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Mechanisms of cancer pain

The first plenary session at the 14th World Congress on Pain was delivered by Professor Patrick Mantyh, professor of pharmacology, University of Arizona, US. The lecture, ‘Cancer pain: from mechanism to therapy’, described some of the mechanistic pathways involved in cancer pain, and the possibilities suggested for therapeutic targets.

In the last decade, there has been a substantial increase in the understanding of the mechanisms that drive different types of cancer pain, enabling the development of models for cancer pain. Through these models therapeutic targets can be identified.

The increasing incidence of cancer can in part be attributed to the increasing age of the general population, as well as a reduction in childhood mortality. Another contributing factor is that deaths in developing countries are decreasing. All these factors come together with the result that more people are living with cancer and becoming cancer survivors, however the implication is that more people are living with pain associated with cancer.

A better model for pain treatment

Before the introduction of the WHO pain ladder in 1986, cancer pain was treated on an ad-hoc basis. The WHO ladder provided a standardised paradigm of care for managing cancer pain. At the time, the prognosis for cancer was poorer than it is today, and the management of cancer pain was associated with end-of-life care.

To that end, any potential impact on daily living of the adverse effects of opioid and NSAID therapy was not considered an important aspect for these patients.

As the numbers of cancer survivors increase, people are living with cancer and its associated pain for longer than ever before. The paradigm offered by the WHO ladder does not adequately take long-term pain management into consideration and may not provide suitable pain relief to allow these patients to live full, functional lives.

Cancer pain can be broken down into different categories:
- Intermittent pain
- Constant pain
- Episodes of breakthrough pain
- Extreme pain associated with normal activity, for example, turning in bed, limb movement or coughing.

Targets for bone cancer pain

Bone cancer pain is the most frequent type of cancer pain, often occurring as result of relapse and metastasis. The rate of cell growth in bone tumours is much lower than that of other tissues and this means these tumours are more likely to escape therapy.

Osteoclast proliferation and hypertrophy often result in bone pain and osteolysis, as well as fracture. In many cases the fracture will never heal because of the presence of the tumour. Once a patient suffers a fracture, their life is irrevocably changed.

However, there is one important question in determining the mechanisms of bone cancer pain. Is it the tumour cells or the osteoclasts that are the causative factor? Which should be the therapeutic target to reduce bone pain?

This question could be answered by determining whether blockage of osteoclasts attenuates bone cancer pain.

The use of denosumab (a monoclonal antibody that targets RANKL, a protein that acts as the primary signal for bone removal), has been shown to result in fewer activated osteoclasts. Use of the bisphosphonate, zoledronic acid, has also been shown to reduce fractures over 30 months, as well as reduce frequency of opioid use.

Components of bone cancer pain

Bone cancer pain has multiple components, including:
- Tumourigenic
- Inflammatory
- Neuropathic.

Each of these components needs to be controlled in order to reduce pain.

Nerve growth factor (NGF) has been shown to regulate the multiple receptors and ion channels expressed by the sensory nerve fibres that innervate bone. Research is ongoing whether the blockage of NGF can attenuate bone cancer pain. Tanezumab, a monoclonal antibody NGF inhibitor currently in development, has been associated with a reduction in joint pain and improvement in function in patients with moderate-to-severe osteoarthritis of the knee. Clinical trials of tanezumab are ongoing and tanezumab is currently not licensed for use in cancer pain.
Pain mechanisms of the urinary tract

One topical workshop at the 14th World Congress on Pain concerned painful conditions involving the urinary tract and was moderated by Professor Matthew Fraser, assistant professor of urology, Duke School of Medicine, North Carolina, US. This workshop, entitled ‘New aspects in peripheral and central mechanisms of painful bladder syndrome/interstitial cystitis’ aimed to cover the current knowledge regarding mechanisms contributing to painful bladder syndrome (PBS) and interstitial cystitis (IC), and which of these may be potential therapeutic targets.

Urothelial mechanisms

The first lecture, entitled ‘Urothelial mechanisms of PBS/IC: Beyond neurons – cystitis and associated epithelium dysfunction’, was delivered by Professor Lori Birder, associate professor of medicine, University of Pittsburgh, US. The lecture outlined the sensory and barrier roles of the urothelium, both of which can be altered by stressors in health and disease.

IC can be studied by looking at cats with feline IC. This has a similar presentation to human IC and provides insight into the role of urothelial cells in health and disease.

A number of proteins play a barrier role in the urothelium, for example, cadherin. Expression of these proteins is reduced in IC and is associated with urothelial weakness and increased susceptibility to damage.

In both human and animals, IC has been shown to be associated with an increased response to acute and chronic stress resulting in structural, functional and barrier changes as well as increased susceptibility to infection. Altered integrity of the bladder/urine interface can also result in IC symptoms, for example, in feline IC, potassium leakage resulting in intravesical potassium has been shown to generate great discomfort.

Potential therapeutic targets

Potential therapeutic targets have been identified based on underlying mechanisms:

- Increased nitrous oxide (NO) has been shown to modulate urothelial barrier function.
- Liposomes may be able to increase urothelial repair, improving the barrier-maintaining function of the urothelium.
- Nerve growth factor (NGF) can alter ion channels, for example, TRPV1, and increased expression of NGF has been shown in feline IC with increased neural excitability and capsaicin sensitivity.

Diagnosis of these chronic disorders should be symptom-based, however symptoms will fluctuate with disease progression. These fluctuations provide challenges, not only for treatment, but also for understanding the underlying mechanisms of the conditions.

Visceral pain and brain alterations

The second lecture of the workshop was delivered by Professor Emeran Mayer, professor of medicine and physiology, University of California, Los Angeles, US. The lecture, entitled ‘Brain alterations in persistent visceral pain syndromes’, described the use of neuroimaging techniques to identify syndrome-related alterations in structural and functional brain networks.

There is an overlap between painful urinary conditions, such as IC and PBS, and GI disorders, such as irritable bowel syndrome (IBS), and other physical and psychiatric co-morbidities.

It is possible that generalised epithelial abnormality could explain the overlap of visceral pain syndromes and/or sensory amplification.

The interaction of environmental triggers

The interaction of genetic and environmental factors can result in a ‘central’ pain-prone phenotype. When exposed to stressors or acute nociceptive inputs, this phenotype produces a particular series of psychological and behavioural responses resulting in an increased pain sensation. This phenotype is more commonly in the female sex and is influenced by genetics and early-life trauma.

The bladder and the brain

A common conceit in the pain field is that of the ‘pain neuromatrix’, when certain regions in the brain are activated in response to acute pain stimuli. However, this pain matrix is also activated in response to bladder signals, and bladder-brain interactions have been shown to affect central processes. The circuitry of the pain matrix can also be induced or amplified by acute effects and chronic stress.

The early trauma to the brain that can result in the chronic pain phenotype could be a means of identifying people who are at risk of these painful conditions.
Immunological mechanisms
The final lecture in the workshop, entitled ‘New aspects in immunological mechanisms of bladder pain syndrome/interstitial cystitis’, was delivered by Dr Tomohiro Ueda, president of the Comfortable Urology Network, Kyoto, Japan. The lecture provided an overview of the different definitions of these conditions, how they should be diagnosed and the associated immunological symptoms.

