**Feature: Research Review**

**TOWARDS THE DEVELOPMENT OF NEW PAIN TREATMENTS**

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**PHARMACOTHERAPY IN PAIN PATIENTS WITH SUBSTANCE ABUSE**

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Prescribing information can be found attached to the back cover and/or on the outside back cover
It is interesting to see a paper from an academic centre in an international journal considering the question of whether acupuncture is associated with reduced pain outcomes for patients with chronic pain compared with sham-acupuncture (placebo) or no-acupuncture control. Many years ago this would not have been a topic for a high impact journal.

The authors examine the case for acupuncture carefully and their conclusion is clear. Acupuncture is associated with improved pain outcomes compared with sham-acupuncture and no-acupuncture control, with response rates of approximately 30% for no acupuncture, 42.5% for sham acupuncture and 50% for acupuncture.

The authors deal with the common and distressing problem of female pelvic pain (vulvodynia). This US group conducted a longitudinal, population-based study of women using a validated survey-based screening test for vulvodynia that was repeated at six-month intervals over 30 months. Women who screened negative for vulvodynia at baseline and were followed up with least one additional survey (n=1,786) were assessed for onset of vulvodynia. The incidence rate was 4.2 cases per 100 person-years, confirming that this is an important clinical problem. Vulvodynia was more common in women who were younger; 7.6 cases per 100 person-years at age 20 years, compared with 3.3 cases per 100 person-years at age 60 years. It was more common in Hispanics (9.5 cases per 100 person-years) and in women who were married or living as married (4.9 cases per 100 person-years).

Factors that increased risk for new-onset vulvodynia included baseline sleep disturbance, chronic pain in general, specific comorbid pain disorders and specific comorbid psychological disorders.

Onset is more likely among women with previous symptoms of vulvodynia or those with intermediate symptoms not meeting criteria for vulvodynia, and among those with pre-existing sleep, psychological and comorbid pain disorders. This suggests vulvodynia is an episodic...
condition with a potentially identifiable prodromal phase.

Bean DJ, Johnson MH, et al.
The outcome of complex regional pain syndrome type 1: a systematic review.

This systematic review examined the outcome of complex regional pain syndrome (CRPS) type 1 and included 18 studies, with 3,991 participants – so it is big!

A quality assessment revealed significant limitations in the literature, with many studies utilising different diagnostic criteria. The three prospective studies demonstrated that for many patients, symptoms improve markedly within six to 13 months of onset. The 12 retrospective studies had highly heterogeneous findings, and documented lasting impairments in many patients. The three cross-sectional studies showed that rates of pain and sensory symptoms were highest amongst those with the longest duration of CRPS.

In addition, most studies showed that motor symptoms were the most likely to persist whilst sudomotor and vasomotor symptoms were the most likely to improve. However, little is known about the prognostic factors that might differentiate between these groups.

Lee J, Ellis B, et al.
Chronic widespread pain, including fibromyalgia: a pathway for care developed by the British Pain Society.

Chronic widespread pain (CWP), including fibromyalgia, is prevalent. The British Pain Society is supporting the treatment of such patients through a care pathway. The authors describe the rationale for the CWP and fibromyalgia pathway. This is a welcome initiative that will benefit a large group of patients in both primary and secondary care settings. This pathway aims to reduce variation in standards of care, reduce delays at all stages of care and to enable clinicians to help patients accept a diagnosis of CWP. This diagnosis should be based on the presence and distribution of symptoms in the absence of another defined pathological process. The history and clinical examination is generally more important than laboratory investigations. There is an emphasis on simultaneously addressing physical, psychological, social and personal needs without an over-emphasis on any one treatment modality. The pathway has focused on potential pitfalls in the use of long-term opioids and provides the rationale for why these are not recommended. People with CWP often value explanation and education, and most clinicians have generic skills in managing long-term conditions that can be supplemented by the interventions and actions detailed in this pathway.

Bourinet E, Altier C, et al.
Calcium-permeable ion channels in pain signaling.

This is a good basic science paper on the different types of voltage- and ligand-gated calcium ion channels involved in pain processing. The functions of these channels include detecting mechanical and chemical insults, generating action potentials, regulating neuronal firing patterns and initiating neurotransmitter release at dorsal horn synapses with ensuing activation of spinal cord neurons that project to pain centres in the brain.

