PAIN MANAGEMENT: PART 3

In the final part of our Q&A feature, our specialist authors answer your questions on managing pain in primary care

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Often treatment is more governed by what is tolerated rather than what is effective

Q. Is the diagnosis of the cause of pain important when deciding on pain management regimens?

A This has been a subject of ongoing debate and it is safe to say that the jury is still divided on this topic. There is very little evidence that understanding the pathophysiology of any particular pain helps to predict response to treatment, although notable exceptions include, for example, the use of duloxetine and gabapentin in diabetic neuropathy. A recent article and editorial in the *BMJ* stated that "most drugs do not work in most people", but at the same time one should pursue analgesic success while expecting analgesic failure. These statements by senior researchers are not surprising when one considers the meaning of numbers needed to treat (NNT). Our most successful drugs, such as amitriptyline and gabapentin, have an NNT of around 2.5-3, so between two and three people need to be treated for one person to experience more than 50% relief over the effect of placebo.

The multiplicity of pathways involved in pain production and their similarities with the mechanisms of cognition means that often treatment is more governed by what is tolerated rather than what is effective. Trials of drugs in patients can be slow, since different drugs have to be tried before combination therapies have to be considered. This requires patience and necessitates controlling patient expectations during the process.

Be aware if one is dealing with high levels of depression, anxiety or distress or there are significant psychosocial problems - these may significantly impair response to treatment, and in such situations treatment of the underlying psychiatric/psychological and social issues may be far more important. Depression has been shown to significantly hamper engagement in pain management programmes. Furthermore, participation in functional rehabilitation / pain management programmes is often best kept for after the conclusion of any ongoing process of litigation.

(See also Q&A on chronic pain syndrome)

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Q Is there a role for non-pharmaceutical topical agents, such as Flexiseq, for treating osteoarthritis?

A Flexiseq is a gel containing nanostructures called "*Sequessome*" vesicles, which appear able to cross the skin and travel to the sites of pain caused by osteoarthritis. This novel technology seems to have demonstrated proof of concept in some studies where the phospholipid Sequessome vesicles have been found within synovial fluid. It is postulated that this causes a "lubricant" action which helps to provide pain relief equivalent to that of an oral NSAID (Conaghan et al. *Curr Med Res Opin*, 2014.30;4:599-611).

No trials have been conducted comparing Flexiseq with other available topical treatments for pain associated with osteoarthritis, but Flexiseq has been studied compared to a commonly prescribed oral NSAID (celecoxib) and has been shown to have comparable efficacy (Conaghan et al. *Rheumatology* 2013;52:1303-12). These data show equivalent reductions in pain and stiffness for Felxiseq compared with celecoxib 100 mg b.d. after 12 weeks – the latter notably being an oral agent not a topical treatment.

It is too early to say definitively whether such a topical agent is going to be helpful to patients in the longer term, but the fact that it contains no pharmacologically active ingredients means that it is not being subject to standard pharmaceutical regulations and is licensed as a non-medicinal product by the MHRA. The company suggest that because there are no pharmacologically active agents and it is a physically active substance, one can avoid all the possible systemic side effects of oral and possibly topical anti-inflammatories, including increased cardiovascular and cerebrovascular thrombotic risk and also the well-known side effects of gastric and kidney toxicity. Flexiseq may therefore have a useful role in those patients who are completely intolerant of NSAIDs, or in whom such drugs are contraindicated. As far as we can tell the long-term side-effects of these liposomes in the human body are not known.

It would be helpful if longer term head-to-head trials with other topical agents were performed.

Q In patients with rheumatic conditions, what factors should inform the decision of whether to offer an oral or topical NSAID?

A Oral non-steroidal anti-inflammatory drugs (NSAIDs), while very frequently prescribed drugs are associated with 25% of all adverse drug reaction reported. Theoretically, topical NSAIDs allow local application with little or no systemic side effects, such as peptic ulcer disease and GI haemorrhage (which occur with a 15% incidence after oral NSAIDS). In contrast the incidence of adverse effects after topical NSAIDs are reported to be in the order of 10-15% and consist mainly of local skin irritation.

Studies suggest that after topical application there is less than 5% systemic bioavailability compared with equivalent oral administration, but there are concerns that apart from dermal penetrations, drug concentrations after topical administration may be variable and poor in deeper tissues, including joints.