Diagnosis of painful bladder syndrome
The European Society for the Study of Interstitial Cystitis (ESSIC) have recommended that the term interstitial cystitis should be replaced with painful bladder syndrome, as it is a symptom-based classification.

The use of biopsy may limit the diagnosis of PBS, as the biopsy may not sample areas that are affected by lesions. Using cystoscopy for diagnosis provides the opportunity to examine larger areas of urinary tract for lesions.

Immunological diagnosis
There is increasing support for the hypothesis that the immune system is involved in PBS and there have been a number of clinical associations between PBS and other autoimmune disorders, for example, rheumatoid arthritis, ulcerative colitis and lupus erythematosis. Stress responses, which increase the incidence of symptoms in PBS patients, have also been shown to increase the reactivity of the immune system. Auto-antibodies have been observed in patients with PBS and other autoimmune diseases; these can affect receptors and ion channels in the bladder wall.
Doctor-patient communication

The second plenary lecture of the 14th World Congress on Pain provided some insight into the importance of doctor-patient communication. In the lecture, entitled ‘Doctor-patient communication: the key to patient care and adherence’, Professor Phyllis Butow, chair in psychology, University of Sydney, Australia, reviewed the role of communication in the care of patients with chronic pain with a focus on how communication can influence adherence. In her opening comments, she emphasised the role of communication and acknowledged that it can be a difficult area, particularly in some diagnoses, for example, cancer.

The primary aim of therapy in pain management is to reduce suffering and distress, while increasing the ability of the patient to function in their daily lives. There is evidence that this aim is not being met due to:

- Lack of effective treatments
- Lack of prescribing of treatments
- Non-adherence.

If a patient does not feel that their current treatment adequately addresses their pain they may express increasing pain in order to try and receive adequate treatment. This may lead to stigmatisation of the patient or misunderstood feelings, and a subsequent under-treatment of pain.

Non-adherence to pain therapies

Communication is key to reducing non-adherence:

- Exercise adherence is associated with an increase in effectiveness
- Non-adherence in patients with chronic non-malignant pain is common, ranging from 7.7% to 52.9% (weighted mean, 29.9%)²

What causes non-adherence?

Non-adherence is more than just a failure to follow orders. It is multifactorial and based on a therapeutic alliance between the patient and doctor. Partial adherence is more common than complete non-adherence and non-adherence is only a concern when it impacts on the effectiveness of therapy.

Factors that may result in non-adherence include:

- Institutional factors
- Healthcare professional factors, for example:
  - Lack of knowledge
  - Lack of communication skills
- Patient factors, for example:
  - Analgesia concerns – addiction, adverse reactions, the fear of masking new pains
  - The meaning of pain – if an increase in pain is thought to mean disease progression, this can result in denial
  - Pain communication concerns – the desire to be a ‘good patient’ or for the healthcare professional to focus on treating the disease rather than the pain.

Improving adherence

The communication skills involved in improving adherence in patients with pain include:

- Correcting misconceptions
- Active listening
- Respecting concerns
- Using lay language.

Active engagement and involvement is critical for making a patient feel part of a team with their doctor.

The 2011 NICE guidelines on medicines adherence offer a guide for improving adherence, including the following:

- Communication
- Asking patients in a straightforward way on their progress with the intervention
- Using a frank, open, no-blame approach
- Identifying specific barriers and recognising that these change over time
- Using a patient-centred approach and allowing the patient the opportunity to make decisions
- Providing evidence-based written information that is relevant and jargon-free
- Adapting consultation style to individual patients.

Multi-target analgesics and the endocannabinoid system

The second lecture of the session was delivered by Professor Vincenzo Di Marzo, research director, Institute of Biomolecular Chemistry – National Research Council, Rome, Italy. In the lecture, ‘Endocannabinoids: a unique opportunity to develop multi-target analgesics’, the potential for exploiting the endocannabinoid (EC) system with regard to improving analgesic therapies was explored.

Receptors of the endocannabinoid system

Research on the properties of cannabis has led to a greater understanding of ECs and the EC system, revealing that the EC system is not as simple as first thought. However, these complexities may provide an opportunity for developing multi-target systems.
It was discovered that the activation of CB1 and CB2 cannabinoid receptors could downregulate pain through a descending nociceptive pathway. However, the complexities of the system become evident, as in some circumstances the activation of these receptors stimulate pain.

**Targeting ligands**

One potential therapeutic strategy is targeting the endogenous ligands rather than the EC receptors. These agonists are:

- Produced on demand
- Locally activated
- Immediately metabolised.

Mimicking the actions of these ligands may result in a reduction in pain. Inhibitors of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) have demonstrated therapeutic effects in animal models of several disorders including neuropathic pain, anxiety and inflammatory bowel diseases.

However, one study showed that FAAH inhibitors failed to induce effective analgesia in patients with pain due to osteoarthritis of the knee.

This incongruity can be attributed to the complicated nature of the EC system. Endocannabinoids, in particular anandamide, an endogenous cannabinoid neurotransmitter, can activate other non-related receptors, for example, TRYPV1. TRYPV1 is an ion channel that stimulates glutamate release. A related channel, TRPA1, can stimulate release of angiogenic compounds.

**A multi-target approach**

The complexities of the EC system can also be exploited when pursuing multi-target active ingredients, for example:

- AA-5-HT is a weak inhibitor of FAAH and competitive antagonist of TRPV1. This agent has been shown to be more efficacious than selective FAAH inhibitors at inhibiting neuropathic pain.

- Dual COX-2/FAAH Inhibitors

Cannabidiol, the sedative cannabinoid constituent of the cannabis plant, can reduce the psychotropic effects of tetrahydrocannabinol (THC), allowing the dose of THC to be increased without increasing the risk of psychotropic side-effects.

The discovery of the EC system and EC-degrading enzymes offers an opportunity to develop analgesics that are potentially safer than CB1 or CB2 agonists. Multi-target agents will potentially allow the use of lower potencies rather than super-potent single-target agents.

**References**

Receptors, risks and benefits

A view on opioid receptors
The second day of lectures at the 14th World Congress on Pain began with a double bill concerning opioids. The first, delivered by Professor Brigitte Kieffer, director of the Institute of Genetics and Molecular and Cellular Biology (IGBMC), Illkirch-Graffenstaden, France, provided an overview of the history of knowledge of the opioid system.

In the opening comments of her lecture, entitled ‘Opioid receptors: old and novel views’, Professor Kieffer suggested that the link between opioids and pain relief is obvious, with effects on physical, psychological and social pain.

Knowledge of opioid receptors
Opioid receptors were first identified in the brain in 1973, and endogenous opioid peptides were first isolated in 1975.

The opioid system has two main functions:
• Learning beneficial behaviours
• Coping with challenging situations.

