NEWS

Introduction to the
CHANGE PAIN News & Reviews Journal

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REVIEWS

Effective physician-patient communication is
crucial to ensure treatment success

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The Vicious Circle in pharmacological treatment
of severe chronic pain

Professor Joseph Pergolizzi

Relevance of neuropathic
components in severe chronic pain

Dr Bart Morlion

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FOREWORD

Professor Giustino Varrassi introduces the CHANGE PAIN News & Reviews Journal

As President of the European Federation of the Pain Society (EFIC) and on behalf of the EFIC I am supporting the CHANGE PAIN Campaign which aims to raise awareness about the unmet medical needs in the management of severe chronic pain at both the patient and the physician level. There are still huge differences throughout Europe in the approach to the pharmacological management of severe chronic pain which can only be improved by better education of physicians, better use of existing treatments and the development of advanced therapeutic agents. Bringing together experts in a group like the CHANGE PAIN Advisory Panel is of high importance, because it allows specialists not only give their scientific input, but also to share their everyday experiences. The International CHANGE PAIN Advisory Panel held its first meeting in June 2009 in Brussels where a consensus was reached on what is needed to improve pain management strategies that are currently not very efficient.

The following key topics were identified:

- Severe chronic pain is multifactorial in nature
- Effective physician-patient communication is key for successful pain management
- Understanding the Vicious Circle in pharmacological pain treatment is important
- Knowledge of pain physiology should guide treatment decisions

The group aims to translate these topics into simple messages that we can pass on to clinicians involved in pain management, both pain specialists and general practitioners. This CHANGE PAIN News & Reviews Journal is the first issue of a new publication that will inform the reader about latest insights in the field of severe chronic pain management and how they can be put into practice. The ultimate aim is to forge a new multidisciplinary, effective approach to pain management to provide patients with the best possible quality of life.

Professor Giustino Varrassi
President of the European Federation of IASP Chapters (EFIC)
INTRODUCTION

Pain is the most common reason why patients seek medical advice and represents a serious problem for a large proportion of the population worldwide. Chronic pain, which has lost its direct relationship to the triggering event and has become a disease in its own right, presents a special therapeutic challenge. Many chronic pain sufferers will have experienced debilitating pain for extended periods of time and may have undergone many years of ineffective therapy. A pan-European survey carried out in a wide range of countries found that 21% of the responders with chronic pain had suffered for more than 20 years and that 40% were dissatisfied with their treatment (Breivik, 2006).1

Chronic pain is multifactorial in nature and manifests with both physical and psychological symptoms, often resulting in a significant reduction of patients’ quality of life. Furthermore, it imposes a strain on healthcare resources and results in a substantial socioeconomic burden.

Inadequate training

One of the reasons for the lack of effective pain treatment is insufficient training of physicians. Many of those treating chronic pain patients are not pain specialists and may not fully appreciate the multifactorial nature of severe chronic pain. As a consequence, much of their treatment relies on tradition and personal experience. The mechanism, prevention and treatment of chronic pain are all topics which should become mandatory in medical schools and specialist training situations in order to avoid an increase in the number of patients suffering from chronic pain.

Lack of communication between physicians and patients is often another reason why pain treatment is likely to be less effective unless individual targets are set. The experience of pain is very individual as is the degree of pain relief obtained from a given therapy. Therefore individual treatment goals are crucial if the therapy is to be effective.

A Vicious Circle

Pharmacological treatment is often limited by the occurrence of intolerable side effects before optimal analgesia is achieved. This is especially true for strong opioids, where physicians and patients are struggling to find a balance between adequate pain relief and acceptable tolerability. The resulting Vicious Circle often leads to reduced quality of life and treatment discontinuation. The consequences are often underestimated by physicians. Therefore, increasing the awareness of this Vicious Circle of pharmacological treatment of severe chronic pain and its impact on patients among the medical community could improve treatment efficiency.

