

Advances with analgesics and NSAIDs for the treatment of spinal disorders

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One of the major developments with regard to chronic non-malignant pain in these last few years has been a better understanding of the mechanisms that act to maintain pain, while inferences about the pathophysiology have facilitated therapeutic decision-making.

This chapter reviews the strength of evidence for the therapeutic effect of pharmacological symptomatic approaches using non-steroidal anti-inflammatory agents, opioids and co-analgesics in acute and chronic back pain with an emphasis on the results of randomized controlled trials as well as on the need for long-term comparative trials of drug efficacy, toxicity and compliance.

Key words: low back pain; analgesics; non-steroidal anti-inflammatory agents; NSAIDs; COX-2 selective agents; opioids; anti-depressants; compliance.

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INTRODUCTION

Non-malignant back pain (BP) encompasses a heterogeneous group of syndromes that are treated in a variety of ways. In contrast to acute pain, chronic BP very often defies satisfactory treatment. One of the major developments with regard to chronic non-malignant pain in recent years has been a better understanding of the mechanisms that act to maintain pain, while inferences about the pathophysiology have clarified therapeutic decision-making.

Pain syndromes fall into two main categories: the term 'nociceptive' is applied to pain that is presumed to be maintained by continuous tissue injury such as bone, joint or muscle inflammation. The term 'neuropathic' pain is used when pain is believed to be sustained by aberrant somatosensory processing in the peripheral or central nervous system. Although neuropathic pain can respond well to conventional analgesics, these syndromes are disproportionately represented among patients whose pain responds poorly to opioid drugs.^{1,2} As a result, the diagnosis of a neuropathic pain syndrome often implies other therapies, including the use of specific non-traditional analgesic drugs such as anti-depressants.³

Nociceptive and neuropathic pain can be acute or chronic. The latter is commonly defined as pain that persists for longer than the expected time frame for healing or pain associated with a progressive disease of malignant or non-malignant origin. Chronic or persistent pain may be due to the persistent stimulation of nociceptors in areas of ongoing tissue damage; for example, chronic pain due to osteoarthritis.

Chronic nociceptive or neuropathic pain needs to be distinguished from particular chronic pain syndromes that persist long after the tissue damage that initially triggered their onset has resolved, or pain syndromes without any identifiable ongoing tissue damage or antecedent injury. These syndromes, such as myofascial pain syndrome, fibromyalgia and somatoform pain disorders, are currently diagnosed on the basis of clinical criteria alone. Knowledge of the underlying pathophysiology of these disorders is limited and pharmacological approaches remain disappointing. The trend over the past decade has been to emphasize the biopsychosocial model and the advantages of a multidisciplinary approach provided by pain centres that carry out comprehensive somatic and psychosocial assessments in addition to providing pharmacological, physical and psychological treatments.⁴ BP may refer to various or even mixed components of chronic pain and it is thus not surprising that in most multidisciplinary pain centres back pain is one of the main reasons for consultation.

There is extensive experimental and clinical evidence documenting the major prevalence of persistent pain and the deleterious biological and psychological consequences of under-treated pain. Experimental studies have confirmed long-standing clinical impressions about the dynamic nature of pain and have shown that inadequately managed acute pain becomes sometimes more difficult to suppress. In fact, if tissue damage is unavoidable, a set of excitability changes in the peripheral and central nervous system take place and sometimes build in a slowly reversible or irreversible pain hypersensitivity in the inflamed and surrounding tissues.⁵ Biological and pharmacological evidence has shown that the induction and maintenance of central hyperexcitability and secondary hyperalgesia is mainly mediated by *N*-methyl-*D*-aspartate (NMDA) receptor activation, which offers a new target for pain modulation in chronic pain patients. Persistent pain syndromes offer no biological advantage and lead to profound biological alterations in both the peripheral and central nervous systems with a potential 'central sensitization' and suffering.^{2,6} Furthermore, persistent pain profoundly affects patients' social relationships, mood and physical functioning.

Concomitant depression and sleep disturbance further decrease overall physical functioning and working disability is typically experienced by chronic pain patients.⁷ Thus, in order to reduce the neurobiological and psychosocial consequences of pain a prompt, vigorous and adapted management of severe pain is mandatory in acute situations and should run concurrently with the aetiological treatment.

The comprehensive management of quality of life in rheumatology encompasses the control of inflammation, the prevention of joint destruction, the maintenance of optimal function and the management of pain. Non-pharmacological interventions, including patient education, psychological support and physical and occupational therapy play a crucial role in the management of chronic pain.

Chronic pain often remains an intricate syndrome where analgesic prescription is only one part of the treatment. However, when analgesics are tailored by taking into account their pharmacological properties and the patient's pain syndrome and comorbidities, they may contribute to a favourable benefit/risk ratio.

PHARMACOLOGICAL APPROACHES TO NOCICEPTIVE PAIN

Various chemicals (bradykinin, histamine, serotonin, prostaglandins, potassium, protons), which are released after tissue damage, induce nociceptive reactions and modify the activity of nociceptors either by direct activation or by modulation.⁸

Several peptides are present within the primary afferent fibres and their profile can be altered by sustained stimulation or by damage to the nerve. Apart from these substances, which are liberated soon after tissue damage, other factors such as the cytokines (interleukins, interferon, tumour necrosis factor (TNF) and nerve growth factor), are released by phagocyte cells and cells of the immune system and have an important role in the inflammatory process.⁸

To treat acute or persistent nociceptive pain in rheumatological conditions, pharmacological approaches, which encompass anti-inflammatory and immunomodulatory agents such as glucocorticoids, methotrexate, ciclosporin, anti-TNF, leflunomide, mycophenolate mofetil, disease modifying antirheumatic drugs (DMARDs), are targeted to the originating factors.

However, many patients remain insufficiently relieved and symptomatic analgesic therapy is needed. The World Health Organisation (WHO) recommends a three-step ladder approach to the use of analgesic drugs, with an initial treatment choice of a non-opioid analgesic, either non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. If one of these agents fails to relieve pain, a 'weak' opioid for mild to moderate pain is used, either alone or in combination with a non-opioid analgesic. If pain persists or increases, a 'strong' opioid for moderate to severe pain should be substituted. Current non-opioid and opioid analgesics have their limitations and physicians' and patients' fears of adverse effects associated with opioids and NSAIDs contribute to the under-treatment of pain. The 'analgesic ladder' approach of the WHO is widely accepted as the basis for treatment guidelines of cancer-related nociceptive syndromes⁹ and this approach is nowadays extended to non-cancer pain, although scientific evidence is still missing.