Advances in knowledge about opioid receptors since their initial identification have indicated that:
• Opioid receptors are G protein-coupled receptors.
• They have a crystal structure.
• Opioid receptors are binding pockets allowing ligand binding.
• Mu opioid receptors dimerise.

Receptor-ligand binding
The receptor isn’t the important entity; it is the active complex between the receptor and the agonist, and there can be many receptor complexes for each receptor.

Mu receptors are essential not just for morphine analgesia, but also for other opioid analgesics or metabolites, for example, morphine-6-glucuronide (M6G), heroin, methadone, buprenorphine and fentanyl, as well as other effects, including adverse drug reactions.

Additionally, mu receptors have been shown to be central to reward processes. Delta receptors are not essential for drug reward processes, but are central for emotional responses.

The benefits and risks of opioid therapy
Following the discussion on the mechanisms behind the opioid system, Mark Sullivan, professor of psychiatry, University of Washington, Seattle, US, provided an interesting discussion on the more practical aspects of opioid therapy, in his lecture entitled ‘Opioid therapy: promise and peril’.

Using the metaphor of the Roman god of doorways, Janus, who was said to look both ways, Professor Sullivan, introduced the content of his lecture – the promises of opioid therapy, both ethical and scientific, and the perils, including risks and the concept of adverse selection.

The promise of opioid therapy
The ethical argument that underpinned the initial use of opioid therapy was that allowing people to die in pain was unacceptable. Over time, that ethical mandate was extended from relieving pain at the end of life to relieving cancer pain, and finally encompassing all people with chronic pain.

One pertinent declaration from the US Institute of Medicine is that prevalent pain should be understood as undertreated pain.

Although it is possible to argue against the traditional opioid dosing paradigm, the right opioid dose is the one that relieves pain. There is also a scientific argument for chronic opioid therapy:

• Demonstrable reduction of pain intensity, with some effect on function
• RCTs have demonstrated benefits in the short term.

80% of global opioid use takes place in the US and this has grown quickly over time, with opioid sales quadrupling from 2000 to 2010.

Adverse selection
Adverse selection describes the phenomenon that the patients who are most likely to abuse substances are also the most likely to need chronic opioid therapy (COT) for pain relief. For example, patients with patterns of substance abuse or mental health problems are more likely to have a clinical need for COT.

There are difficulties in obtaining data to demonstrate efficacy of opioid therapy in the long term. In a double-blind, placebo-controlled RCT, it would be very difficult (and perhaps unethical) to keep patients in the placebo-controlled arm of a trial over a period of months or years, and there would be a high level of discontinuation if patients were experiencing high levels of pain.
An opioid management conundrum
One management conundrum is that of a pregnant woman on COT. There is the option of either continuing COT or discontinuing it. If the therapy is withdrawn, there is the risk of premature labour. However, if the therapy is continued, there is the risk of neonatal drug withdrawal in the first few days of life. In situations such as this the promises and perils of opioid therapy become difficult to balance.

References
Psychosocial interventions and complex persistent pain

Outcomes and implications of psychosocial interventions for pain
Francis Keefe, professor of psychology and neuroscience, Duke University School of Medicine, Durham, US, gave the John D Loeser distinguished lecture at the 14th World Congress on Pain. Professor Keefe, who is to be the editor-in-chief of the Pain journal, discussed a psychosocial approach to pain management in the lecture, entitled ‘Psychosocial interventions for managing pain in older adults: outcomes and implications for clinical practice’.

More than the traditional model
Despite the traditional model that tissue damage leads to pain, there is not a 1:1 correspondence between evidence of tissue damage and generation of pain. This model also ignores other factors present, particularly in older adults. One factor is the psychosocial aspect of pain.

Beliefs about pain and its treatment can pose a challenge to the effective management of pain. Catastrophising – rumination and feeling powerless in the face of pain – can be a particular challenge. Catastrophisers have been shown to have changes in brain activity.

The social context of catastrophising
One study has demonstrated a social impact of catastrophising. Patients with GI cancer who catastrophised about their pain were shown to impact on the strength and quality of life of their carers.

Patients who catastrophise may also have an increased level of perceived care and this communal approach to pain can contribute or reinforce attention to pain.

Socioeconomic impact of pain
Socioeconomic factors contribute to pain, with the level of deprivation in a neighbourhood being a predictor for the onset of chronic widespread pain. This can be explained by psychological factors such as life stress, sleep problems and illness behaviours.

Psychosocial interventions
One of the stalwarts of psychosocial intervention is cognitive-behavioural therapy (CBT), which combines aspects of cognitive therapy and behaviour therapy:

- Cognitive therapy
  - Active learning of new thought patterns
  - Identifying overly negative thoughts and challenging them
  - Developing new ways of thinking
- Behaviour therapy
- Active learning of new behaviours
- Structured learning environment
- Positive reinforcement
- Increasing level and variety of adaptive behaviours.

CBT has been widely investigated as a pain management strategy. The osteoarthritis (OA) model is particularly useful in examining this type of therapy, as it is a common painful condition which progresses with age. Some data using the OA model have shown that CBT training resulted in decreased pain.

Information versus experience
A good psychosocial intervention should be experiential and involve the active participation of the subject, rather than being information-focused.

Interventions involving spouses or significant others can also be useful. By building on positive experiences, these can improve communication between the pair and draw on humour and shared strengths.

New technologies are advancing psychosocial interventions, with telephone, video calling and interactive rapid response technology allowing for individualised experiences.

The mysteries of complex persistent pain conditions
Professor William Maxiner, director of the Center for Neurosensory Disorders, University of Iowa, US, gave a lecture on the genetic background to complex persistent pain conditions (CPPCs) entitled, ‘Unravelling complex persistent pain conditions with genetic and phenotypic biomarkers’.

CPPCs are composed of aggregates of phenotypes that are associated with peripheral and central nervous system dynamics, stress responsiveness and inflammatory states. These conditions are common with a high prevalence (3-15% of the general population) and there is a co-prevalence with multiple sensory and motor disorders.
Examples of CPPCs include:
- Temporomandibular joint disorder (TMD)
- Headaches
- Back pain
- Interstitial cystitis.

Factors in complex persistent pain
One confusing aspect in CPPCs determining whether a patient has one condition or several. This is made difficult to gauge by the co-prevalence of CPPCs with other conditions. Data suggest that the greater the number of idiopathic pain conditions experienced by a patient, the more likely they are to have TMD.

In addition, there also seems to be a genetic component to CPPCs. Heritability has been demonstrated in a number of clinical and experimental pain characteristics, including low back pain, fibromyalgia, punctuate hyperalgesia and heat pain threshold. There are a multiplicity of genes and polymorphisms that are associated with chronic pain conditions.

Conceptualising complex persistent pain
A conceptual model for CPPCs has been created by putting together key variables and these can be grouped into two domains:
- Variables leading to high psychological distress
- Variables leading to a high state of pain amplification.

Increased environmental factors can act upon the genetic code to produce cumulative and individual effects, leading to a change in expression pathways and intermediate phenotypes.