Due to the multifactorial nature of chronic pain, many conditions, such as low back pain, may have both a nociceptive and a neuropathic pain component which often requires the use of combination therapy with the associated possibility of increased side effects. Neuropathic pain, when present, is acknowledged to be more severe and difficult to treat and poses a particular challenge for physicians. It is frequently undetected by physicians and thus not adequately treated, which causes considerable distress to sufferers. At present there is limited awareness within the medical community of the physiological differences between neuropathic and nociceptive pain, and the specific pharmacological options which are available. Improving this knowledge with the help of educational tools that are universal and user-friendly could lead to better treatment decisions.

CONCLUSION

Thus, there are a number of issues responsible for inadequate treatment of severe chronic pain that need to be addressed in order to make progress in providing severe chronic pain patients with the level of treatment they deserve.

Reference

Current management of severe chronic pain is often inadequate. Physician-related reasons why therapy fails include difficult or inadequate diagnosis, incomplete understanding of the underlying mechanism that generates pain, inappropriate selection of treatment options, inadequate outcome measures, and a failure to understand co-morbid conditions which influence pain response.

Individual treatment goals
Most importantly, in many cases individual patient treatment goals are not sufficiently recognized. Only a small number of chronic pain patients are referred to pain specialists, so the onus of diagnosis and treatment will often fall on the general practitioner. Communication between patients and physicians is of vital importance so that the clinician can fully understand the patient’s situation. Many of the pain classification systems in use are outdated, although newer versions such as pain DETECT have been designed to identify neuropathic pain components, which is especially important in low back pain (Freynhagen, 2006).

However, in clinical practice this questionnaire is still not broadly used.

A typical severe chronic pain patient may have a long medical history of many years of pain suffering, during which time they may have seen numerous clinicians. Many will have a history of ineffective therapies. Co-morbidities and other medication will also have to be taken into account by the physician as well as any psychosocial problems.

Degree and type of pain
Pain is individual and subjective and many patients have a problem describing their condition to the physician. Although they may be able to indicate the location, frequency and type of pain they are experiencing, they find it difficult to express the intensity of pain. Estimates of intensity using standardized pain measurement tools are still fairly subjective and variable and there are indications that such tools are infrequently used. In clinical reality, patients are rarely asked to describe their pain intensity using e.g. numerical rating scales or questionnaires.

Pain-related impairment
Assessment of pain-related impairment made by the patient and the physician may differ, with the physician failing to appreciate the extent, or the effect, that pain is having on the patients’ normal physical and mental functioning and quality of life. When comparing the assessment of the degree of pain-related impairment, the physicians’ view often does not match the one of their patients.
Most physicians tend to either over- or underestimate the pain-related improvement of their patients.

**Expectations of treatment**
Clinicians and patients often have very different expectations of treatment. The main objectives of pain management include the prevention or reversal of pain chronification, activation of endogenous pain control, improvement in physical functioning, and psychosocial rehabilitation. Standardised treatment targets frequently consider a 50% reduction of pain score to be a clinically relevant outcome, however, the degree of pain relief necessary to regain a substantial level of quality of life varies according to the individual. For many chronic pain patients even a 30% reduction of pain intensity can be a meaningful pain relief. As individual patients may have differing treatment goals and expectations, those need to be clearly identified. Setting individual treatment targets is likely to make pain management more efficient. For this purpose, simple, user-friendly tools that support physician-patient communication are needed.

**Opiophobia**
Pharmacological reasons for the current inefficiency of pain relief often arise through poor or outdated education of physicians and undertreatment of pain. The use of opioids in chronic pain varies widely in European countries with opioiphobia being more relevant in Southern Europe. Many physicians resist opioid use due to fears of side effects, addictive potential, analgesic tolerance and safety concerns over long term use. The cultural beliefs of both physicians and patients are also known to play a part. Due to their common use in cancer pain, opioid treatment might be understood to be an indicator of “terminal illness” leading patients to refuse opioid therapy in order to appease themselves and avoid being categorised as a “doomed” person. Physicians need to be able to communicate with their patients to allay such fears.