BENEFITS AND LIMITS OF NSAIDS AND ACETAMINOPHEN

Finding the best clinically available evidence for making decisions about the selection of an analgesic in painful spinal disorders remains a necessary purpose. Systematic reviews

of randomized controlled trials provide the best level of evidence for selecting a treatment, despite some pitfalls such as the inclusion of low-quality trials, unpublished trials and the many variations possible among drugs, doses, routes of administration and pain conditions which make meaningful comparisons difficult.^{10,11}

Single-dose analgesic trials using reproducible clinical procedures (dental extraction, post-surgical, or post-partum models) are not sufficient to assess their value in clinical practice, although such trials may be helpful in determining the relative efficacy of NSAIDs. Effective relief can be achieved in these models with oral non-opioids and NSAIDs. The results of a meta-analysis that included 42 randomized, controlled trials using these models allowed the comparison of the dose–response curves for diclofenac and ibuprofen, for example. Although diclofenac has long been regarded by clinicians as a more effective NSAID than ibuprofen, they both showed the same level of efficacy when the dosage was adjusted, i.e. 50 mg of diclofenac orally was no more efficient than 600 mg of ibuprofen.¹² With regard to BP, a systematic review that included 51 randomized, controlled trials (6057 patients) that assessed the benefits of NSAIDs, suggested that there was a significant clinical benefit over placebo and a strong level of evidence that various types of NSAIDs were, somehow, equally effective for the short-term relief of acute BP.¹³ For chronic inflammatory BP one study has suggested that a 1-year trial might be of optimum value compared to a 6-week assessment in order to define better the efficacy and tolerability of NSAIDs in ankylosing spondylitis. Evidence of long-term efficacy from randomized, controlled trials is still lacking and safety issues remain the most important problem.¹⁴

The most commonly prescribed NSAIDs reduce the synthesis of prostaglandins and thromboxane by the inhibition of the enzyme cyclo-oxygenase 1 (COX-1), a constitutive form of the enzyme. Inhibition of COX-1 is responsible for the gastrointestinal irritation and ulceration and for the blockade of platelet aggregation. The COX-2 inducible form of the enzyme is selectively inhibited by various new COX-2 NSAIDs that reduce the risk of these adverse effects and are effective in relieving the chronic pain conditions associated with rheumatoid arthritis or osteoarthritis.^{15,16} The rate of confirmed gastrointestinal events in 8076 randomized rheumatoid arthritis patients who received 50 mg of rofecoxib daily was 50% lower than the rate observed with naproxen 500 mg twice daily (4.1 events/100 patient-years). A number of studies in patients with osteoarthritis, rheumatoid arthritis and acute pain have confirmed that the clinical efficacy of COX-2 selective inhibitors is similar to that of conventional NSAIDs.¹⁷ Rofecoxib is currently licensed in Europe only for the treatment of osteoarthritis. Some other selective COX-2 NSAIDs such as nimesulide have been investigated in BP. A randomized prospective double-blind trial evaluated the efficacy of nimesulide (100 mg twice daily for 10 days) claimed to be COX-2 selective agent versus ibuprofen (600 mg three times daily) in 104 patients (18–65 years) suffering from acute common BP. There was a clear improvement in all parameters of pain and back function from the third day of treatment onwards with both treatments versus placebo.¹⁸ A 6-week randomized controlled study in 246 patients with ankylosing spondylitis showed an improvement in pain and functional impairment that was greater in the celecoxib or ketoprofen 200 mg/day treatment groups than in the placebo group.¹⁹ Since the available COX-2 selective inhibitors are still not 'pure' COX-2 drugs, especially if considering nimesulide, they may not display as dramatic an improvement on the adverse effects profile as was previously hoped. Well-documented cases of acute hepatic injury have been reported with nimesulide and with a number of NSAIDs such as diclofenac.²⁰ Furthermore, COX-2 selective agents are not expected to differ in terms of cardiovascular and renal adverse events, particularly when one takes into account the

long half-life of rofecoxib or celecoxib compared to the classically short-acting non-selective NSAIDs.

This can be of particular concern for the elderly population, who commonly experience chronic pain with acute exacerbations. Indeed, the available data demonstrate that the same frequency and type of renal toxicity should be expected with the new selective COX-2 inhibitors as with the NSAIDs. The selective COX-2 inhibitors represent a real therapeutic advance with a better gastrointestinal safety profile, but their renal safety has yet to be demonstrated, especially when used in high-risk patients or with other drugs that influence the renal haemodynamics. This assertion is borne out by recent clinical studies showing that the COX-2 inhibitors rofecoxib and celecoxib produce qualitative changes in urinary prostaglandin excretion, glomerular filtration rate and sodium retention.²¹ It is, therefore, unlikely that these COX-2 selective inhibitors will have greater renal safety benefits over non-selective NSAID therapies, and it is reasonable to assume that all NSAIDs, including COX-2-selective inhibitors, share a similar risk for adverse renal effects.²² These adverse effects include functionally acute renal failure, sodium and water retention, hyperkalaemia and immunoallergic nephritis. Moreover, it is possible that the improved gastrointestinal safety will increase the use of the selective COX-2 inhibitors in older and high-risk patients, which may lead to more renal adverse effects. The overall incidence of adverse renal events after celecoxib was similar to that observed after NSAID use in a post-hoc analysis of the renal toxicity of celecoxib, using the safety database generated during its clinical development programme which included data from more than 5000 subjects.

The burden of illness resulting from NSAID use may exceed that resulting from renal damage in the elderly. A recent case-control study showed that the use of NSAIDs, other than low-dose aspirin, in the previous week was associated with a doubling of the odds of a hospital first admission with cardiac heart failure (adjusted odds ratio (OR) = 2.1) with a greater increase when patients had a history of heart disease (OR = 10.5) compared to those (OR = 1.6) without such a history. The odds of a first admission to hospital with cardiac heart failure was positively related to the NSAID intake dose in the previous week and was increased to a greater extent because of the long half-life of NSAIDs. Assuming these relationships are causal, it was estimated that NSAIDs were responsible for approximately 19% of hospital admissions for cardiac heart failure.²³ Therefore, the long half-life of NSAIDs in particular should be used with caution in patients with a history of cardiovascular disease.