The majority of these variables are common and may have small effect sizes, but the aggregate of these effects can influence intermediate phenotypes.

This can be summarised in Figure 1.

The OPPERA study
There are two components to the basic understanding of the punitive mechanisms of CPPCs:
- Biopsychosocial factors
- Genetic factors.

The latter of the two is being investigated in large-scale studies to assess risk factors and identify risk determinants. One such study, the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) study is headed by Professor Maxiner.

The OPPERA study, now in its seventh year, will have recruited over 6,000 participants by the time it concludes.

Using pain sensitivity constructs such as pressure pain thresholds, cutaneous mechanical pain thresholds and heat pain thresholds, the study seeks to identify some of the genetic biomarkers for CPPCs.

Interesting results from the study include:
- Psychological stress across several domains has been shown in patients with TMD
- Demonstration of polymorphisms that capture functional distress
- Putative genetic polymorphisms associated with TMD case status.

However, the variance in responses presents a research challenge, and sophisticated clustering methods may be required to provide a complete understanding of the genetic background of these conditions.
One of the topical workshops at the 14th World Congress on Pain covered the area of endogenous analgesia. The workshop, entitled ‘Limits of endogenous analgesia in patients with chronic pain: assessment and consequences’, consisted of three lectures discussing assessments of pain modulation, characterisation of pain modulation and differences in pain sensitivity in the general population.

**Predicting a pain response**
The first lecture of the workshop, entitled ‘Between pro- and anti-nociception: prediction- and treatment-based individualization of pain medicine’, was delivered by Professor David Yarnitsky, director of the Department of Neurology, Rambam Health Care Campus, Haifa, Israel.

There are two facets of pain characterisation:
- Pain inhibition capacity – this can vary between less-efficient conditioned pain modulation (CPM) on the pro-nociceptive end of the inhibitory spectrum, and efficient CPM on the anti-nociceptive end.
- Pain facilitation capacity – this can vary between enhanced temporal summation (TS) on the pro-nociceptive end of the facilitatory spectrum, and non-enhanced TS at its anti-nociceptive end.

Patients with idiopathic pain (for example, temporomandibular disorder [TMD], tension headaches or interstitial cystitis) exhibit pro-nociceptive pain modulation, although the exact details of this correlation have not been identified. A clinical example of this association is that patients with less efficient CPM have a higher risk of chronic pain after surgery.

The effect of CPM differs between pain-free subjects and those with pain. In pain-free subjects, pro-nociception predicts more pain, both after future surgery and after analgesia. In subjects with pain, pro-nociception predicts a better efficacy of analgesic interventions.

There seems to be a spectrum of nociceptivity, from pro-nociception to anti-nociception. The parameters of this are dynamic and clinically relevant, although further work is required to fully understand the mechanisms behind these nociceptive pathways.

**Characterising endogenous pain modulation**
The second lecture, delivered by Roland Staud, professor of medicine, University of Florida, US, provided an overview of methods available for characterising endogenous pain modulation in pain-free and painful subjects.

The lecture, entitled ‘Endogenous pain modulation in patients with local and widespread pain’, detailed the methods of assessing endogenous pain modulation (EPM), namely:
- Conditioned pain modulation
- Offset analgesia
- Temporal summation of pain testing.

Most of the work in the EPM field has traditionally separated the facilitatory and inhibitory pathways of EPM, however, there is a balance between the two, with top-down and bottom-up modulators affecting the ascending and descending pathways. The influence on modulating factors on pain inhibition and facilitation can be seen in Figure 1.

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**Figure 1: Modulating factors on pain inhibition and facilitation**

- **Inhibition**
  - Bottom up
  - Pain inhibition
  - Top-down sensitivity

- **Facilitation**
These pathways can be explored using a hypothesis in which wind-up magnitude is affected by pain facilitation (wind-up) and pain inhibition (wind-down), each individual’s balance of pain facilitation and inhibition is unique. Using this hypothesis, EPM could be assessed by using graded wind-up heat stimuli. These response functions may be useful for assessment of pain modulation in clinical trials and clinical practice.

**Pain sensitivity in the general population**

The final lecture in the workshop, entitled ‘Pain sensitivity and chronic pain in the general population’, was delivered by Dr Christopher Nielsen from the Department of Mental Health, Norwegian Institute of Public Health.

There are a number of limitations with case control studies which use sampled cases and sampled controls, compared with random samples from the population.

Ascertainment bias, representativeness and true effect size issues can lead to the appearance of a larger effect than would be observed in the general population. The relationship between stimulus and response can be described as pain stimulus, but it is a complex process. There are differences in pain processing between individuals, and pain sensitivity is a dynamic factor, influenced by facilitation and inhibition due to a number of causes.

Tests, such as the cold-pressor test, pressure pain threshold and heat pain threshold can be used to assess pain sensitivity. However, these can vary in their short-term and long-term accuracy.

Blood pressure also has a role in pain homeostasis:
- Pain leads to activation of the sympathetic nervous system (SNS)
- Activation of the SNS increases blood pressure (BP)
- Increased BP leads to inhibition of pain.

However, in patients with chronic pain, this last step is diminished, so that an increase in BP does not result in inhibition of pain.

There are trait-like differences in pain sensitivity in the general population that are related to core dimensions of chronic pain in a dose-dependent manner, and there is evidence for altered dynamic pain regulation in chronic pain.
One size fits one

Running alongside the 14th World Congress on Pain was a satellite symposium, sponsored and arranged by the Mundipharma/Norpharma/Napp independent associated companies, entitled ‘One size fits one: tailoring pain therapy to individuals’ needs’. The symposium, chaired by Sean Mackey, associate professor in anaesthesia and neuroscience, and chief of the Pain Management Division, Stanford University, US, aimed to:

- Explore the use of personalised therapy for the treatment of pain, considering its use across a range of patients
- Define personalised therapy in terms of acute and neuropathic pain
- Describe current use and new advances in neuroimaging
- Provide an overview of modern scientific approaches to cancer pain management and discuss how personalised therapy could be used in cancer pain.

Genetics and pain therapy

The first lecture of the symposium, entitled ‘Pain therapy: phenotypes, genes and drugs’, was delivered by Professor Rolf-Detlef Treede, chair of neurophysiology at the Center for Biomedicine and Medical Technology, University of Heidelberg, Germany, who discussed the parameters that can be used to individualise therapy.

The lecture began with a simple explanation of the differences between pain and chronic pain:

- Pain – a warning signal for actual or potential tissue damage
- Chronic pain – often no longer a warning signal for anything.

Is chronic pain a disease or an entity? There is a need for pain to have its own diagnostic procedures and specific interventions, and clinicians need a diagnostic system in order to investigate pain and make appropriate treatment decisions.

Genotypes and phenotypes for pain

Pain has a genetic background and it can be classified through genotypes (rare) or through phenotypes. This is more common as it is symptom-based.

- An example of a genotype for pain is a mutation in sodium channels that can lead to chronic pain.
- Examples of phenotypes include loss of function of touch and/or proprioception, or gain of function through hyperalgesia.