Long-term changes in ion channel expression and function are believed to contribute to chronic pain. Many of the channels involved in the afferent pain pathway are permeable to calcium ions, suggesting they have a role in cell signalling beyond simply generating electrical activity. This paper reviews different types of calcium-permeable ion channels in the afferent pain pathway and their role in pain pathophysiology.

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The neurobiology of pain and analgesia exhibits plasticity in different pain states. Mixed pain states are more difficult to model and research in this area, and so could fail if aetiology alone was the rationale for prescribing, or an entrance criterion for the trial in the case of investigational drugs. Therefore, some form of data gathering of sensory phenotypes in clinical studies would be valuable for the future.

Plasticity of pain states
It is very clear that the neurobiology of pain and analgesia exhibits plasticity in different pain states, in that the signalling mechanisms change following pathophysiological events. By better understanding this plasticity, improved therapies for the two major types of pain, neuropathic pain where there is a lesion or disease of somatosensory neurons, and inflammatory pain resulting from damage to tissue, may emerge. Cancer pain can consist of one or the other or a combination but has unique features as well. The peripheral mechanisms of these types of pain are very different; neuropathic pain primarily involves ion channels and inflammatory pain is generated by chemical mediators, yet within the central nervous system the signalling systems appear to be largely common to both, as is their modulation by the enhancement of inhibitors.

We have a framework for understanding mechanisms at play in different pain states and thereby using treatments that reflect the underlying events. Animal studies using models of these different pain states can elucidate these mechanisms, but this is very hard to do in patients.

Sensory profiling
A breakthrough has been the sensory phenotyping of patients based on the logic that the individual sensory profile will reflect the ongoing mechanisms. Approximately five subgroups have been identified in a range of neuropathic pain disorders and in fibromyalgia, and in the former, aetiology is not a predictor of sensory profile. If treatments have different effects on the subgroups we will be able to move towards more predictive treatments. At the same time, given the subgroups of patients identified within a pain phenotype, a drug may not be effective in all patients with that pain type, and so could fail if aetiology alone was the rationale for prescribing, or an entrance criterion for the trial in the case of investigational drugs. Therefore, some form of data gathering of sensory phenotypes in clinical studies would be valuable for the future.

Contribution of preclinical studies
There has been considerable discussion of the predictive value of animal models for the development of new clinical drugs. Personally, I am not clear why it is suggested that drugs fail in patients as a result of the limitations of animal models. The mechanisms of action and thus rationale for use of certain established drugs in pain management, such as gabapentin, pregabalin, tricyclic antidepressants and selective serotonin–noradrenaline reuptake inhibitors, have come from the preclinical realm, as have more recent agents such as anti-TNF and anti-nerve growth factor agents, tapentadol and others. A major step forward is the ability to encompass measures of evoked and recently, ongoing pain in animal models, bringing them more closely in line with patients. A remaining problem could be the overriding use of behavioural measures of pain in drug development. Patients in clinical trials have pain ratings of about 7 on a scale of 0–10. Behavioural measures can determine the withdrawal response, and this informs on pain thresholds and reflex responses. However, the threshold must be around 1–2 on the scale and so behaviour will only inform on mechanisms and modulations at low pain levels. Drugs that are able to modulate thresholds may not be effective enough for pain that is rated as more severe, and so would fail in the clinic. But by the use of neuronal recording in fully anaesthetised animals we can apply necessary higher stimuli in non-sentient animals and study the pathways, plasticity and pharmacology that reflect the pains many patients have. For example, parallel rodent and human studies have shown a remarkable correlation of spinal neuronal measures in rats with human perception and evoked potentials. This type of measure would appear critical to the true assessment of drug efficacy.

Having said this, animal studies clearly have limitations: one obvious issue is that subtle or unexpected side-effects in humans, not apparent in preclinical studies, may reduce tolerability and these would be hard to predict in the clinical setting.
Genetic factors – ion channel mutations

Another area of great interest and importance are inherited pain disorders, which have been driven by the functional identification of protein products from animal genetic studies. Alongside this, polymorphisms in human genes can also provide an excellent proof-of-concept for pain-related roles of gene products.

In the former case, the most numerous disorders are those of ion channels. It has long been known that a calcium channel mutation leads to migraine (but also motor problems) but recently, a list of sodium channels and irritant sensor dysfunctions has accumulated. This is of great importance since Na1.7 and TRPA1 were first identified in animal studies and verification of their roles in human pain states comes from the inherited disorders, prior to the production of selective drugs to validate the target. Na1.7 and also Na1.8 and Na1.9 are therefore important targets for pain control since the channels have selective locations in peripheral pain signalling fibres. The hope would be that drugs acting on these sodium channels could be the equivalent of systemic local anaesthetics, since they should have selective effects on only pain-related sodium channels.