Furthermore, the rate of serious thrombotic adverse events (such as myocardial infarction) was significantly higher in patients receiving rofecoxib.¹⁶ The most likely explanation for the difference in cardiovascular events is that there is a protective effect of naproxen use, possibly related to anti-platelet activity. That is, a large number of elderly patients should remain on aspirin if they receive celecoxib or rofecoxib. In this case, the advantage in terms of gastrointestinal tract security remains an open question. In 2000, 1120 safety issues were reported to the Committee on Safety of Medicine in the UK for rofecoxib on 557 000 estimated prescriptions. Half of these issues concerned the gastrointestinal tract (GI), while 12% concerned bleeding, ulcers and perforations. Five patients had a fatal outcome. Over two-thirds of the patients were over 65 years in age and a quarter were taking aspirin.²⁴ The Committee on Safety in Medicine in the UK also reminded practitioners that COX-2 selective inhibitors were contraindicated in the presence of an active peptic ulceration or GI bleeding. Celecoxib, in the CLASS study, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications, compared with NSAIDs at standard dosages; however, this benefit was reduced in patients taking aspirin concomitantly.¹⁵

Indeed, in terms of safety and cost, short half-life NSAIDs, even if they are not COX-2 selective agents, can still be considered in acute painful conditions. This is especially the case when chronic persistent nociceptive pain is affected by short-lasting acute exacerbation. When moderate pain persists, either COX-2 selective agents such as celecoxib or rofecoxib or the combination of classical NSAIDs with a proton pump inhibitor when digestive risk factors have been identified, can be used.

Several non-NSAIDs non-narcotic therapies are available when inflammation is not the foremost issue in pain management. Since its introduction in 1893, acetaminophen has been widely used for the treatment of pain. Despite many attempts to elucidate its mechanism of action, it still remains unclear. It has been shown that acetaminophen selectively inhibits central nervous tissue COX but has little effect on enzyme preparations from peripheral tissues.^{25–27} Although this is not unequivocally accepted, many experiments in animals^{28–30} and humans³¹ have suggested that descending spinal serotonergic pathways are essential for maintaining its efficacy.³² This centrally acting analgesic is devoid of the gastric or renal adverse event profile usually seen with NSAIDs. Acetaminophen is as effective as NSAIDs for the management of mild-to-moderate osteoarthritic pain. The advantages is of NSAIDs over acetaminophen in painful spinal conditions remain at best, conflicting, and acetaminophen is still the first-line therapy recommended by the European and American societies of Rheumatology³³ for treating pain associated with osteoarthritis and is safer in the elderly population.³⁴

A PLACE FOR OPIOIDS IN LOW BACK PAIN?

Primary care physicians frequently face the challenge of treating chronic debilitating pain. Whether or not treatment with opioids is effective and justified in the treatment of pain that is unrelated to cancer is a matter of great controversy. In recent years, growing experience with opioid administration in cancer patients and the publication of some controlled studies have promoted a more liberal attitude. Certain carefully selected patients could benefit from short-term opioid treatment within the context of a more permanent pain treatment regimen. However, potential pitfalls such as prescribing opioids for myofascial pain syndrome, fibromyalgia, or somatoform pain disorders should be taken into account as well as the psychosocial dimensions surrounding the prescription of opioids.

In chronic nociceptive pain conditions, regular use of low-dose, long-acting opioids, although controversial, can effectively control chronic pain in selected patients.^{35–37} Opioids can improve the quality of life of patients in pain, but their use requires particular precautions, both in the choice of the specific opioid and in singling out patients with a high risk of drug abuse. Several randomized controlled studies have been performed in rheumatological chronic pain conditions evaluating the efficacy of opioids in BP. An open, randomized 4-month comparison of naproxen and two opioid regimens of oxycodone and sustained-release morphine sulphate in 36 patients with chronic BP has been performed. The opioid groups were significantly better than the naproxen alone group, with less pain and emotional distress, but opioids had little impact on daily activity and sleep and one of the participants showed signs of abuse.³⁸ Another study evaluated 380 chronic BP outpatients (aged 21–79 years) enrolled on an enriched 1-month randomized placebo controlled trial.³⁹ During the preceding 4-week open-label phase, patients were treated with tramadol in doses up to 400 mg/day. Because of adverse events, 20% withdrew, but 254 patients entered the double-blind phase, during

which daily doses were maintained (200–400 mg tramadol) and compared to placebo. The Kaplan–Meier estimate of the cumulative discontinuation rate due to therapeutic failure was 20% in the opioid group compared to 51% in the placebo group.³⁹ In osteoarthritis, a randomized controlled study on 236 patients (mean age 60 years) showed that the addition of an opioid allowed for a reduction in NSAIDs without compromising pain relief.⁴⁰ This can be of benefit in the mainstay of chronic pain management, since NSAIDs are known to be associated with cardiac and renal toxicities, a particular problem for the elderly population.

Although some open-label studies have suggested a possible benefit of long-term opioid analgesic therapy for some well-selected patients with refractory BP,⁴¹ factors responsible for chronification, such as the psychosocial situation, should systematically be taken into account and an interdisciplinary approach to the treatment of pain should be proposed. This is the case for common BP, fibromyalgia⁴², or failed back surgery where nociceptive and neuropathic pain syndromes may, moreover, coexist; one should therefore be extremely cautious as far as opioid prescription is concerned. Choosing the optimal analgesic treatment is not easy considering the multitude of currently available opioid derivatives, the commercialization of new galenic preparations, and the difficulty of evaluating their risk/benefit ratio. Basic principles for selecting an opioid treatment on an individual basis rely on various selection criteria such as the pharmacodynamic (PD) and pharmacokinetic (PK) properties of available opioids, the presence of comorbidities and concomitant medications, and the PK situations that are prone to increase the risk of substance abuse.

Addiction is a concern among patients and health-care providers, and drug-seeking behaviour is seen among patients with chronic pain. When opioids are used appropriately, addiction is rare, but patients should be monitored to ensure that they are using the opioid correctly. The risk can be minimized by prescribing opioids to patients with a history of drug abuse only with great caution and under strict medical supervision. To reduce the risk even further, the drug chosen should be given at the lowest effective dosage, with regular monitoring, have the least addictive potential and not be prescribed indefinitely. The risk of addiction can be reduced by avoiding their prescription in pain syndromes that are poorly responsive to opioids, such as psychogenic or neuropathic pain, and by selecting an opioid with an appropriate PK and PD profile. Certain PK drug characteristics lower the addiction potential. The rate of CNS drug delivery for example, influences positive reinforcement. Giving an oral formulation, a slow release formulation, or even a drug whose opiate component necessitates bioactivation, such as codeine or tramadol, reduces the risk of addiction. An optimal PK profile would also avoid negative reinforcement such as physical dependence and this can be accomplished with slow release formulations or long half-life opioids. Physical dependence should be sharply differentiated from addiction. Physical dependence can occur in the clinical setting, but does not involve inappropriate drug-seeking behaviour. Withdrawal symptoms and signs can be prevented by gradually decreasing the opioids' dosages. An optimal PD profile would favour selectivity on μ opioid receptors and avoid a high intrinsic activity.