**Conclusion**
Pain is individual and subjective and unless there is good communication between physicians and patients and individual treatment targets are set, pain treatment is less likely to be effective.

**References**
1. Freynhagen R et al. 2006. (See abstract on p.11).

**COMMENTARY**

Dr med Gerhard H.H. Müller-Schwefe, President of the German Association for Pain Therapy (DGS) points out that poor communication between patient and physician often leads to inadequate treatment

CHANGE PAIN intends to resolve several problems in chronic pain treatment.

One is identification of the many patients who lose several years before they receive appropriate treatment. The development of chronic pain and its prevention is not taught to medical students or when physicians specialise, so that they are not trained in the issues they face when they meet patients. Optimally, pain needs to be treated immediately before it has the chance to become chronic. In order to do this we have to ask the patient “how intense is your pain” , “how does it impact your quality of life” and “how much pain would be tolerable for you” so that we know more about the individual patient’s goals before deciding on the optimal treatment.

In Europe we have many different approaches to diagnose and treat pain. CHANGE PAIN is a chance to understand what is happening in different countries and from that standpoint to develop a consensus on how to continue, how to improve diagnosis and treatment, and how to increase public awareness of chronic pain and its consequences.
The Vicious Circle in Pharmacological Treatment of Severe Chronic Pain

One of the main reasons why the treatment of severe chronic pain remains insufficient is the problem caused by the side effects of the drugs used. This is especially true for strong opioids where side effects often limit the effective analgesic dosage that can be achieved. Side effects, lack of efficacy and the development of analgesic tolerance can all lead to treatment discontinuation. An increased awareness among the medical community of how these factors are linked is necessary if effective treatment is to be achieved.

Pain relief and tolerability
One of the major challenges in the pharmacological treatment of severe chronic pain is to achieve a balance between sufficient pain relief (analgesia) and medication tolerability. Insufficient analgesia leads to dose increases in order to achieve satisfactory pain relief. Since classical opioids demonstrate dose-dependent efficacy this results in effective analgesia, but at the same time it increases the risk of side effects. When tolerability then becomes unacceptable or the side effects uncontrollable, physicians or even patients by themselves may reduce the analgesic dose again with the unintentional consequence that analgesic efficacy decreases. This can in turn prompt another increase in the analgesic dose leading to a cyclical pattern of treatment or the so-called Vicious Circle. As a result of the Vicious Circle, patient compliance (i.e. adhering to the recommendations with regard to timing, dosage and frequency of administration) is often poor and the level of patients discontinuing treatment may be high.

Non-compliance
Evidence of poor patient satisfaction and treatment adherence exists among patients with chronic pain. Reviews of clinical trials show that 20 – 30% of patients who receive opioids for chronic non-cancer pain stopped their treatment due to adverse events or lack of efficacy in short to mid term treatment (Moore and McQuay, 2005; Kalso, 2004).

In reality this level may be much higher, and many patients drop out of opioid therapy in the beginning of the treatment because side effects are experienced and the optimal analgesic effect is not fully achieved.
Neuropathic pain
Lack of efficacy as a reason for discontinuation of treatment seems to affect a smaller proportion of patients. In some cases insufficient analgesia is due to an incorrect diagnosis of the type of pain or the use of an incorrect drug or dose. Where pain has a neuropathic component, the analgesic potency of opioids can be limited by patho-physiological mechanisms; opioid receptors are down regulated and central neurotransmitters are released, reducing opioid responsiveness and producing relative opioid tolerance (Davis 2007)3. Although there is evidence that neuropathic pain does respond to opioids (Ballantyne 2008)4, higher doses may be required than for treatment of nociceptive pain, and these may initiate the Vicious Circle. Because effective treatment of this type of pain requires more than one mechanism of action, the combination of analgesics with other agents such as anti-convulsants and anti-depressants is frequently used. However, combination therapy increases the risk of side effects and the possibility of drug-drug interactions.