But other findings have challenged this hypothesis. Firstly, the inherited pain Na1.7 mutation conditions, namely inherited erythromelalgia and paroxysmal extreme pain disorder, as well as the TRPA1 gain of function, do not correspond to the whole body anaesthesia seen with the loss of function mutation of Na1.7. Thus, erythromelalgia is explicable in terms of the long fibres, hands and feet but the other pains range from visceral, ocular regions and upper body. Are local conditions interacting with the channel in the mutated state to localise the pain? This problem is reminiscent of the drugs effective in craniofacial pains. Thus carbamazepine, a sodium channel blocker, has efficacy in trigeminal neuralgia while the triptans, effective in headache, do not appear to be effective in somatic pain states. These are intriguing issues. One other consideration is the finding that the Na1.7 channel is important for olfaction in mice judging by reports of loss-of-function mutations. It is unclear whether a specific Na1.7 channel blocker would be tolerated by patients if anosmia ensued.

Pain from deep tissues

Another area that is important for the effective treatment of pain conditions in patients is pain arising from deep tissues. There has been detailed cutaneous sensory testing of patients with neuropathy, and to a lesser extent with fibromyalgia and arthritis, although it is clear that patients with the latter two painful conditions have major pain problems with pain from deep tissues. The majority of stimuli used in sensory testing are cutaneous, since these are easier to apply and assess. Yet, even with neuropathy, patients complain of deep pains. Activation of deep tissue independent of skin is a clinically relevant issue: there are millions of patients with joint, muscle, bone and visceral pains and yet we know much less about the signalling and mechanisms behind these pains. Thus, understanding whether skeletal or muscle pains use the same or different pathways and mechanisms as cutaneous systems is important.

Mixed pain states

Even more of a problem is when pains involve more than one type of pain state. The example of cancer-induced bone pain is illuminating since the advent of animal models have revealed that the pain can have both inflammatory and neuropathic components, but also some unique features. Thus, understanding mechanisms could aid better treatment, especially since there are increasing numbers of cancer survivors. Here the difficulty of carrying out clinical pain studies in these patients due to complications of fluctuating pain, concurrent medications, surgery, chemotherapy and radiotherapy is indicated by the preclinical models. In other pain states, back-translation of clinical findings from patients must inform preclinical studies.

Combination therapy

Combination therapy is frequently used in patients where single agents are insufficiently effective, or are effective at dosages where side-effects are not tolerable. These issues have been recently reviewed for neuropathic pain and the premise is that targeting more than one mechanism at the same time could be useful. The principle of combining drugs with differing but complementary actions is sound. For example, this could involve one drug with a peripheral action and one with a central action, but another approach would be to block excitations whilst enhancing inhibition. Careful clinical studies on the benefits and problems with combinations would be valuable.

Conclusions

In summary, there is an unmet need for new pain treatments, as pain treatments can fail in many patients and there have been relatively few breakthroughs in terms of new treatments in recent years. Studies of the mechanisms of pain and analgesia are increasingly shedding light onto the reasons why treatments fail, there are a number of promising avenues of research, such as sensory phenotyping, ion channel disorders and the neurobiology of deep tissue pain that have the potential to inform the development of more effective treatments.

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References

Pharmacotherapy in pain patients with substance abuse

Treatment of patients with substance abuse for acute or chronic pain is a real challenge, explain Michael Schäfer and colleagues

Definitions
When dealing with patients suffering from substance abuse, there are often misconceptions about the terms used. Physical dependence describes adaptive changes in the body in response to a repeated drug intake, which may cause tolerance. Abrupt omission of the drug provokes symptoms of withdrawal. Physical dependence and withdrawal can be prevented by a stepwise reduction in the drug’s dosage.

Addiction describes a compulsive drug behaviour (‘craving’), such as an inability to stop using a drug despite harmful consequences. To prevent withdrawal symptoms, reduce ‘drug craving’ and stabilise the life of a drug addict, some countries (including the UK, US and Germany) offer replacement therapy with long-acting, less euphoric drugs such as methadone, buprenorphine or prolonged-release morphine, under medical supervision.