Chronic pain is often a leading symptom, not just a warning signal, and these syndromes can differ in location and in mechanisms. The neurobiological mechanisms result in a constellation of symptoms and signs, which result in a number of pain phenotypes.

Endogenous pain systems

There are two descending pathways in endogenous pain modulation (EPM) – a serotonin pathway and a noradrenaline pathway. These are involved in descending facilitation.

Duloxetine inhibits re-uptake of noradrenaline and serotonin, and is licensed for treatment of peripheral neuropathic pain in diabetic neuropathy. As described in the endogenous pain topical workshop, a lack of conditioned pain modulation (CPM) may predict a positive effect for duloxetine, and vice versa.

It may be predicted from this finding that personalised therapy of chronic neuropathic pain should be effective in individuals with deficient EPM, which may restore function of the endogenous pain control system.

Genetic profiles and codeine therapy

Codeine is a valuable example of how different genetic variations can influence a drug’s profile.

Breast-fed infants are unlikely to experience adverse events if the mother takes codeine, as low doses are expressed in breast milk. However, if the mother is an ultra-rapid metaboliser of CYP2D6, then higher levels of morphine will be found in breast milk, and opioid toxicity can occur. Another genetic aspect to codeine therapy is due to the fact that it is a prodrug that is bioactivated to morphine by CYP2D6, so the efficacy and safety profile is governed by CYP2D6 polymorphisms. People who are poor CYP2D6 metabolisers will experience little therapeutic effect from codeine, whereas ultra-rapid metabolisers may have a higher risk of codeine toxicity.

Neuroimaging of pain

The second talk of the symposium, entitled ‘Neuroimaging of pain in the brain – a step towards personalized pain therapy’, was delivered by Professor Sean Mackey, who discussed the individual subjective nature of pain, and how this can be detected using neuroimaging.

It has been shown that the amount of nociception is not equal to perceived pain in the brain. There
are a number of factors which influence an individual’s response, including:

- Cognitive
- Mood
- Context
- Individual factors.

**Genetics and pain sensitivity**

Genes are thought to account for 26-60% of the variability in pain response.6-7

The differences in pain response have been observed using neuroimaging, with a high pain sensitivity correlating with greater activation in the specific areas of the brain, such as:

- Caudal and perigenual anterior cingulate cortex
- Primary somatosensory cortex
- Prefrontal cortex.

The medial prefrontal gyrus is involved in self-focused elaboration of the negative personal implications of pain (that is, catastrophising).8

**The role of brain plasticity**

The relationship between changes in the brain and pain has been investigated and some data have shown that chronic low back pain (CLBP) causes premature brain grey matter atrophy:

- Age-related losses in grey matter occur at a rate of 0.5% per year.
- In CLBP patients, this occurs at a rate of 5.4% per year.

The magnitude of grey matter atrophy caused by CLBP is equivalent to 10-20 years of ageing, and is associated with memory and cognitive dysfunction.9

In the absence of an externally-cued task or stimulus, brain activity will continue and is measurable, showing spontaneous fluctuations. Non-tasked based activity can be measured by asking patients to sit in the imaging apparatus and not think of anything. However, in fibromyalgia patients, there is increased functional connectivity in sensory and pain-related areas, even at resting state.

**Neuroimaging and treatment**

Treatment may affect these brain changes, for example, six months after treatment for CLBP, patients showed increased cortical thickness in the dorsolateral prefrontal cortex, which correlated with pain and disability reduction.10

There are a number of neural markers of pain persistence associated with decreased grey matter in the nucleus accumbens (NaCC), insula and left sensorimotor, as well as increased functional connectivity of the NaCC with the prefrontal cortex. Connectivity has been shown to independently predict persistence.

Physicians currently rely on self-reporting of pain, but this excludes some vulnerable populations, such as the very young, older patients with dementia or patients in intensive care. There is a need for objective, measurable biomarkers of pain and individualised treatments, and brain imaging may provide the means to investigate these.

**The pain matrix: more than meets the eye?**

The limitations of the ‘pain matrix’ model are apparent with neuroimaging. On observation, it is a similar area of the brain that detects four different stimuli:

- Nociceptive somatosensory
- Non-nociceptive somatosensory
- Auditory
- Visual

**Personalising cancer pain therapy**

The final lecture of the symposium, delivered by Sam Ahmedzai, professor of palliative medicine, University of Sheffield, UK, took a more clinical approach, focusing on current knowledge and where it could lead, in the lecture entitled ‘Managing cancer pain: towards evidence-based individualised therapy’.

In the previous century, physicians took a pragmatic view. Cancer was a terminal disease, and they needed a simple, ‘one size fits all’ approach to dealing with cancer pain. This led to the development of the WHO analgesic ladder that championed opioids, especially morphine, over all other interventions. However, the randomised trial literature for morphine was small, with most trials recruiting less than 100 participants and it did not provide appropriate data for meta-analysis.11,12

As cancer treatments improved, so did the mortality rates for cancer. Cancer is no longer a terminal disease; people with cancer are living longer and becoming cancer survivors.13 The simple three-step approach of the WHO ladder is no longer sophisticated enough for the complex problem of cancer pain.

Knowledge gained about the mechanisms of pain and analgesics needs to be put to use.

**Pain in cancer**

Bone cancer models have shown how inflammatory mechanisms at the interface of cancer and bone trabeculae initiate pain transduction,14 with important molecules involved being TRPV1, NGF and various cytokines, chemokines and prostaglandins.

Treatment-related pain, for example chemotherapy-induced neuropathies and post-surgical pain syndromes, are significant problems in cancer survivors and can be a major dose-limiting side-effect
of chemotherapeutic agents. This can result in dose reductions or cessation of chemotherapy, with the overall result of reducing the chance of survival.

**Opioids in cancer pain**

There are a variety of opioids available for the treatment of pain in cancer patients, the range of which goes beyond simply morphine. Not all opioids are the same, and with insights into genetic polymorphisms and pharmacogenetic influences on metabolism, care should be taken in selecting the appropriate opioid for a patient.

One factor to consider is side-effect profile, with common side-effects such as constipation, cognitive impairment and vomiting affecting patient quality of life. Side-effects such as immunosuppression, impotence and respiratory depression are less common but are more serious.1619

Comparing other opioids to morphine:

- **Oxycodone** – works on mu, kappa and delta receptors (morphine primarily acts on mu opioid receptors). It has higher oral bioavailability with reduced interpatient variability than morphine, with no clinically significant active metabolites and a short half-life that allows rapid titration.1619
- **Fentanyl** – has reduced incidence of side-effects compared with morphine, including constipation, nausea and somnolence.20

**An individualised pain model**

As cancer survival rates increase, cancer is becoming a chronic illness, rather than a terminal one. There are three key points that are yet to be addressed:

- Treatment of pain has to fit in with more active and demanding lifestyles.
- Patients are unwilling to tolerate long-term side-effects.
- The one-size-fits-all simplistic approach is no longer appropriate.