Tolerance
Analgesic tolerance development is another condition which may affect chronic pain patients taking opioids. This occurs when a constant dose of a substance loses its analgesic effect over time. Besides the option to switch to another opioid, the normal response to this situation is to increase drug dose. Often at the same time the drug’s potential to evoke side effects will be increased, so that the Vicious Circle will start again. These factors will all affect reliability and stability of treatment.

Adverse events
However, adverse events are found to be the main reason for treatment discontinuation in about one out of four patients taking opioids (Moore and McQuay, 2005; Kalso, 2004). Evidence from reviews of clinical trials have indicated that at least half of the patients taking opioids experience at least one adverse event, with gastrointestinal (GI) and CNS side effects being the most common. Nausea and vomiting can be highly distressing to the patient and constipation can impose a substantial impact on quality of life. CNS side effects such as somnolence and dizziness are also common side effects likely to lead to reduced treatment success.

Conclusion
Overall, physicians and patients are often struggling to find a balance between sufficient analgesia and acceptable tolerability, indicating that current treatment of severe chronic pain often remains inefficient.

References
1. Moore R, McQuay H 2005. (See abstract on p.8)
2. Kalso E et al. 2004. (See abstract on page 8)

COMMENTARY
Professor Joseph Pergolizzi, of the Johns Hopkins University School of Medicine discusses the difficulties in balancing pain relief and tolerability

Achieving optimal analgesia for patients suffering from severe chronic pain can be difficult, especially if a neuropathic component exists. Three main reasons for this are the lack of efficacy, tolerance with the drug, and issues of tolerability. All three can create a Vicious Circle that can limit the effectiveness of pharmacological management strategies. A clear understanding of these issues is essential in order to optimise our management of chronic pain. Therefore, we need to re-evaluate our approach to the treatment and management of severe chronic pain.
Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids
Moore R and McQuay H. Arthritis Research and Therapy 2005; 7:R1045-51

This meta analysis was designed to establish prevalence rates for oral opioid use in chronic non-cancer pain of different aetiology and also to investigate any major differences in opioid adverse events. Thirty-four trials with 5,546 patients were included with 4,212 patients contributing some information on opioid adverse events. Ninety percent of the patients studied were suffering from moderate rather than severe pain. The use of any oral opioid produced higher rates of adverse events than did placebo. 51% of patients experienced at least one adverse event. There was no obvious relationship between high or low rates of adverse events and drug, dose, or dosing regimen. Different painful conditions produced comparable result patterns. A high proportion of those patients on opioids (22%) discontinued treatment due to the adverse events whereas only 6.5% withdrew because of lack of efficacy. Because of the relatively short duration of these trials (less than 4 weeks) and limited use of dose titration these results have limited applicability for longer-term opioid use in clinical practice. Future trials should be designed to consider a number of crucial variables including dose and duration of treatment as initial adverse events may improve with time.

SUMMARY OF PUBLICATIONS

Opioids in chronic non-cancer pain: systematic review of efficacy and safety

Controversy exists about the effectiveness of opioids for treatment of certain types of chronic pain e.g. neuropathic pain and also their safety with long-term use. This study has analysed available randomised, placebo-controlled efficacy and safety trials of WHO step 3 opioids from various databases until September 2003. Inclusion criteria were randomised comparisons of oral, transdermal or intravenous WHO step 3 opioids with placebo in chronic non-cancer pain. The mean decrease in pain intensity in most studies was at least 30% with opioids and was comparable in neuropathic and musculoskeletal pain. Adverse events prevented many patients from increasing the opioid dose to the maximum allowed to improve pain relief. About 80% of patients experienced at least one adverse event; constipation (41%), nausea (32%) and somnolence (29%) were most commonly encountered. Only 44% of 388 patients on open label treatments were still on opioids after therapy for between 7 and 24 months. The short-term efficacy of opioids was good in all pain conditions. However, only a minority of patients in these studies went on to long-term treatment. The relatively small number of patients studied and the short follow-ups times limit any conclusions that can be drawn concerning problems such as tolerance and addiction.