Addiction and pain
The brain responds to natural rewards such as food. Reinforcing these responses to natural rewards is evolutionarily important for survival, reproduction and fitness. Drugs of abuse act on this reward system in the brain to produce a state of pleasure, well-being and relaxation. This euphoric effect reinforces their continuous intake, whereas a sudden interruption in drug intake causes withdrawal symptoms. Both the reinforcement of euphoric effects and the avoidance of withdrawal symptoms are the drivers of addictive behaviour. The faster the onset and decline of these euphoric effects, the higher the reinforcement and, thus, abuse potential.

Pain interferes with drug-seeking behaviour and addiction. Untreated or undertreated pain, as well as inadequate opioid treatment in patients with a history of substance abuse will reinforce opioid-seeking behaviour.

Management of acute pain
A comprehensive history detailing a patient’s drug abuse should help to differentiate between drug addicts, drug addicts currently using opioid replacement therapy and former drug addicts who are currently abstinent. In the latter, opioid therapy should be avoided, if possible, and regional anaesthesia techniques or non-opioid analgesics are preferred. However, in the former patient groups, pain should be treated adequately and withdrawal symptoms, either from the drugs of abuse or the replacement therapy, should be prevented. However, in situations of intense acute pain, opioids are not contraindicated in abstinent former addicts.

Individual relapse-prevention strategies should be discussed with the patient. When opioids are used in drug addicts they should be switched to an oral prolonged-release formulation as soon as possible. This prevents fast on-and-off euphoric effects as well as the occurrence of withdrawal symptoms, both of which are major contributors to addictive behaviour. In acute pain patients currently using opioid replacement therapy, withdrawal symptoms need to be controlled and additional opioid analgesia should be given as needed. Buprenorphine at very high doses may antagonise the efficacy of opioids given for supplemental analgesia. If this occurs, buprenorphine may be discontinued and switched to a prolonged-release full opioid agonist. It is problematic to treat patients on long-term naltrexone maintenance therapy, because naltrexone displaces opioids to leave them ineffective when used in normal doses.

Management of chronic pain
In chronic pain patients with substance abuse, a thorough evaluation should assess the current state of addiction, pathophysiology of pain, functional impairment and psychological comorbidities. Although opioids may provide pain relief for many types of chronic non-cancer pain, alone they are rarely sufficient. Treatment of chronic non-cancer pain should start with non-opioid analgesics accompanied by non-pharmacological therapies and treatment of psychological comorbidities. However, opioid analgesics may be necessary and should not, in principle, be withheld from drug addicts. The decision to use opioids should be based on careful consideration of the risks and benefits and this should be regularly reassessed. Ideally, chronic pain patients currently using opioid replacement therapy should receive only one opioid. Patients on methadone do not obtain adequate pain control with a single daily dose, therefore, it may take several days or longer to stabilise a patient on methadone.

A substantial percentage of patients with or without substance abuse will fail to benefit from prolonged opioid therapy, in which case it should be discontinued. Patients on buprenorphine may be titrated with slowly increasing doses for additional analgesia. However, with high doses, a ceiling effect occurs and additional opioids will fail to be effective. Patients then need to be switched onto other opioids; however, these should only be the prolonged-release formulations.

Chronic pain patients with substance abuse are a real management challenge and should be treated by an interdisciplinary approach in which pain specialists, substance abuse specialists, psychologists and other medical specialists communicate with the patient and with each other.

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References
Treat the whole patient, and be aware of drug interactions

Pain expert Professor Harald Breivik discusses how a localised pain complaint can be symptomatic of serious underlying health problems

Scenario

A 79-year-old man, previously in good general health, has a decades-long history of bilateral shoulder pain, initially treated with repeated injections of depot methylprednisolone. About 20 years ago he experienced a rotator cuff rupture on the right side while trying to start his snow-blowing machine, to which the methylprednisolone injections may have been a contributing factor. This was treated successfully by surgery, immobilisation and active rehabilitation of functions of his shoulder muscles and tendons.

About 10 years ago the rotator cuff on the left side ruptured. In part because of the positive outcome of surgery on the right side, the surgeon repeated the procedure. However, this time his pain persisted after surgery, gradually spreading to the neck and arm. Now the patient is taking medication for elevated blood pressure (BP), including an ACE-inhibitor and a diuretic. He has left shoulder and arm pain, especially during physical activity, recently also causing shortness of breath. His pain was initially relieved by paracetamol (acetaminophen), but it gradually increased, disturbing his sleep at night. He has been prescribed sustained release tramadol tablets 200mg twice daily, but he admits to taking three tablets (that is, 600mg tramadol) daily with only moderate pain relief. Therefore, he now adds OTC diclofenac 25mg three times daily.

