known phenomena for pain physicians. Therefore, based on the

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FDA recommendations NSAIDs should be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals so NSAIDs have very limited use in the management of chronic pain [9].

Opioids are pretty effective in the treatment of chronic/neuropathic pain, however, the potentially severe side effects and and high risk of addiction rolls back their widespread use. They can be prescribed as rescue drugs for short time as the therapeutic effect of the antineuropathic medication is tapered up within several weeks or can be used as add-on medication in therapy-resistant cases [5].

Tricyclic antidepressants (TCA) are also known as early antidepressant medications. These first-generation medications were effective in the treatment of depression because they enhanced serotonergic or noradrenergic mechanisms or both. They had also were the first medication category that proved effective for neuropathic pain in placebo-controlled trials [5]. Unfortunately, the TCAs also blocked histaminic, cholinergic, and alpha 1-adrenergic receptor sites, and this action brings about unwanted side effects such as weight gain, dry mouth, constipation, drowsiness, and dizziness. However, they can be used in the treatment of insomnia. The cardiovascular effects of TCAs are well characterized and include orthostatic hypotension, slowed cardiac conduction, type 1A antiarrhythmic activity and increased heart rate. Although much of them are temporary and mild effect and they are generally well-tolerated. On the other hand, their use should be avoided in post-infarct states and in the case of conduction disturbances and cardiac arrhythmias (IA antiarrhythmic effect) [5].

Selective serotonin reuptake inhibitors (SSRI) are increasingly being used to treat a spectrum of depressed patients, including the elderly. As a class, SSRIs have comparable efficacy to TCAs against depression but are generally better tolerated. Despite their wide use there is still limited evidence for the role of classical SSRIs in the treatment of chronic pain [5].

The class of serotonin and norepinephrine reuptake inhibitors (SNRIs) now comprises three medications: venlafaxine, milnacipran, and duloxetine. These drugs block the reuptake of both serotonin (5-HT) and norepinephrine with differing selectivity. Whereas milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity, duloxetine has a 10-fold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT. All three SNRIs are efficacious in treating a variety of anxiety disorders which is beneficial with regard to the concomittant neuropsychiatric complications of chronic pain patients [5].

Antiepileptic drugs (AEDs) have a long history of effectiveness in the treatment of chronic/neuropathic pain, dating back to case studies of treatment of trigeminal neuralgia with phenytoin in 1942 and carbamazepine in 1962. Since 1993, nine new AEDs (felbamate, gabapentin, pregabalin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, and zonisamide) have received Food and Drug Administration (FDA) approval for the adjunctive treatment of partial seizures. In addition to providing efficacy against epilepsy, these new AEDs may also be effective in chronic/neuropathic pain.

However, only gabapentine and pregabaline seem to be effective agents in the treatment of chronic pain syndromes. Pregabalin also has shown efficacy in generalized anxiety disorders and in insomnia. Persons taking them can expect to suffer dizziness, somnolence, peripheral oedema, and gait disturbance. On the other hand, serious adverse events were no more common than with placebo [5].

The efficacy of valproic acid and lamotrigine is doubtful, they are not recommended routinely. Using the Cochrane criteria carbamazepine seems to be effective, while no trial was longer than four weeks, of good reporting quality, using outcomes equivalent to at least moderate clinical benefit. In these circumstances, caution is needed in interpretation, and meaningful comparision with other interventions is not possible. The efficacy of topiramate is also neutral in this condition [5].

Coginitive, psychosocial, and emotional factors have a critical influence on pain perception, due to the connectivity of brain regions controlling pain perception, attention or expectation, and emotional conditions [2]. Coginitive-behavioural therapies (CBTs) are promising techniques in the complex management of chronic pain. CBTs focus on increasing flexibility in thoughts and behaviors to respond more adaptively to challenges. In the context of chronic pain, CBTs often include psychoeducation about pain, coginitive restructuring of maladaptive pain-related beliefs, problem-solving, relaxation training, behavioural activation and pacing improving the coping strategies of the individual patient [10]. A recent evidence-based review showed the efficacy of this techniques [10].

In summary, the introduction of the neurophysiological model of pain during the past decades stimulated the development of more therapeutically effective and cost-effective interdisciplinary chronic pain management programs including both pharmacological and coginitive therapies.

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Keywords: Acetaminophen, Antiepiloptic drugs, Chromic pain, Opioids, Nonsteroidal anti-inflammatory drugs, Selective serotonin reuptake inhibitors, Tricyclic audidepress auts

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