Pain is often inadequately treated due, in part, to a reluctance to use opioid analgesics and fear of abuse behaviour. Every day throughout the world patients, caregivers and their governments face difficulties in obtaining opioid analgesics for the relief of severe pain. The WHO has promoted guidelines to avoid national narcotic laws that interfere with making these drugs available for medical use. These guidelines, recognizing that physicians should have the flexibility to decide the dose and duration of opioid treatment based on individual patients' needs, recommend that a country's narcotic

legislation not restrict the amount of opioids prescribed at one time and a survey conducted by the International Narcotics Control Board shows that 52% of governments do not have this provision in their legislation.⁴³

A retrospective survey of medical records from 1990–1996 stored in the databases of the Drug Abuse Warning Network and the Automation of Reports and Consolidated Orders System in the USA from 1990–1996 showed an increased medical use of opioid analgesics to treat pain, but that did not seem to contribute to an increase in opioid abuse.⁴⁴ Among opioids, tramadol is not scheduled in the USA and Europe and it has been recently marketed in the USA. A proactive post-marketing surveillance programme was carried out; monthly population exposure to tramadol had grown to just under one million patients over a 3 year period. Reports of abuse over the same period, however, grew no higher than 2/100 000 patients, recorded during a brief period of experimentation in the first 18 months. Since then the reported rate of abuse has significantly declined to levels of less than 1/100 000 patients by the year 2000. Moreover, 97% of abuse cases occurred in patients with a history of drug abuse. Because of its dual mode of action, tramadol, compared to other opioids, may have a better safety profile. On the down side however, the monoaminergic profile may increase CNS susceptibility. Convulsions, for instance, have been described with tramadol, although this occurred mainly after overdoses. In addition, due to the monoaminergic action of tramadol, concomitant anti-depressants should be used with caution to avoid a serotonergic syndrome.

In case of insufficient control of pain symptoms, the use of a 'stronger' opioid such as a slow release morphine formulation can be recommended when one bears in mind the prescribing guidelines for non-cancer pain (Table 1).⁴⁵

IS THERE A ROLE FOR ANTI-DEPRESSANTS IN THE MANAGEMENT OF PAINFUL SPINAL DISORDERS?

There is evidence that anti-depressants (ADs) have pain relief effects, which are either acute as observed in experimental pain studies or chronic as demonstrated in patients.^{46–48} Therefore, they have been commonly used to treat chronic pain for years. There are many assumptions about the mechanisms involved in the analgesic effects of ADs. Tricyclic ADs are known to inhibit noradrenaline (NA) and serotonin (5-HT) pre-synaptic re-uptake, but they also block $\alpha 1$ adrenergic, muscarinic and H1 histaminergic receptors. Some of the tricyclics present a balanced inhibition of NA and 5-HT re-uptake, such as amitriptyline or imipramine, or a relatively selective inhibition of NA re-uptake, such as desipramine or the tetracyclic maprotiline. The selective serotonergic re-uptake inhibitors (SSRIs) act mainly on 5-HT. A new agent, venlafaxine, which is chemically distinct from tricyclics and SSRIs, has shown an inhibition in re-uptake of NA and 5-HT with a relatively selective action on 5-HT, particularly at low dosages.⁴⁹

Some authors have argued that ADs might decrease pain through the improvement of masked or manifest depression. Although an improvement in mood may contribute to reports of decreased pain in some patients, there is clear evidence for pain relief in patients without pre-existing mood disorders and with smaller doses than the usual doses recommended for depression.^{50,51} The relationship between depression and pain could be even more complex, since an antagonist for substance P, which is a peptide involved in pain endings in the spinal cord, has shown anti-depressant properties that are equivalent to paroxetine.⁵² As well as their inhibitory mechanisms on 5-HT and/or

Table 1. Recommendations for the prolonged administration of opioids in chronic pain patients.

1. A history of drug abuse or other substance abuse (alcohol), of severe personality disorders and of a disturbed social environment should be considered as relative contra-indications.
2. Only one physician should be responsible for prescribing opioids. At each visit (at least once a month), s/he should evaluate the analgesia, the adverse effects and possible behavioural signs of psychological dependence. The preset goal is a partial analgesia as well as an improvement in physical activity and quality of life.
3. Knowledge of the opioid's pharmacology and the kinetic consequences of renal or hepatic insufficiency.
4. Start the treatment progressively, with low doses of opioids having pharmacological characteristics adapted to the clinical situation.
5. Adjust the route of administration to the patient's needs, while favouring the galenic forms which offer stable plasmatic concentrations.
6. Repeated administration at fixed intervals is needed in order to maintain efficient plasmatic levels and prevent anticipation anxiety.
7. Anticipate a 'rescue' dose for the predictable or unpredictable breakthrough pain.
8. The optimal dosage should be determined after reaching the steady-state (4 half-lives to reach stable plasmatic concentrations).
9. Avoid interactions between opioids and sedative non-analgesic drugs (benzodiazepines and neuroleptics used as tranquilizers) or the association of opioids such as tramadol with other serotonergic psychotropic drugs (anti-depressants).
10. Anticipate and treat adverse effects (constipation, nausea, vomiting, sedation) or neurological complications (myoclonia, confusion, hallucinations).
11. Discuss with the patient his/her representations about the use of morphine or of any other opioid. The patient should give an informed consent before being prescribed opioids and after having received information about the low risk of dependence and the possible cognitive problems due to opioids.
12. Assess the appearance of tolerance (increase doses, change of analgesic).
13. Anticipate a withdrawal syndrome by stopping opioid treatment progressively.

Adapted from the recommendations of the American Society of Pain, the consensus of the Canadian Pain Society and Limoges recommendations.