Q: How much should I worry about adverse effects from the analgesic drugs, and their interactions with his BP medication? How should his shoulder and arm pain best be treated?

A: This patient is at serious risk of cardiovascular complications and renal failure: his hypertension and left arm pain when physically active indicate coronary artery problems. These must be investigated and treated as soon as possible.

Although a potent COX-1 and COX-2 inhibitor and therefore an effective analgesic for acute pain, diclofenac is not a suitable long-term analgesic in this elderly patient with cardiovascular disease.1,3 Most analgesic-guidelines for elderly patients recommend NSAIDs only for short-term pain relief, at the lowest effective dose and duration.1 For persistent pain in the older adult NSAIDs should be used with great caution, and only after safer treatments have not provided adequate pain relief.4 NSAIDs increase risks of GI and renal complications, hypertension, myocardial infarction and stroke, especially in elderly patients.1,3,5 Also, NSAIDs may interact with concomitantly prescribed diuretics and ACE-inhibitors, increasing the risk of kidney failure, even when used for acute postoperative pain.2,3

Tramadol, with its opioid agonist and serotonergic effects, can precipitate a dangerous serotonin syndrome,6 even at dosages of 600mg per day. The serotonin syndrome is characterised by a triad of: 
- mental symptoms (anxiety, agitation, insomnia),
- autonomic instability with hypertension and tachyarrhythmias, and
- lively tendon reflexes.7

If the serotoninergic medication is not stopped, this may progress to hyperpyrexia and a life-threatening condition requiring treatment in an intensive care unit.4,8

Tramadol can cause sleep disturbance as a symptom of incipient serotonin syndrome,7 and particularly in elderly patients tramadol can cause obstinate constipation, adding to this patient’s burden of disease.

Given the above, the treatment of this patient should be as follows:
First of all, discontinue the diclofenac and tramadol. He needs a thorough general medical health evaluation; a focused shoulder examination alone would be highly inappropriate.

How bad is his coronary insufficiency? How much are his kidneys suffering from the unfortunate combination of an ACE-inhibitor and the potent NSAID? In addition, how appropriate is his BP management? It may be that most of his left shoulder/arm pain will disappear when these issues are addressed.

Abrupt discontinuation of tramadol 600mg daily will precipitate opioid withdrawal with breakthrough pain, and the increased autonomic sympathetic outflow aggravates his cardiovascular problems. This may be relieved by clonidine 25microgram 2-3 times daily.9

A better alternative: Stop tramadol and start a buprenorphine patch 10 microgram/hour, subsequently reduced to 5 microgram/hour; this should dampen any opioid-withdrawal symptoms and relieve any remaining somatic shoulder pain. However, discontinuing tramadol is often complicated by similar discontinuation problems as seen after abruptly stopping a serotonergic antidepressant drug.9

Above all, he needs continued monitoring of his cardiovascular and renal functions by qualified care providers until his medications are optimised and his overall health situation is stabilised. The safest alternative is to hospitalise this patient, at least for two weeks. Subsequently he will need follow-up by a qualified HCP-team for several weeks.

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The treatment options described in this case scenario are based on the global literature and the long clinical experience of the author. Not all the medications listed are licensed for use in the settings described and physicians should consult the relevant SPCs prior to prescribing

References

THE ATTRACTIVENESS OF OPPONENTS

Agonists and antagonists

Professor Tony O’Brien explains the seemingly counter-intuitive approach of co-prescribing an agonist and an antagonist

Introduction

The undertreatment of both cancer and non-cancer pain is well documented.  

1 The individual, societal and economic consequences are profound. Uncontrolled pain is associated with a variety of negative impacts across a range of QoL domains, including physical, cognitive, emotional and behavioural functions.  

The Declaration of Montreal recognises that pain management is inadequate in most of the world and asserts that access to pain management is a fundamental human right. Whilst pain management requires a multidimensional approach, in many instances the skilled use of opioid medications is essential.  

In 1973, a number of research groups demonstrated the existence of stereospecific opiate binding sites in the CNS. In 1976, Martin et al demonstrated the existence of a number of opioid receptor subtypes. Opioid receptors are found throughout the nervous system including the brain, spinal cord and peripheral nerves. In addition, opioid receptors are found in the gut and opioid-induced bowel dysfunction results from the activation of mu-receptors in the enteric nervous system, resulting in uncoordinated and dysfunctional propulsion, increased fluid absorption and reduced secretion of water and electrolytes into the bowel lumen. Because the entire gut expresses opioid receptors, the effects of opioids are not confined to the large bowel. Opioid use is associated with dry mouth, oesophageal dysmotility, delayed gastric emptying, increased pyloric tone, delayed transit times, a decrease in the secretion of water and electrolytes into the intestinal lumen, a net increase in the absorption of luminal fluid and an increase in resting anal sphincter pressure.  