In terms of reported efficacy, topical NSAIDs are an effective and safe short-term treatment for acute musculoskeletal pain due to sprains or strains or acute sporting injuries. The greatest benefit has been seen in the first week following injury. For the subsequent week there continued to be some be some benefit in 65% of patients given topical NSAID, compared with 43% taking placebo. Some studies report placebo responses of up to 80%, hence the numbers needed to treat (NNT) – which always compares response against placebo – is unreliable, with figures in the range of 4.5, a significant underestimation of the actual number of patients who will respond to the treatment in clinical practice. There is little or no data supporting a role for such topical treatments beyond two weeks.

The efficacy of medium term *oral* NSAIDs has been well established, with usually over 70% of patients practically experiencing significant benefit in clinical practice and NNTs ranging from 1.5-2.6 for commonly used doses of ibuprofen, diclofenac and Naproxen – albeit with the side-effects indicated above.

In practice, therefore, topical NSAIDs may be recommended for an acute superficial soft tissue injury for up to two weeks. Because of the high placebo response it may not be necessary to use a particularly strong formulation. If the patient finds it beneficial after two weeks, ask them to buy their own over-the-counter. Continued use, in our opinion, of topicals may be warranted in those who are at significant risk of gastrointestinal and renal side effects, particularly the elderly. For more systemic symptoms it is better to use an oral preparation if tolerated.

Q What is chronic pain syndrome, and how should it be managed?

A Chronic pain syndrome (which may be referred to as "chronic pain disorder" by psychiatry colleagues) occurs where psychological and physical factors interact, giving rise to an entrenched, chronic and difficult to treat condition – often associated with levels of pain and disability in excess of that which would be expected based upon physical findings and known injuries alone.

Chronic pain syndrome/disorder involves a complex mixture of persistent pain and learned behaviours including:

- Fear avoidance (See below)
- Catastrophisation of pain (which is defined as cognitive and emotional processes encompassing magnification of pain-related stimuli, feelings of helplessness, and a generally pessimistic orientation)
- Entrapment (which may be through conscious as well as unconscious means)

The resultant cycle of disability may be aggravated by external factors, such as the benefit system (e.g. by becoming "stuck in the rut" of the sick role) or the medicolegal process (e.g. by constantly having to dwell upon and relive one's symptoms within endless appointments and interviews, rather than "letting go" and focusing on the future – and also sometimes by means of the temptation to exaggerate disability for financial gain).

The presence of depression, anxiety or symptoms of psychological trauma (such as post-traumatic stress symptoms following a serious accident) is likely to contribute to the establishment of "vicious cycles" of depression, anxiety and enhanced pain. In such situations, assessment in the specialist pain clinic with access to effective multidisciplinary components – ideally including psychiatric and psychological services – is important. The depressed, anxious or otherwise psychologically traumatised patient requires psychiatric / psychological treatment in addition to analgesic or other treatment for their physical pain. To treat such patients with simply large doses of morphine should be actively resisted.

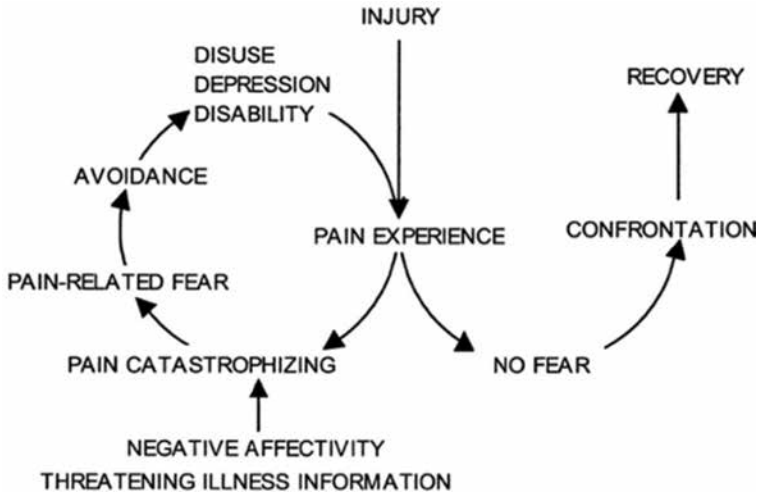

Figure 1. Fear-avoidance model of chronic musculoskeletal pain
Adapted from *Vlaeyen and Linton, Pain*. 2012 Jun;153(6):1144-7

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NEXT ISSUE

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