NA re-uptake, their analgesic effects could also be mediated through an involvement in the opioidergic system. ADs have additional effects on various ion channels such as inhibition of cardiac or neuronal Na^+ channels. This latter blockade could be involved in the analgesic effects of ADs. Some authors have claimed that the analgesic effect of ADs could be an epiphenomenon of their sedative effects. Meta-analysis has shown that non-sedative ADs are as effective as sedative ones. Furthermore, lorazepam, a benzodiazepine, did not relieve neuropathic pain, in contrast to amitriptyline.⁵³ The majority of clinical trials that have assessed the analgesic effects of ADs have done so using subjective scales usually rating pain intensity, fatigue, sleep, physical or social activities and quality of life. Numerous clinical trials have been done with ADs in various chronic pain syndromes. Evidence of their efficacy is conclusive for diabetic neuropathy, post-herpetic neuralgia, atypical facial pain, tension and migraine headache, fibromyalgia, rheumatic pain and chronic pain of mixed aetiologies.⁴⁸ Evidence is less clear for chronic BP given the methodological biases in many of the studies e.g. small sample sizes that lack statistical power, inadequate specification of inclusion and exclusion criteria, failure to use standardized outcome measures, absence of rigorous assessment for major depressive disorder and failure to maintain study blinding.⁵⁴ Furthermore, the differences among the chronic back pain studies in terms of patients' characteristics, medications, doses and outcome measures limit the use of a meta-analysis for a synthesis of this literature. In two recent placebo-controlled studies, which included patients suffering from chronic BP referred to primary practice, nortriptyline and maprotiline showed an analgesic effect in non-depressed individuals and were also associated with a lessening of disability in daily functioning, predominantly in the psychosocial domain.⁵⁰ These gains seemed to be more important for patients with radicular pain. Further studies are needed to investigate the effect of ADs on chronic BP with a neuropathic pain component. As in the experimental assays, the numerous clinical studies used the whole range of ADs from the first tricyclics to the newest ADs such as SSRIs causing fewer severe adverse effects. A large majority of these studies used a tricyclic, particularly amitriptyline, which was superior to placebo or to a SSRI. More specifically, in neuropathic pain, most of the studies showed a higher efficacy of tricyclics compared to SSRIs.^{46,55} These conclusions were confirmed in meta-analyses and non-selective tricyclics remain the most effective. Several dose–response studies in patients did not produce consistent findings regarding the relationship between dose, serum levels and analgesic effect. There is no established therapeutic concentration of ADs and as a consequence no dosing recommendations for AD use in any chronic pain disorder, reflecting the importance of first considering individual metabolic capacity. Thus, the monitoring of plasma drug concentrations should be restrained to compliance or toxicity problems or inefficiency after an adequate period of treatment. ADs are associated with a relatively high incidence of adverse effects in therapeutic usage. Many of the commonly observed adverse effects, such as dryness of mouth, blurred vision and drowsiness can be troublesome particularly at the start of tricyclic treatment. Studies have shown higher adverse effect scores at the start of treatment than 4–6 weeks later. The most common cardiovascular adverse effect appears to be orthostatic hypotension; more severe cardiac complications could arise in subjects with pre-existing cardiovascular disease. There appears to be a dose-dependent relationship such as has been found for venlafaxine and frequency of hypertension. In a meta-analysis, the risk of central toxicity (e.g. tremor, ataxia) was positively correlated with plasma drug concentration.

ANALGESICS AND COMPLIANCE

Compliance has been defined as 'the extent to which a person's behavior (in terms of taking medication or executing lifestyle changes) coincides with medical or health advice'.⁵⁶ Non-compliance may refer to many behaviours such as not having a prescription filled, taking an incorrect dose, taking the medication at the wrong times, forgetting one or more doses of the medication, increasing the frequency of doses and stopping the treatment too soon, either by ceasing to take the medication sooner than the physician recommended or failing to obtain a refill prescription. The most common forms of non-compliance are delaying or omitting doses except for narcotic analgesics and benzodiazepines.⁵⁷

Although consistently found to occur in about one half of all patients, non-compliance has been found to vary according to the type and state of disease. Chronicity is associated with decreased compliance as shown in some chronic pain problems such as headache⁵⁸, rheumatoid arthritis⁵⁹ and ankylosing spondylitis.⁶⁰

During the last decade many methods have been devised to assess compliance, but the complexity of the problem has prevented the development of a 'gold standard' method of measurement. The most frequently used methods are drug levels in blood or urine as direct measures and interviews, diaries and tablet counts (e.g. medication event monitoring system (MEMS)) as indirect measures.

For patients, compliance is not an issue: they do not perceive taking drugs entirely in terms of obeying the doctor's orders. Instead, they weigh up the costs and benefits of taking a particular medication, as they perceive them within the contexts and the constraints of their everyday lives and needs. This perspective implies the patient's active participation in the therapeutic relationship, leading to a shared decision making process. It also implies that non-compliance may not be due to disregard for the doctor's orders but may result from reasoned behaviour based on the patients' beliefs and previous experiences. Compliance appears to be high when practitioners and patients have common representations, agree on treatment procedures and share criteria for outcome appraisals.⁶¹

Studies have shown that adverse effects and beliefs about adverse effects are major determinants of non-compliance in patient populations suffering from a variety of diseases or problems. Occurrence and severity of adverse effects have been described as decreasing compliance to cholesterol-altering drugs, to anti-epileptic drug regimes as well as to migraine medication.⁶² Non-compliance due to fear of becoming dependent on the medication has been pointed out in populations as divergent as asthmatic patients, general practice patients taking long-term medication or patients suffering from ankylosing spondylitis.⁶⁰ Such findings in rheumatoid arthritis and ankylosing spondylitis patients may lead them to consider compliance with medication intake as a last resort, when the symptoms are more unacceptable than the fears of adverse effects and possible dependence.⁶³

For ADs, a fear of adverse effects has been shown in depressive patients as well as in the general population.⁶⁴ The results of a large opinion poll in Germany showed that even for the treatment of severe mental disease, psychotropic drugs are not well accepted in comparison to cardiac drugs: they are believed to cause significantly more severe adverse effects and raise a greater fear of losing control.⁶⁴ However, a patient's attention to adverse effects does not only lead to compliance problems. Wynne & Long's⁶⁵ study has shown that this attention might help the patient to cope adequately with his/her medication intake and thus avoid detrimental adverse effects. Adverse effects are thus of major interest when dealing with medication intake.⁶⁵

Since information about chronic pain patients' beliefs on ADs is scarce, we have conducted a pilot study to investigate these beliefs.⁶⁶ Seventy-six chronic pain patients (CPPs) and 54 pain-free non-patient controls (Cs) were included. CPPs were representative of the population referred to the Geneva Multidisciplinary Pain Centre and the sample included 30 chronic back pain patients (CBPs) and 46 patients suffering from other chronic pain problems; Cs were matched for age, gender, socioeconomic status and nationality. Semi-structured interviews were conducted, explicitly referring to individuals' definitions of medication and ADs. We chose to ask the individuals to give their own definitions instead of using multiple-choice questionnaires, since the latter mainly call up recognition memory. Moreover, the items in a questionnaire might inhibit a further search for alternative answers. The data analysis procedure was a content analysis. All responses were transcribed and categorized. Bivariate statistical procedures were used to evaluate within-group and between-group differences.