Opioid-induced bowel dysfunction is a major limiting factor in the use of opioids in pain management. Constipation and associated bowel symptoms occur in up to 90% of patients taking opioid medications and, not surprisingly, constipation is described as the most common aspect, is a major limiting factor in the use of opioids for pain management. The availability of an oral, long-acting formulation of oxycodone and naloxone represents a highly significant development in pain management. The combination of an opioid analgesic with an opioid antagonist offers reliable pain control with a significant reduction in the burden of opioid-induced constipation.  

Key learning points

- Opioid-induced bowel dysfunction, of which constipation is the most common aspect, is a major limiting factor in the use of opioids for pain management.
- The availability of an oral, long-acting formulation of oxycodone and naloxone represents a highly significant development in pain management.
- The combination of an opioid analgesic with an opioid antagonist offers reliable pain control with a significant reduction in the burden of opioid-induced constipation.

Agonist with an antagonist – a counter-intuitive approach?

The co-prescription of an agonist and an antagonist seems almost counter-intuitive. Medical students and junior doctors quickly learn that naloxone is a powerful opioid antagonist and as such, it seems strange to want to use it with an opioid agonist. Oxycodone is a semi-synthetic thebaine derivative that has been in clinical use since 1917. It became commercially available as a single agent in 1981. In 1996, it was launched as a sustained-release formulation. The analgesic potency of oral oxycodone relative to oral morphine is in the order of 1.5:1 to 2:1. Oxycodone has a relatively high oral bioavailability of up to 87%.  

The availability of an oral, long-acting formulation of oxycodone and naloxone in a fixed 2:1 ratio represents a significant development in our therapeutic options when managing severe pain. The strengths currently available in Ireland are 5mg/2.5mg, 10mg/5mg, 20mg/10mg and 40mg/20mg. It is important to remember that this formulation is a WHO step III opioid and the effects of the antagonist component (naloxone) are limited to the gut. This compartmentalisation of effect ensures that central analgesia is maintained and the risk of opioid withdrawal is avoided. The oxycodone dose in the combination product is bioequivalent to the same dose administered as a single agent.  

Once ingested, both the oxycodone and naloxone progress along the gut in the normal fashion and the rate of their release into the gut lumen is determined by the characteristics of the sustained release formulation. Within the gut, the naloxone will bind preferentially to the mu-opioid receptors because of its greater affinity. Thus, the agonist oxycodone is largely prevented from binding to opioid receptors in the gut, thereby conferring a degree of protection from the more usual intestinal opioid-associated adverse effects. In time, both the oxycodone and naloxone are absorbed and transported via the portal system to the liver. Within the liver, the naloxone is extensively metabolised by glucuronidation, such that 97–98% of the naloxone is metabolised in the first pass. Negligible amounts of naloxone reach the systemic circulation, thus preserving central analgesia.  

The liver plays a vital function in the metabolism and clearance of most opioids. Patients with impaired liver function will
patients on the oxycodone/naloxone combination compared with those on single agent oxycodone, with maintenance of analgesic efficacy. The 2:1 oxycodone/naloxone ratio was identified as the most suitable for further development. Bowel function was assessed using the Bowel Function Index (BFI) in all studies. Ahmedzai et al (2012) studied a group of 185 patients with chronic cancer pain. The combination product of oxycodone and naloxone provided a significant improvement in OIC, as measured by the BFI, compared with oxycodone alone, without compromising analgesic efficacy or safety.

**Conclusion**

This approach, using an established and familiar step III opioid (oxycodone) in combination with an opioid antagonist (naloxone) in a fixed-dose ratio prolonged release oral formulation, offers the prospect of predictable and reliable analgesia with a significant reduction in the burden of OIC.