Like modern cancer treatment, over the last few years cancer pain management has become more sophisticated, including:

- Multimodal therapies to maximise efficacy and minimise toxicity
- Opioid switching to exploit incomplete cross-tolerance as with second- and third-line cytotoxic chemotherapy
- Targeted prevention as well as management of adverse effects

An example of this is the reduction of opioid-induced constipation (OIC) through blockade of peripheral Gl opioid receptors while allowing CNS penetration for analgesia, with prolonged release oral oxycodone/naloxone combination (Targin®).21

The fixed-dose combination of oxycodone and naloxone in a prolonged release form has been shown to significantly improve bowel function as measured by BFI, compared with prolonged release oxycodone alone. After four weeks, there was improvement in constipation-related quality of life (European Organization for Research and Treatment of Cancer QoL Questionnaire-Core 30 [EORTC QLQ-C30]) with no reduction in brief pain inventory (BPI).22

Old, pragmatic models of pain management need to be abandoned in order to achieve better harmony between cancer treatment and pain, with a move towards targeted treatments.

* Targin® is licensed for severe pain which can be adequately managed only with opioid analgesics. Targin® is also known as Targin®® and Targinact® in other countries. Prescribing information can be found at the back of this booklet.

**References**

Neuropathic pain and cutaneous nociceptors

Characterising neuropathic pain
The John D Bonica distinguished lecture is given at the World Congress on Pain in honour of the founder of IASP. This year, the lecture was given by Professor Troels Jensen, director of the Danish Pain Research Center, Aarhus University Hospital, Denmark. The lecture, entitled ‘Neuropathic pain: is it an entity?’, began with the story of Karen Blixen, the Danish author of Out of Africa. She contracted syphilis from her husband, which was diagnosed in 1915. From 1922, she suffered from severe cramping, aching pains and had reduced sensation to pinprick and touch. The pain descriptors were insufficient for a diagnosis. The correct pathological diagnosis is essential for correct pain treatment.

The discovery of neuropathic pain
The first paper on neuropathic pain was published in 1988, and it has been cited 2,854 times since. There are approximately 1,500 neuropathic pain publications yearly.

Neuropathic pain has a place in the clinical classification of pain types (Table 1), although syndromes can have different aetiologies and present with multiple forms of pain.

<table>
<thead>
<tr>
<th>Neurpathic</th>
<th>Inflammatory</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory loss</td>
<td>No sensory loss</td>
<td>No sensory loss</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Specific signalling neuron</td>
<td>Specific signalling neuron</td>
<td>No specific descriptors</td>
</tr>
<tr>
<td>Specific descriptors?</td>
<td>Specific descriptors?</td>
<td>Unknown signal neuron</td>
</tr>
<tr>
<td>Respect neuroanatomy</td>
<td>Inflammatory signs</td>
<td>Widespread pain</td>
</tr>
<tr>
<td></td>
<td>Focal pain</td>
<td></td>
</tr>
</tbody>
</table>

Classifying pain
One approach to pain classification using Linné’s traditional classification structure:
1. Kingdoms
2. Classes
3. Orders
4. Genera
5. Species
6. Ranks
7. Subspecies

However, three problems prohibit it being useful for pain:
• No gold standard
• The nociceptive system is dynamic
• Pain is subjective.

Pain and amputation
A great deal of progress has been made in the field of neuropathic pain in amputees. One example is a football player who had minor knee surgery in 1967, which progressed over the course of about 20 years with a number of amputations, leading to exarticulation in the hip in 1985.

He had post-amputation pain in the form of a severe pain reaction to touch. He was heavily medicated and addicted to opioids. 25 years ago, the diagnosis was phantom pain, severe psychological disorder and addiction, whereas now, the level of insight into conditions like this is much greater.

Individualised therapy for neuropathic pain
There are a number of developments in individualised neuropathic pain therapy, for example, sodium channels blockade could reduce neuropathic pain through reducing N-methyl-D-aspartic acid (NMDA) mechanisms. However, these treatment options are in their infancy.

Nociceptor priming

The electrophysiological properties of sensory neurons activated by noxious stimuli (otherwise known as nociceptors) have been investigated for 50 years, but it is only in the last 10 years that the knowledge of the molecular basis of nociceptor transduction has increased. The understanding of the intracellular signalling mechanisms that regulate nociceptor sensitisation has yet to grow significantly.
From genes to clinical to pain
Research is moving toward a cell biology of chronic pain that needs to take into account all the different components of a cell, for example, organelles like mitochondria, secondary messengers, electron transport, cytoskeletons or lipid rafts.

One of the issues in this area is that chronic pain is defined as pain that persists longer than a particular length of time, rather than having a definition that distinguishes it mechanistically from acute pain.

He suggested an alternative, more impressionistic definition of pain:
- **Type 1**: acute pain may persist without ever undergoing chronicisation/neuroplasticity of its underlying mechanism.
- **Type 2**: a non-arbitrary transition from acute to chronic pain, associated with disconnection of the generation of pain from the initial tissue injury and/or loss of responsiveness to therapies that successfully treat acute pain.

**Sensitisation to stimuli**
In a patient with chronic pain, one particular stimulus intensity would generate a greater degree of pain intensity than it would in a patient without chronic pain. This may suggest mechanisms relating spontaneous to elicited pain.

However, the difficulties in translating knowledge about of the mode of action of acute pain, such as mediators, transducers and ion channels, into successful therapies for chronic pain are numerous: “drug development, lost in translation”.

**Molecular basis of sensitisation**
The last decade has shown an increase in knowledge of receptors and molecules, for example the molecular basis of thermal transduction, involving transient receptor potential cation channel subfamily V member 1 (TRPV1), also known as the capsaicin receptor. TRPV1 is one of a large number of receptors, secondary messengers and ion channels that are potential targets for blockade in therapy for chronic pain.

**Receptor blockade: classical versus modern approaches**
There are differences between classical and modern approaches to blockades for reducing pain (Table 2).

**Table 2: Classical and modern approaches to blockades for reducing pain**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Classical approaches: blocking mediator synthesis</th>
<th>Modern approaches: blocking receptors on nociceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drawbacks</strong></td>
<td>Proportional to level of immunosuppression and does not impact nociceptor plasticity</td>
<td>Polypharmacy, effect on non-neuronal cells and does not impact nociceptor plasticity</td>
</tr>
</tbody>
</table>

**References**
Functional brain imaging, stress and visceral pain

Functional brain imaging and neuropathic pain
The Ronald Melzack lecture, sponsored by The Louise and Alan Edwards Foundation at the 14th World Congress on Pain was delivered by Dr Luis Garcia-Larrea, research director, Research Unit Central Integration of Pain (U-879 INSERM), University of Lyon, France. The lecture, entitled ‘Functional brain images in neuropathic pain’, examined the insights derived from functional (electrophysiological and metabolic) imaging.

Historical advances in brain imaging
The pain matrix model could be described as a conceptual advance over the previous model. Determinants of pain come from the reaction pathway to brain, and this hypothesis can be endorsed with functional imaging.