Apart from depression, CBPs' description of the indications for ADs included mood improvement, soothing effects, but also loss of desire. Pain was more often mentioned in this group (Table 2). However, this response was much less frequent than expected when compared to their reported intake of ADs and also to their medical records.

One-third of the CBPs considered that ADs were used to address severe psychological problems including madness, and 19% of them expected ADs to induce personality changes. Accordingly, 24% of CBPs considered ADs to be a dangerous medication, having many adverse effects including addiction (37%). Up to 19% would refuse to take ADs, 41% would accept but with great reluctance and 33% would accept only if they were convinced that it would affect their pain problem. The effect of ADs on pain is barely known among chronic pain patients. Patients' beliefs may hinder their understanding of the physician's prescription and their compliance with it. Non-congruence between patients' beliefs and physicians' prescription may account for part of the difficulties when prescribing such medication.

We have also been investigating the way individuals get information about medication.⁶⁷ Patient information leaflets (PILs) were the main reported source of information about medication in the patients as well as in the controls. Expected 'ideal' information included the possibility of discussing PILs and adverse effects with the physician. Content analysis of the PILs showed that leaflets on ADs point to indications that have a clear psychological, if not psychiatric, connotation. This is in line with patients' and controls' representations of ADs, so they may consider such medication to be inappropriate for the treatment of pain. In the context of chronic pain, where the

Table 2. Intake of ADs and beliefs about AD medication.

	CBPs	CPPs	Cs	Significance
1. Intake of ADs				
Present intake of ADs (%)	37	33	7	$P < 0.001$
Ever taken ADs (%)?	63	69	33	$P < 0.001$
2. Beliefs about ADs				
Against pain(%)	33	20	8	$P = 0.001$
Mood improvement(%)	30	41	63	$P = 0.008$
Severe psychological problems(%)	33	27	24	NS
Dangerous medication(%)	24	20	17	NS
Somatic adverse effects(%)	63	53	41	NS
Psychological adverse effects(%)	45	35	30	NS

causes of pain persistence often remain elusive, prescription of ADs may be seen as a 'delegitimation' – referring to the denial of the patient's experience of pain and suffering.⁶⁸ Even when ADs are prescribed because of their analgesic effect, indications as described in the PILs may lead the patient to think that the physician does not truly believe s/he is in pain. Thus, non-congruence between the motive for prescribing ADs and PILs may also account for part of the difficulties when prescribing such medication.

A study conducted with a sample of the Geneva population aged 18–75 showed that the vast majority of the interviewees did not differentiate between the various classes of psychotropic drugs (PTDs) and their use for psychiatric illnesses.⁶⁹ Similarly, for PTDs, more than 80% of the subjects referred to real or presumed somatic and/or psychological harmful effects (e.g. lethargy or drowsiness, loss of contact with reality, changes of personality). They criticized, in the same proportion, the addiction and the dependency created by PTDs and society itself, which promoted their use. Subjects' attitudes regarding PTDs, as well as medication in general, and compliance were strongly associated. Thus, both aspects seemed to be related to the subjects' degree of adherence to medicine and to its therapeutic approaches.

SUMMARY

Experimental studies have confirmed long-standing clinical impressions about the dynamic nature of pain and have shown that inadequately managed acute pain may become more difficult to suppress. Persistent pain syndromes offer no biological advantage; they could be the result of profound neurobiological alterations and be complicated by major psychosocial consequences. In order to reduce the neurobiological peripheral or central sensitization and the psychosocial consequences of severe pain, one should uncompromisingly handle acute pain in parallel to the aetiological treatment.

Chronic pain syndromes fall into several main categories that imply different therapeutic strategies. As a result, nociceptive pain can be adequately reduced using NSAIDs, acetaminophen or opioids, whereas neuropathic pain often implies the need for other therapeutic approaches including the use of specific non-traditional analgesic drugs such as anti-depressants or anti-convulsivants.

For nociceptive pain the selective COX-2 inhibitors are a real therapeutic advance with a better gastrointestinal safety profile, but their renal and cardiovascular safety are not expected to be particularly different when one takes into account the long half-life of some of them.

Indeed, in terms of efficacy, safety and cost, short half-life NSAIDs, even if they are not COX-2 selective agents, can still be suggested for use in acute painful conditions. This is especially the case when chronic persistent nociceptive pain is affected by short-lasting acute exacerbations. When moderate pain persists, either COX-2-selective agents such as celecoxib or rofecoxib or a combination of the classical NSAIDs with a proton pump inhibitor when digestive risk factors are identified, can be used. Several non-NSAID non-narcotic therapies such as acetaminophen are available when inflammation is not the foremost issue in pain management and they remain the first choice analgesic for mild to moderate nociceptive non-malignant pain. In chronic nociceptive pain conditions, regular use of low-dose long-acting opioids, although controversial, can effectively control chronic pain in selected patients. Opioids can improve the quality of life of patients in pain, but their use requires particular precautions, both when choosing the opioid and when singling out patients at risk of drug abuse. There is evidence that

anti-depressants offer benefits in chronic pain: meta-analyses have confirmed that non-selective tricyclics remain the most effective especially when a neuropathic component is present. Like any pharmacological treatment, anti-depressants raise the issue of patients' compliance. Various factors, such as beliefs and previous experiences, may affect it. The analgesic effect of anti-depressants is barely known, whereas the adverse effects are highly emphasized. Regarding beliefs, the case of opioids has not yet been settled by both patients and therapists.

Chronic pain remains an intricate syndrome where analgesic treatment is only one part of the treatment. However, when analgesics are tailored to the individual by taking into account their pharmacological properties and the patient's co-morbidities, they may contribute to a favourable benefit/risk ratio in these complex clinical conditions.