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Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options
Porreca F and Ossipov M. Pain Medicine 2009; March 19

One of the major reasons for discontinuation of opioid analgesic treatment in patients treated with opioids for chronic pain is side effects such as nausea and vomiting. These have a negative effect on treatment efficacy and successful patient management because they limit the effective analgesic dosage that can be achieved. A number of mechanisms by which opioids produce nausea and vomiting have been identified, involving both central and peripheral sites. The effects are mediated via interaction with specific opioid receptors (mu, delta, and kappa subtypes) in the brain and spinal cord and sometimes at peripheral sites. Strategies to control nausea and vomiting include the use of antiemetic drugs and also opioid switching, neither of which is ideal, as they are not always effective and incur additional costs. One novel approach to the problem is to combine more than one analgesic principle in one molecule so that the drug has two analgesic modes of action. This concept has been realised in tapentadol which combines mu opioid receptor agonist activity with norepinephrine re-uptake inhibition. Preclinical studies have indicated that this combination of two analgesic actions is less likely to produce opioid-induced side effects and thus help to alleviate this problem.
Neuropathic pain is defined by the International Association for the Study of Pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system.” Examples of neuro-pathic pain conditions include radiculopathy, post-herpetic neuralgia, diabetic polyneuropathy, trigeminal neuralgia, phantom limb pain and spinal cord injury. Today there is also an increasing awareness of a neuropathic component in some pain conditions such as cancer pain and chronic low back pain.

**Clinical studies**

Studies have indicated that 77% of severe chronic back pain patients have a detected neuropathic component and that these patients suffer longer and more severely than those with only nociceptive pain (Freynhagen, 2006). A more recent study has indicated that approximately 4% of the general adult population experienced chronic back pain with a neuropathic component (Schmidt, 2009). This study has also indicated that neuropathic components are more frequent in people with severe back pain compared to people with mild back pain.

The awareness of the physiological differences between neuropathic and nociceptive pain and knowledge on the range of specific pharmacological options that are available is still rather low.

However, it is recognised that when a neuropathic component is involved, pain is more difficult to treat and often requires the use of combination therapy. There exists a variety of treatment options that target the ascending and/or descending pain pathways in different ways, however not all of them are efficient in every case.

**Treatments**

NSAIDs are powerful inhibitors of prostaglandin synthesis and act mainly peripherally. Prostaglandins sensitize peripheral nociceptors. Therefore, NSAIDs primarily treat hyperalgesia or secondary pain, particularly the pain resulting from inflammation. The role of NSAIDs in the treatment of neuropathic pain is extremely limited.

Opioids act by binding to opioid receptors in the CNS and peripheral organs. Opioids reduce pain signal transmission both presynaptically and postsynaptically. Activation of presynaptic opioid receptors inhibits the release of the excitatory neurotransmitters. Postsynaptically, opioid receptor binding hyperpolarizes the membrane thereby reducing the probability of an action potential being generated. Opioids also affect supraspinal structures of pain processing, so that pain is still perceived but no longer experienced as unpleasant or threatening.
COMMENTARY

Dr Bart Morlion – Leuven Centre for Algology and Pain Management, University Hospitals Leuven, Belgium

Pain management can be extremely challenging. Many pain conditions can’t be classified to clear cut clinical categories. In my experience, especially chronic pain patients often suffer from mixed pain. Different pathophysiological mechanisms interplay. Moreover, in our chronic pain patients, the affective and evaluative dimensions of pain outgrow the sensory-discriminative dimensions, increasing the complexity for the physician and the suffering for the patient.