Functional brain imaging has shown that pain in the left side of the body shows brain stimulation in the right hemisphere. In a number of regions in the brain, blood flow has been shown to correlate with pain intensity and perceived sensation.

A matrix of matrices
However, as described elsewhere at the congress, the pain matrix model is overly simplistic. It is a matrix of matrices, involving many different inputs that are not specific for pain, there could be many non-specific mechanisms for detecting an event, regardless of the sensory channel.

The areas of the so-called pain matrix have been determined through experimental noxious stimuli and include the thalamus, somatosensory and insular cortices, mid- and anterior cingulate, and, with some variability, the posterior parietal and prefrontal regions, brainstem and cerebellum.

Activity in these areas has been shown to increase with the intensity of experimental pain. However, neuropathic pain is associated with a decrease in activity in some of these areas, particularly the thalamus and anterior/perigenual cingulate. This activity has been shown to be reversed by pain-relieving procedures.

Understanding the functional relationship between the location and magnitude of brain activities is essential to fully understand the neuropathic pain experience.

Stress and visceral pain
This plenary lecture was given by Shin Fukudo, professor and director of behavioural medicine, Tohoku University, Sendai, Japan, who discussed recent advances in the understanding of brain function and emotion, in the lecture entitled ‘Stress and visceral pain’.

Irritable bowel syndrome and stress
Emotion can affect conscious feeling and cause emotional stress, and in turn, emotion can be heightened by the stress response.

Using irritable bowel syndrome (IBS) as an example, there are a number of influencers on visceral pain, including:
• Bottom-up processing from gut to brain
• Top-down autonomic/neuroendocrine mechanisms from brain to gut.

The emotional aspect to IBS has been demonstrated in patients, who show an exaggerated response to stress. This leads to the assumption that there is an association with the brain/gut signalling circuit.

Factors in the pathophysiology of irritable bowel syndrome
Among the candidate substances that may have roles in pathophysiology of IBS is corticotropin-releasing hormone (CRH). This is a major mediatory of stress response in the brain-gut axis, which influences heart rate and colonic motility. Administration of CRH antagonists will likely alleviate IBS pathophysiology.

Some data have shown that relaxation techniques, such as autogenic training, have a positive effect on IBS patients, highlighting the emotional stress component to this disease. In common with other chronic pain conditions, IBS has also been shown to result in changes in grey matter in the brain, with increases and decreases in specific brain areas.

Further studies on neuropathways for visceral pain are warranted, concentrating on the three aspects common to visceral conditions: pain, emotion and stress.
Glia and migraine

Glia – potential targets for chronic pain treatment
The final day of the 14th World Congress on Pain began with a lecture by Professor Ru-Rong Ji, chief of pain research, Department of Anesthesia, Duke University Medical Center, Durham, North Carolina, US. The lecture, entitled ‘Glia and pain’, examined the increasing focus on glial activation, which is emerging as an important concept in pain research.

The macrophages of the CNS
More than 50 laboratories around the world have contributed to the area of glial activation and the number of publications has increased dramatically over the last 10 years, highlighting the emerging importance of this area in pain research.

There are three types of glial cells and each have different reactions in different types of pain:
- Microglia – the ‘macrophages of the CNS’ - they mediate the innate immune response. They are a major source of cytokines and chemokines, including TNF.
- Astrocytes – these are the most abundant, and are involved in the maintenance of chronic pain.
- Satellite glial cells – these cells line the exterior surfaces of neurons.

Unlike neurons, glial cells cannot conduct signals to the brain. Rather, they are involved in neurologica interactions. There is increasing evidence that glial cells, such as microglia and astrocytes in the spinal cord and brain, and satellite glia in the dorsal root ganglions, are activated after:
- Nerve injury
- Inflammation
- Drug treatment, for example, opioid or chemotherapy.

The glial involvement in pain
Glia reaction is not the direct cause of pain. This occurs by the activation of glial cells and the subsequent production of glial mediators that they are involved in pain modulation. These include pro-inflammatory cytokines such as TNF or interleukin-1B (IL-1B), chemokines such as monocyte chemotactic protein-1 (MCP-1), and growth factors such as brain-derived neurotrophic factor (BDNF).

Light and headache: pathophysiology and modulation
Dr Rami Burstein, academic director, Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, US, delivered a plenary lecture on the relationship between migraine and light. The lecture, entitled ‘The pathophysiology of migraine headache and its modulation by light’, examined the mechanisms by which light exacerbates symptoms of migraine.

Pathophysiology of migraine
The past 15 years of research has focused on the pathophysiology of migraine, particularly the pain pathways involved and the changes in brain function before the onset of migraine.

Five to 10 minutes after migraine onset, an increased intracranial pressure and pain can be observed and 30 minutes to one hour after migraine onset, 70% of migraineurs will experience central sensitisation, such as skin sensitivity or muscle tenderness.

When using therapy, patients will often become pain-free if they commence treatment with triptans before the onset of central sensitisation. However, the response rate to triptans decreases after the onset of central sensitisation. In some non-responding patients, the CNS doesn’t return to baseline activity.

From dark to light
Shifting from dark to light results in increased spontaneous activity of trigeminovascular neurons in the posterior nucleus (PO) and lateral posterior nucleus (LP).

Investigations into the role of light in migraine were indicated by the fact that 88% of migraineurs are photophobic. However, the question remained whether the optic nerve or the trigeminal nerve was involved.

Blind migraineurs provided the answer, if patients were photophobic, it was due to the optic nerve. If they weren’t photophobic, then the optic nerve was not involved in migraine sensitivity.

It was determined that there was an absence of photophobia in blind migraineurs devoid of any photoreceptor, although there was an effect on migraine aura in some circumstances. This meant that the optic nerve was the path to follow in this investigation.

There are three types of photoreceptor cells – rods, cones and, discovered in the 1990s, photosensitive ganglion cells. Once the optic nerve had been
identified as the target, the next question was which photoreceptor was involved in photophobia in migraine patients.

Observations that migraine patients were worse on cloudy snowy days than on sunny days, indicated that they were more sensitive to blue light. However, research is only just beginning to understand how thalamic neurons respond to different colours of light.
Determining efficacy and spinal cord injury

What works for whom? Outcomes in pain therapy are a matter of perspective
In the penultimate plenary lecture of 14th World Congress on Pain, Professor Andrew Moore, senior research fellow, Nuffield Department of Anaesthetics, University of Oxford, UK, provided an interesting look at evidence-based pain therapy, encouraging utilising new insights in clinical trial interpretation to look for clinical practice effectiveness, rather than clinical trial efficacy, in a lecture entitled ‘What works for whom? Determining the efficacy and harm of treatments for pain’.

A matter of perspective
The question of what works is an expansive one, and outcomes are a matter of perspective. Most of the largest trials undertaken are to demonstrate ‘efficacy and safety’ with results delivered in order to gain regulatory approval.

However, while these results may be what trialists look for, patients may have a different perspective, with much higher expectations of what they need from their medications.