- Professor Tony O’Brien is a consultant physician in palliative medicine at Marymount University Hospital & Hospice/Cork University Hospital, Ireland and at the College of Medicine and Health, University College, Cork, Ireland

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**Efficacy and safety profile evidence**

In 2008, Vondrackova et al evaluated the safety profile and efficacy of oxycodone in combination with naloxone in a prolonged release formulation in a population of 463 patients with chronic non-malignant pain. The analgesic efficacy of the combination formulation was comparable to single agent prolonged release oxycodone and additionally, an improvement in OIC was observed. Simpson et al (2008) studied a population of 322 adult patients with non-cancer pain requiring opioid therapy. The fixed-ratio combination of oxycodone and naloxone offered patients effective analgesia whilst significantly improving OIC, compared with prolonged release oxycodone alone. In a study by Meissner et al, 202 patients with mainly non-cancer pain under stable oral oxycodone therapy were randomised to receive naloxone or placebo. The study demonstrated a significant improvement in OIC in those patients on the oxycodone/naloxone combination compared with those on single agent oxycodone, with maintenance of analgesic efficacy. The 2:1 oxycodone/naloxone ratio was identified as the most suitable for further development. Bowel function was assessed using the Bowel Function Index (BFI) in all studies. Ahmedzai et al (2012) studied a group of 185 patients with chronic cancer pain. The combination product of oxycodone and naloxone provided a significant improvement in OIC, as measured by the BFI, compared with oxycodone alone, without compromising analgesic efficacy or safety.

**The goal of therapy is to enable a person to live a fuller and more meaningful life; clinicians are not treating pain or opioid receptors — they are treating the person**

have increased plasma concentrations of both oxycodone and naloxone compared with normal healthy subjects. However, the levels of naloxone are proportionately higher than the oxycodone in such circumstances. Thus, caution must be exercised when using the combination product in patients with mild hepatic dysfunction and in those deemed at risk of developing hepatic dysfunction. This combination product is contraindicated in patients with moderate or severe hepatic dysfunction. Normal vigilance is advised when using this product in the elderly and in patients with renal impairment. Plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment. Naloxone concentrations are affected to a higher degree than oxycodone.
**Management of severe pain due to lumbar disc protrusion**

Dr Liam Conroy presents the case of a 40-year-old male referred acutely to the pain service with severe low back pain, exacerbated by sitting down and straining at stool.

**Background**

This article describes a case where strong opioid medication was required to relieve pain and where prolonged release oral oxycodone/naloxone (Targin®*) presented the advantage of limiting situations where opioid-induced constipation would cause exacerbation of existing pain.

**Discussion**

This case illustrates that many patients with lumbar disc protrusion complain of a significant exacerbation of their back and radicular pain as a consequence of coughing, straining at stool and so on. Many of these patients require opioid medication to control their pain; however, the ever-present problem of opioid-induced constipation can exacerbate their pain.1–4 The use of prolonged release oral oxycodone/naloxone in this situation could therefore be beneficial.

**CASE ASSESSMENT**

A 40-year-old male sales representative was referred acutely to the pain clinic by his family doctor. He had been previously diagnosed with type 2 diabetes mellitus. He had severe right-sided low back pain radiating to his right buttock and down the lateral aspect of his right thigh and calf. This pain occurred suddenly two weeks prior to review. His family doctor had prescribed diclofenac 50mg three times daily and pregabalin 75mg 12-hourly. The pain did not settle, so his doctor had prescribed prolonged release oxycodone 10mg twice daily and this was increased to 10mg three times daily two days later, in addition to immediate release oxycodone 10mg 2–4 hourly for acute exacerbations of pain.

The patient complained that sitting down and, in particular, straining at stool exacerbated his pain. He stated that this exertion increased his pain score to ‘20/10’ on the visual analogue scale. He did not have any symptoms associated with cauda equina syndrome, or other ‘red flag’ symptoms.

MRI of the lumbar spine confirmed the presence of an annular tear at L4–5 and a broad-based right posterolateral disc protrusion at L5–S1, with impingement of the exiting L5 spinal nerve. Because of difficulties arranging a day case admission for a therapeutic right-sided transforaminal epidural injection of steroid, the patient was commenced on prolonged release oxycodone 20mg/naloxone 10mg combined tablet twice daily in conjunction with a faecal softener/stimulant, two capsules at night.

There was a four-day delay in gaining admission to hospital for treatment, however the treatment regimen described above was successful in controlling the patient’s pain and there were no exacerbations of pain due to straining at stool.

The patient underwent a successful transforaminal injection under radiological screening and he was referred for neurosurgical opinion. As his pain was well controlled and there were no further complications, surgery was deferred and the patient was scheduled for a repeat transforaminal injection of steroid. His oxycodone/naloxone dosage was decreased to 10/5mg twice daily immediately post-procedure and this achieved adequate pain control. It is envisaged to discontinue the oxycodone/naloxone immediately following the repeat injection.