Practice points

- distinguishing nociceptive from neuropathic and somatoform pain disorders (or components) will help in selecting the best therapeutic approach
- in terms of efficacy, safety and cost, short half-life NSAIDs, even if they are not COX-2 selective agents, can still be suggested for use in acute painful conditions. This is especially the case when chronic persistent nociceptive pain is affected by short-lasting acute exacerbations
- the selective COX-2 inhibitors are a real therapeutic advance with a better gastrointestinal safety profile, but their renal and cardiovascular safety has yet to be demonstrated, and they should be used with caution in high-risk patients or with other drugs that influence renal or cardiovascular haemodynamics
- COX-2 selective inhibitors are contraindicated in the presence of an active peptic ulceration or gastrointestinal bleeding
- prophylactic use of aspirin should not be removed when COX-2 selective inhibitors are prescribed
- acetaminophen is available when inflammation is not the foremost issue in pain management and remains the first choice analgesic for mild to moderate nociceptive non-malignant pain
- opioids can improve the quality of life of patients in pain, but their use requires particular precautions, both when choosing the specific opioid and singling out patients at risk of drug abuse
- the risk of opioid addiction can be reduced by avoiding their prescription in pain syndromes that are poorly responsive to opioids, such as psychogenic or neuropathic pain, and by selecting an opioid with a good pharmacokinetic and pharmacodynamic profile
- the risk can be minimized by prescribing opioids to patients with a history of drug abuse only with great caution and under strict medical supervision. To reduce the risk even further see the recommendations in [Table 1](#).
- oral formulations, slow-release formulations, or even a drug whose opiate component necessitates bioactivation, such as codeine or tramadol, should be given
- there is evidence that anti-depressants have analgesic properties in chronic pain conditions
- non-selective tricyclics remain the most effective

Research agenda

- epidemiological studies to evaluate the prevalence and incidence of the different pain components in common chronic back pain are needed
- experimental studies are needed to evaluate the importance of 'central sensitization' in chronic back pain.
- prospective longitudinal studies to evaluate the efficacy and the incidence of renal and cardiovascular incidents related to NSAIDs versus acetaminophen or opioids in chronic back pain are needed
- prospective longitudinal studies to evaluate the efficacy and the safety of different opioids in chronic back pain are needed
- further studies are needed to investigate the dose response/effect of anti-depressants on chronic back pain and the influence of the neuropathic pain component when it is present

REFERENCES

1. Ossipov MH, Lai J, Malan TP Jr & Porreca F. Spinal and supraspinal mechanisms of neuropathic pain. *Annals of the New York Academy of Science* 2000; **909**: 12–24.
2. Woolf CJ & Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999; **353**: 1959–1964.
3. Anonymous. Drug treatment of neuropathic pain. *Drug Therapeutic Bulletin* 2000; **38**: 89–93.
4. Allaz AF, Vannotti M, Desmeules J et al. Use of the label 'litigation neurosis' in patients with somatoform pain disorder. *General Hospital Psychiatry* 1998; **20**: 91–97.
5. Woolf CJ & Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000; **288**: 1765–1769.
6. Perrot S & Guilbaud G. Pathophysiology of joint pain. *Revue du Rhumatisme (English edn)* 1996; **63**: 485–492.
7. Ashburn MA & Staats PS. Management of chronic pain. *Lancet* 1999; **353**: 1865–1869.
8. Besson J-M. The neurobiology of pain. *Lancet* 1999; **353**: 1610–1615.
9. Anonymous. *Cancer Pain Relief and Palliative Care*. Geneva: WHO Guidelines, 1996.
10. Furlan AD, Clarke J, Esmail R et al. Critical review of reviews on the treatment of chronic low back pain. *Spine* 2001; **26**: E155–E162.
11. McQuay HJ. In McQuay HJ & Moore RA (eds), In: *An evidence-based Resource for Pain Relief*. pp 1–13. Oxford: Oxford University Press.
12. McQuay HJ. Oral ibuprofen and diclofenac in postoperative pain. In McQuay HJ & Moore RA (eds) *An Evidence-based Resource for Pain Relief*, pp 78–83. Oxford: Oxford University Press, 1998.
13. Van Tulder MW, Scholten RJ, Koes BW & Deyo RA. Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane collaboration back review group. *Spine* 2000; **25**: 2501–2513.
14. Dougados M, Gueguen A, Nakache JP et al. Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial. *Rheumatology* 1999; **38**: 235–244.
15. Silverstein FE, Faich G, Goldstein JL et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *Journal of the American Medical Association* 2000; **284**: 1247–1255.
16. Bombardier C, Laine L, Reicin A et al and VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England Journal of Medicine* 2000; **343**: 1520–1528.
17. Cannon GW & Breedveld FC. Efficacy of cyclooxygenase-2-specific inhibitors. *American Journal of Medicine* 2001; **110** (supplement 1): 6–12.
18. Pohjolainen T, Jekunen A, Autio L & Vuorela H. Treatment of acute low back pain with the COX-2-selective anti-inflammatory drug nimesulide: results of a randomized, double-blind comparative trial versus ibuprofen. *Spine* 2000; **25**: 1579–1585.