Quality of evidence
Certain qualities of evidence should be looked for, including:

• Avoiding averages
• Large numbers of patients – small studies have a tendency to overestimate treatment effect
• Avoiding last observation carried forward (LOCF) – carrying an observation forward implies a measure of success, which the patient may not agree with if they have not been able to maintain their treatment
• Outcomes that define responders – that is, those with a high level of pain relief and able to continue taking the product; withdrawal should be defined as non-response.

Defining outcomes
For patients, at least a 50% reduction in pain intensity from baseline is required for them to feel that their medication is successful, which correlates to ‘very much improved’ on a patient global impression of change.

One alternative to looking at average values of pain relief is to predefine success and failure for a particular therapy, and measure success by the percentage of patients obtaining a ‘successful’ outcome.

The perspective of the individual patient provides essential insight and clinical trials should be designed and conducted in order to provide value to clinical practice as well as regulatory authorities.

Spinal cord injury and pain
The last lecture of the 14th World Congress of Pain was entitled ‘Pain in patients with spinal cord injury’. The lecture, delivered by Dr Nanna Finnerup, associate professor, Danish Pain Research Center, Aarhus University, Denmark, discussed pain following spinal cord injury, with a particular focus on neuropathic pain.

A background to spinal cord injury
The earliest recorded mention of spinal cord injury (SCI) was in 1700 BC and survival rates did not improve until the 20th century.

SCI can be divided into two forms:

• Non-traumatic SCI – most common in elderly patients
• Traumatic SCI – more common in younger adults.

The consequences to SCI can be severe and potentially long-term if occurring in a younger adult, and include:

• Paresis
• Bladder, bowel and sexual dysfunction
• Autonomic changes
• Spasticity
• Sensory changes and pain.

Two thirds of SCI patients will have chronic pain and it has a major impact on quality of life.

Classification of spinal cord injury
A new classification system for SCI, known as the International Spinal Cord Injury Pain (ISCIP) classification system, classifies SCI according to three tiers according to pain type, pain subtype and pain mechanism.

Neuropathic pain following SCI can be divided into:
• Below-level pain – central neuropathic pain
• At-level pain – peripheral or central neuropathic pain, or a combination thereof.

Neuropathic pain can be persistent in SCI patients, present in 52% of patients at five-year follow-up.

The type of SCI pain can be divided into different phenotypes:
• ‘Discomplete SCI’ – gradual onset of below-level burning pain
• At-level evoked pain below-level, with spontaneous pain in complete SCI
• Squeezing pain
• Diffuse at- and below-level evoked pain
• At-level shooting pain cauda equina lesions.

Pain is a common problem following SCI and represents a major clinical problem. Both spinal and supraspinal mechanisms may be involved and further research is needed to improve treatment.
**Targinact® ▼**
(oxycodeine hydrochloride/naloxone hydrochloride)

5 mg/2.5 mg, 10 mg/
5 mg, 20 mg/10 mg and 40 mg /20 mg
prolonged release tablets

**Prescribing Information**

**United Kingdom**

Please read the Summary of Product Characteristics (SmPC) before prescribing.

**Indications:** Severe pain, which can be adequately managed only with opioid analgesics.
Naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

**Dosage and administration**

**Adults over 18 years:**
Usual starting dose for opioid naïve patients: 10 mg/5 mg taken orally at 12-hourly intervals. Patients already receiving opioids may be started on higher doses depending on their previous opioid experience. **Targinact** 5 mg/2.5 mg is intended for dose titration when initiating opioid therapy & individual dose adjustment. The dosage is dependent on the severity of the pain and the patient’s previous history of analgesic requirements.

Maximum daily dose of **Targinact** is 80 mg oxycodeone hydrochloride & 40 mg naloxone hydrochloride. **Targinact** is not intended for the treatment of breakthrough pain. Please refer to SmPC for further details. **Targinact** must be swallowed whole & not be broken, chewed or crushed.

**Children under 18 years:**
Not recommended.

**Contra-indications**

Hypersensitivity to active substances or excipients, any situation where opioids are contra-indicated, severe respiratory depression with hypoxia and/or hypercapnoea; severe COPD, cor pulmonale, severe bronchial asthma, non-opioid induced paralytic ileus, moderate to severe hepatic impairment.

**Precautions and warnings**

Respiratory depression, elderly or infirm, opioid-induced paralytic ileus, severely impaired pulmonary function, myoxedema, hypothyroidism, adrenocortical insufficiency, toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypo- or hyper-tension, pre-existing cardiovascular diseases, head injury, epileptic disorder, predisposition to convulsions, patients taking MAO inhibitors, history of alcohol/drug abuse, galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption, renal impairment, mild hepatic impairment, pre-operative use or within the first 12 - 24 hours post-operatively. Not suitable for treatment of withdrawal symptoms.

Not recommended in cancer associated with peritoneal carcinomatosis or sub-occlusive syndrome in advanced stages of digestive & pelvic cancers. Concomitant use of alcohol and Targinact may increase the undesirable effects of Targinact and should be avoided.

Tolerance and dependence may occur. It may be advisable to taper dose when stopping treatment to prevent withdrawal symptoms.

**Interactions**

Substances having a CNS-depressant effect (e.g. other opioids, sedatives, hypnotics, anti-depressants, sleeping aids, antihistamines, neuroleptics, anti-histamines and anti-emetics) may enhance CNS-depressant effect of **Targinact** (e.g. respiratory depression). Alcohol may enhance the pharmacodynamic effects of Targinact; concomitant use should be avoided. Interaction with coumarin anticoagulants may increase/decrease INR.

**Pregnancy and lactation**

Not recommended.

**Side-effects**

Common: decreased/loss of appetite, restlessness, dizziness, headache, vertigo, decrease in blood pressure, abdominal pain, diarrhoea, dry mouth, constipation, flatulence, vomiting, nausea, dyspepsia, increased hepatic enzymes, hiccups, altered mood, personality change, decreased activity, psychomotor hyperactivity, agitation, dysuria, pruritus, skin reactions, hyperhidrosis, drug withdrawal syndrome, feeling hot & cold, chills, asthenic conditions.

Uncommon but potentially serious: hypersensitivity, confusion, depression, euphoric mood, hallucinations, paraesthesia, speech disorder, convulsions, sedation, syncope, visual disturbances, palpitations, angina pectoris, tachycardia, increase in blood pressure, dyspnoea, respiratory depression, biliary colic, erectile dysfunction, urinary retention, peripheral oedema, tooth disorder, chest pain and injuries from accidents.

Refer to SmPC for further details of other uncommon side-effects and oxycodone class-effects.

**Legal category**

CD (Sch2) POM

**Package quantities and price**

Blisters of 28 tablets 5 mg/2.5 mg - £ 17.56
Blisters of 56 tablets
10 mg/5 mg - £35.11
20 mg/10 mg - £70.22
40 mg/20 mg - £ 140.44

**Marketing Authorisation numbers**

PL 16950/0157-158, PL16950/0161-162

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**Date effective**

March 2012

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