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**Key learning points**

- Lumbar intervertebral disc protrusion can cause excruciating pain in severe cases, which can be exacerbated by activity such as sitting down and straining at stool.
- Acute sciatica due to disc rupture will improve within 1–3 months.
- The efficacy of drugs used for the management of sciatica in primary care is unclear.
- Severe cases can require opioid analgesia, however people taking opioids for pain relief frequently present with opioid-induced bowel dysfunction.
- The use of transforaminal steroid injections is a controversial issue and repeat steroid injections should be considered in light of the risk–benefit profile of the individual patient.

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*X-ray of the normal spine: where there is protrusion of the spinal discs this can cause pain*
Dr Liam Conroy is director, Department of Pain Medicine, Mercy University Hospital, Cork, Ireland

In the next issue of paineurope, Dr Conroy presents another case illustrating appropriate and effective use of prolonged release oxycodone/naloxone combined tablet in the acute hospital setting

* Targin® (oxycodone/naloxone) is licensed for severe pain which can be adequately managed only with opioid analgesics. Targin® is also known as Targinact® and Targiniq® in other countries. Prescribing information can be found attached to the back cover and/or on the outside back cover.

References

Case review: Sweden

Dr Annica Rhodin, pain specialist, Multidisciplinary Pain Center, University Hospital Uppsala, Uppsala, Sweden

This patient has a few weeks history of severe pain due to right posterolateral disc protrusion with impingement on the L5 spinal nerve but no signs of cauda equina impact. He also has type 2 diabetes. His pain mechanism, as described, would be mixed nociceptive–neuropathic. There is inadequate pain relief with diclofenac 50mg three times daily and pregabalin 75mg twice daily. Prolonged release oxycodone 10mg three times daily and immediate release oxycodone 10–40mg as needed is added. However constipation and straining at stool increases the pain.

In the described case, oxycodone is switched to prolonged release oxycodone 20mg/naloxone 10mg together with a faecal stool softener/stimulant, relieving the problem with constipation contributing to the pain experience. This certainly improves the situation for the patient. However, the invasive procedure of transforaminal injection of steroid in a patient with acute pain is a controversial issue.1–3 Even if there is a low risk of complications as cited in many reviews, there are cases of neuronal damage, bleeding and infection.4–6 Repeat steroid injections should be carefully considered in respect of the risk–benefit profile of this patient with diabetes. Also, this procedure is not easily accessible in most hospitals.

An alternative conservative treatment would be to try a different anti-inflammatory drug to diclofenac, as individual patients may respond differently to different NSAIDs. Furthermore, amitriptyline 10–50mg could be started at night together with physiotherapy and TENS. Most cases of acute sciatica resolve within 1–3 months.3

References

Case review: Israel

Professor Elan Eisenberg, director, Pain Research Unit, Technion Institute of Technology, Haifa, Israel

This case raises three important issues: first, the majority of patients with acute sciatica due to disc rupture will improve within 1–3 months; only a small proportion of patients, typically those with intractable pain or with significant neurological deficits, require surgery.1 This means that the majority of the patients with sciatica should be managed in the primary care/pain clinic setting, rather than being referred to spine surgeons. Primary care practitioners should therefore be capable of diagnosing and managing patients with uncomplicated acute sciatica.

Second, although sciatica is the most common form of neuropathic pain, a recent systematic review on drugs for the relief of sciatic pain concluded that ‘the efficacy and tolerability of drugs commonly prescribed for the management of sciatica in primary care is unclear’.3

No wonder there that the selection of analgesics prescribed for this condition is often arbitrary. Nonetheless, if pain is severe and image-guided steroid injections are not readily available, the use of a ‘strong’ opioid in combination with an adjuvant drug (anticonvulsants, antidepressants or steroids) or an anti-inflammatory drug may make sense.

Third, studies show that, on average, approximately 40% of patients who consume opioids are constipated.1 Reduced mobility associated with the acute or subacute phases of severe sciatic pain may also be expected to cause constipation.3 Constipation, in turn, often exacerbates sciatic pain around strained bowel movements, as seen in the presented patient. Hence, the use of oxycodone/naloxone combination for acute sciatica (and perhaps for additional forms of acute exacerbations of chronic pain) seems reasonable.

References
Om man inte ser problemet — finns det då?