Clinically, signs and symptoms of neuropathic pain are often present but not always assessed. Attention to detail is an important issue in pain management. By improving awareness and education on the issues of neuropathic and mixed pain, more physicians will pay attention to it.

The search for the Holy Grail goes on. Magic bullets do not exist in chronic pain management. Chronic pain problems are not likely to be resolved by acute interventions. Effective pain management warrants careful titration of several powerful analgesic drugs, often leading to combination therapy. In theory, drugs targeting several receptor systems might be beneficial for our patients. They should be monitored and assessed regularly. Balancing pain relief to acceptable side effects means tightrope walking for the physician. For the benefit of our patients, more efforts are needed to shift pain management from an art to a science. Initiatives like CHANGE PAIN can contribute to these goals.

Anticonvulsants were originally developed for the treatment of epilepsy, and their analgesic action is thought to be related to their membrane-stabilizing effect, partly by blocking sodium channels and reduction of neuronal excitability which is often a typical feature of neuropathic pain. Newer anticonvulsants interact with voltage-gated calcium channels to decrease excitatory neurotransmitter release.

Tricyclic antidepressants (TCAs) inhibit the neuronal reuptake of noradrenaline (NA) and serotonin (5-HT) from the synaptic cleft. The resultant increase in neurotransmitter concentration intensifies activity in the descending inhibitory pain pathway, producing analgesia. TCAs also affect histaminergic, cholinergic, and glutaminergic neurotransmission and block sodium channels.

Serotonin and noradrenaline reuptake inhibitors (SNRIs) can also produce analgesia by inhibiting pain transmission in the spinal cord by increasing levels of NA and/or 5-HT.

Conclusion

Improving the knowledge about the underlying pain-inducing mechanisms and specific mechanisms of action of current treatment options could lead to more fact-based treatment decision, resulting in more effective management of pain.

References

1. Freynhagen R et al. 2006
(See abstract on page 11)
(See abstract on page 11)
PainDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain

Nociceptive and neuropathic components both contribute to pain and since these components require different pain management strategies, correct pain diagnosis is important. The painDETECT questionnaire (PD-Q) was developed as a validated screening tool to detect neuropathic pain components in chronic low back pain (LBP) patients. It was used in a prospective, multicentre study and subsequently applied to approximately 8,000 LBP patients. The study showed that patients ultimately report symptoms rather than pain mechanisms, therefore screening tools that identify neuropathic pain on the basis of symptoms and signs seems rational. The data demonstrated that about 2/3 of the patient population had predominantly neuropathic pain or pain with a neuropathic component whereas only about 1/3 had suffered from predominantly nociceptive pain.

The distinction between neuropathic and nociceptive pain types and the estimation of its relevance are important, since different pain types require different therapeutic approaches. This paper has demonstrated that the prevalence of neuropathic pain components correlates with more intense pain, more severe co-morbidity and poorer quality of life. Therefore, accurate diagnosis is a milestone in choosing appropriate therapy.

Modelling the prevalence and cost of back pain with neuropathic components in the general population

This study aimed to estimate the prevalence of neuropathic components in back pain and to assess the proportion of direct and indirect associated costs. Data from three studies: painDETECT 1, painDETECT 2, and the German back pain research network (GBPRN) study were combined, representing a total of 21,047 subjects. A strong association between pain severity and the proportion of patients with neuropathic pain components was found. Neuropathic pain components were substantially more frequent in persons with severe back pain (up to 77%) compared to persons with mild back pain. The model suggests that almost one in five adults with persistent back pain experiences neuropathic pain symptoms, which would correspond to approximately 4% of the general adult population. Among patients with persistent back pain, typical costs associated with a person suffering neuropathic back pain were significantly higher than those of an average back pain patient, and those patients with nociceptive pain only.

Back pain with neuropathic components is likely to affect a relevant proportion of the general adult population and cause a disproportionately high share of back pain-related costs. The identification and adequate treatment of back pain with neuropathic components could have a beneficial economic impact.
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