19. Dougados M, Behier JM, Jolchine I et al. Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis and Rheumatism* 2001; **44**: 180–185.
20. Van Steenberghe W, Peeters P, De Bondt J et al. Nimesulide-induced acute hepatitis: evidence from six cases. *Journal of Hepatology* 1998; **29**: 135–141.
21. Whelton A, Maurath CJ, Verburg KM & Geis GS. Renal safety and tolerability of celecoxib, a novel cyclooxygenase-2 inhibitor. *American Journal of Therapeutics* 2000; **7**: 159–175.
22. Brater DC, Harris C, Redfern JS & Gertz BJ. Renal effects of cox-2-selective inhibitors. *American Journal of Nephrology* 2001; **21**: 1–15.
23. Page J & Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Archives of Internal Medicine* 2000; **160**: 777–784.
24. Committee on safety medicine. *Current Problems in Pharmacovigilance* 2000; **26**: 13.
25. Flower RJ & Vane JR. Inhibition of prostaglandin synthetase in brain explains the antipyretic activity of acetaminophen. *Nature* 1972; **240**: 410–411.
26. Tolman EL, Fuller BL, Marignan BA et al. Tissue selectivity and variability of effect of acetaminophen on arachidonic acid metabolism. *Prostaglandins Leukotrien Medicine* 1983; **12**: 347–356.
27. Ferrari RA, Ward SJ & Zobre CM. Estimation of the in vivo cyclooxygenase inhibitors on prostaglandin E2 levels in mouse brain. *European Journal of Pharmacology* 1990; **179**: 25–34.
28. Carlsson KH & Jurna I. Central analgesic effect of paracetamol manifested by depression of nociceptive activity in thalamic neurones of the rat. *Neuroscience Letters* 1987; **77**: 339–343.
29. Ferreira SH, Lorenzetti BB & Correa FMA. Central and peripheral antialgesic action of aspirin-like drugs. *European Journal of Pharmacology* 1978; **53**: 39–48.
30. Tjolsen A, Lund A & Hole K. Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotonergic systems. *European Journal of Pharmacology* 1991; **193**: 193–201.
31. Piletta P, Porchet H & Dayer P. Central analgesic effect of acetaminophen but not of aspirin. *Clinical Pharmacology and Therapeutics* 1991; **41**: 350–354.
32. Pelissier T, Alloui A, Paele C & Eschaliere A. Evidence of central antinociceptive effect of paracetamol involving spinal 5HT3 receptors. *Neuroreport (England)* 1995; **6**: 1546–1548.
33. Schnitzer TJ. Non-NSAID pharmacologic treatment options for the management of chronic pain. *American Journal of Medicine* 1998; **105**: 455–525.
34. Ray WA, Stein MC, Byrd V et al. Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: a randomized controlled trial. *Medical Care* 2001; **39**: 425–435.
35. Bannwarth B. Risk-benefit assessment of opioids in chronic noncancer pain. *Drug Safety* 1999; 283–296.
36. Federation of State Medical Boards of the US. *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain*. Eulless: Federation of State Medical Boards of the United States, Inc, 1998.
37. Dellimijn P, van Duijn H & Vanneste J. Prolonged treatment with transdermal fentanyl in neuropathic pain. *Journal of Pain and Symptom Management* 1998; **16**: 220–229.
38. Jamison RN, Raymond SA, Slawsby EA et al. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine* 1998; **23**: 2591–2600.
39. Schnitzer TJ, Gray WL, Paster RZ & Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *Journal of Rheumatology* 2000; **27**: 772–778.
40. Schnitzer TJ, Kamin M & Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. *Arthritis and Rheumatism* 1999; **42**: 1370–1377.
41. Schofferman J. Long-term opioid analgesic therapy for severe refractory lumbar spine pain. *Clinical Journal of Pain* 1999; **15**: 136–140.
42. Buskila D. Drug therapy. *Bailliere's Best Practice Research in Clinical Rheumatology* 1999; **13**: 479–485.
43. WHO. New Guidelines to Evaluate National Opioid Policy. 2001; **14**: 1.
44. Joranson DE, Ryan KM, Gilson AM & Dahl JL. Trends in medical use and abuse of opioid analgesics. *Journal of the American Medical Association* 2000; **283**: 1710–1714.
45. Perrot S, Bannwarth B, Bertin P et al. Use of morphine in nonmalignant joint pain: the Limoges recommendations. The French Society for Rheumatology. *Revue de Rheumatology (English Edition)* 1999; **66**: 571–576.
46. McQuay HJ, Tramer M, Nye BA et al. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68**: 217–227.
47. Fishbain D. Evidenced-based data on pain relief with antidepressants. *Annals of Medicine* 2000; **32**: 305–316.
48. Ansari A. The efficacy of newer antidepressants in the treatment of chronic pain: a review of current literature. *Harvard Review of Psychiatry* 2000; **7**: 257–277.

49. Tatsumi M, Groshan K, Blakely RD & Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *European Journal of Pharmacology* 1997; **340**: 249–258.
50. Atkinson JH, Slater MA, Williams RA et al. A placebo-controlled randomized clinical trial of nortriptyline from chronic low back pain. *Pain* 1998; **76**: 287–296.
51. Max MB. Antidepressant drugs as treatments for chronic pain: efficacy and mechanisms. In Bromm B & Desmedt JE (eds) *Pain and the Brain: from Nociception to Cognition. Advances in Pain Research and Therapy*, vol 22, pp 501–515. New York: Raven Press, 1995.
52. Nutt D. Substance-P antagonists: a new treatment for depression? *Lancet* 1998; **352**: 1644–1645.
53. Max MB, Schafer SC, Culnane M et al. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology* 1998; **38**: 1427–1432.
54. Turner JA & Denny C. Do antidepressant medications relieve chronic low back pain? *Journal of Family Practice* 1993; **37**: 545–553.
55. Sindrup SH, Gram LF, Brosen K et al. The selective reuptake serotonin inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990; **42**: 135–144.
56. Haynes RB, Taylors DW & Sackett DL. *Compliance in Health Care*. London: Hopkins Press, 1979.
57. Kouyanou K, Pither CE & Wessely S. Medication misuse, abuse and dependence in chronic pain patients. *Journal of Psychosomatic Research* 1997; **43**: 497–504.
58. Ferreri A, Stefani M, Sternieri S et al. Analgesic drug taking: beliefs and behavior among headache patients. *Headache* 1997; **37**: 88–94.
59. Brus H, van de Laar M, Taal E et al. Compliance in rheumatoid arthritis and the role of formal patient education. *Seminars in Arthritis and Rheumatism* 1997; **26**: 702–710.
60. De Klerk E & van der Linden SJ. Compliance monitoring of NSAID drug therapy in ankylosing spondylitis experiences with an electronic monitoring device. *British Journal of Rheumatology* 1996; **35**: 60–65.
61. Nordin M, Cedraschi C & Skovron ML. Patient-health care provider relationship in patients with non-specific low back pain: a review of some problem situations. *Baillière's Clinical Rheumatology* 1998; **12**: 75–92.
62. McGregor EA. The doctor and the migraine patient: improving compliance. *Neurology* 1997; **48**: S16–S20.
63. Donovan JL & Blake DR. Patient non-compliance. Deviance or reasoned decision-making? *Social Sciences and Medicine* 1992; **34**: 507–513.
64. Benkert O, Graf-Morgenstern M, Hillert A et al. Public opinion on psychotropic drugs: an analysis of the factors influencing acceptance or rejection. *Journal of Nerve and Mental Disease* 1997; **185**: 51–58.
65. Wynne HA & Long A. Patient awareness for the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs). *British Journal of Clinical Pharmacology* 1996; **42**: 253–256.
66. Cedraschi C, Piguet V, Fischer W et al. Beliefs about antidepressants in back pain patients: a clue to non-compliance. *The Annual Meeting of the International Society for the Study of the Lumbar Spine*. Adelaide, 2000.
67. Cedraschi C, Piguet V, Fischer W et al. Patient information leaflets and antidepressant prescription in chronic pain patients. Proceedings of the 9th World Congress on Pain. In Devor M, Rowbotham M & Wiesenfeld-Hallin Z (eds) *Progress in Pain Research and Management*, vol 16, pp 887–895. Seattle: IASP, 2000.
68. Piguet V, Cedraschi C, Fischer W et al. Antidepressants representations in chronic pain patients *The 9th World Congress on Pain, Vienna*. p. 471 Vienna, 1999 (Abstract).
69. Fischer W, Goerg D, Zbinden E & Guimón J. Determining factors and the effects of attitudes towards psychotropic medication. In Guimón J, Fischer W & Sartorius N (eds) *The Image of Madness. The Public Facing Mental Illness and Psychiatric Treatment*, pp 162–186. Basel: Karger, 1999.