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Risk-Benefit Assessment of Opioids in Chronic Noncancer Pain

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Abstract

Opioids have been accepted as appropriate treatment for acute and cancer pain, but their role in the management of chronic nonmalignant pain is the subject of much debate, mainly due to concerns about waning efficacy, the potential for neuropsychological impairment and the development of drug addiction.

Controlled clinical trials demonstrated that opioids may be effective in both nociceptive and neuropathic noncancer pain, although the former responded more consistently than the latter. Gastrointestinal and CNS adverse effects were frequent in most studies.

Observational studies have generated contradictory findings regarding efficacy and safety as well as the risk of drug addiction in patients with chronic noncancer pain receiving long term opioid therapy. However, they suggest that opioids may be effective in individual cases, whichever the pathophysiological mechanism of pain.

Taken together, the available data indicate that the outcomes associated with opioid therapy vary markedly across patients experiencing chronic nonmalignant

pain. The main consensus is that a subset of these patients may gain substantial benefit from opioid analgesics without requiring rapidly escalating doses or developing intolerable adverse effects or drug addiction. Prescribing guidelines have been developed to assist practitioners in selecting the appropriate patients and ensuring an acceptable risk : benefit ratio of opioid therapy. Finally, it must be emphasised that chronic pain is a complex entity wherein analgesics, including opioids, are only part of the treatment.

Chronic pain is usually defined by a duration of more than 3 months. Chronic noncancer pain may also be considered as 'persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient, attributable to any nonmalignant aetiology'.[1] Both clinical trials[2] and clinical practice[3] offer good evidence that non-opioid analgesics do not provide satisfactory pain relief in a number of patients experiencing this type of pain. In fact, only nociceptive pain (arising from an identifiable stimulus, such as any kind of tissue damage) responds consistently to these drugs; neuropathic pain (caused by a primary lesion or dysfunction of the peripheral or central nervous system) and psychogenic pain (without demonstrable organic pathology, but where psychological components are primary factors) usually do not.[4,5] Additional reasons may account for some therapeutic failures. First, nonpharmacological interventions, including patient education, social support and physical and occupational therapy play a crucial role in the management of chronic pain, particularly in patients with rheumatic diseases.[6] Secondly, there is evidence for interindividual variation in the response to a given analgesic, and also to the adverse effects experienced.[4] Finally, there may be a place for opioids in patients who are unsatisfied with other types of analgesics. However, there are potential barriers to opioid therapy for nonmalignant pain.[7-9] These include uncertainty about its therapeutic efficacy as well as fears that opioid use will lead to addiction. Furthermore, there are concerns regarding deterioration of physical and psychological functioning. These issues highlight the need to assess the risk : benefit ratio of opioids in noncancer pain.

1. Clinical Pharmacology of the Opioids

1.1 Weak and Strong Opioids

On the basis of their interactions with the different receptor subtypes (μ, κ, δ), opioid analgesics can be divided into pure agonist, partial agonist and mixed agonist-antagonist classes.[10] The 2 last categories are characterised by a ceiling to analgesic effect, i.e. an inability to relieve pain beyond a certain intensity despite an increase in dose.[11] Conversely, as the dose of a pure agonist is raised, analgesic effect increases theoretically in a log-linear function until analgesia is achieved or dose-limiting adverse effects occur. Practically, a ceiling effect for analgesia may be an intrinsic property of the drug, or may be due to toxicity at high doses.[11] In this respect, pure agonists such as codeine and dihydrocodeine display limited analgesic efficacy because of unacceptable adverse effects at high dosages.[11] Thus, for clinical purposes, opioids are primarily classified as either 'weak' or 'strong' analgesics according to the pain intensity for which they may be efficacious (table I).[10]

These 2 classes constitute the second and third steps, respectively, on the World Health Organization analgesic ladder, the first step being non-opioid analgesics.[5] Accordingly, weak opioids, including codeine, dihydrocodeine, dextropropoxyphene and tramadol, are conventionally used for moderate pain whereas strong opioids, especially morphine, are intended for severe pain. An alternative approach for patients with moderate pain incorporates the use of low doses of a strong opioid.[10] For instance, oxycodone is currently marketed at low doses in combination with aspirin (acetylsalicylic acid) or paracetamol (acetamino-

Table I. Classification, equi-analgesic oral doses and duration of action of opioid analgesics commonly used or studied in chronic noncancer pain[10,12]

Drug	Receptor interaction	Oral dose (mg)[a]	Duration of action (h)[b]
Weak opioids			
Codeine	Agonist	200	4
Dihydrocodeine	Agonist	200	4
Dextropropoxyphene	Agonist	100	4
Tramadol	Agonist[c]	120	4-6
Strong opioids			
Morphine	Agonist	30[d]	3-6
Methadone	Agonist	10[d]	4-8
Oxycodone	Agonist	30	4
Buprenorphine	Partial agonist	0.8	6-9
Pentazocine	Antagonist μ/ agonist κ	100	4

a Equivalent to morphine 10mg administered intramuscularly or subcutaneously.

b The mean duration of action from a dose may increase with long term administration and controlled release formulations.

c In addition to spinal inhibition of monoaminergic reuptake and enhancement of serotonin (5-hydroxytryptamine) release.

d Dose equivalence in the multiple dose context of chronic pain.

phen) in some countries.[12] These combination products are intended for moderate pain.[10]

1.2 Pharmacological Properties

1.2.1 Analgesia

No opioid analgesic has proven to be clinically superior to morphine in relieving pain.[12] Therefore, morphine remains the gold standard among strong opioids.[12] Data derived from clinical trials allowed the development of an equi-analgesic dose table that provides guidelines for dose selection when the drug or route of administration is changed (table I).[10,12] However, responses of an individual patient may vary dramatically with different morphine-like compounds.[12] Except for differences in drug disposition, mechanisms underlying variations in individual responses are generally not understood. Nevertheless, poor response to an opioid may sometimes arise because of altered metabolism of the drug.

The polymorphic cytochrome P450 (CYP) isoform CYP2D6 catalyses *O*-dealkylation of several opioids, such as codeine, dihydrocodeine and oxycodone.[13-16] About 7 to 10% of Caucasians do not express functional CYP2D6, and hence are practically unable to convert codeine to morphine; since the morphine formed accounts for most or all of the analgesic effects of codeine, these individuals experience little or no analgesia after administration of codeine.[14-16] Similarly, the *O*-demethylated metabolite dihydromorphine may contribute to a large extent to the therapeutic efficacy of dihydrocodeine.[13] However, this view has been challenged recently.[17] Conversely, the analgesic effect of oxycodone is primarily due to the parent compound, and not to the metabolite oxymorphone.[15] Some cases of 'paradoxical pain' or 'overwhelming pain syndrome' observed in morphine-treated patients may be related to abnormal metabolism of morphine, wherein large amounts of morphine-3-glucuronide are formed with little morphine-6-glucuronide.[18] There is some evidence that the former is an opioid antagonist, whereas the latter contributes to the analgesic effect of morphine.[18] Methadone, which is metabolised by other pathways, may be effective in such circumstances.[19] However, short term intravenous administration of morphine-6-glucuronide displayed no analgesic effect in an experimental pain model in healthy volunteers.[20] In fact, there is controversy over the precise definition of 'paradoxical pain' and, indeed, on whether this phenomenon actually exists.[21]

1.2.2 Adverse Effects

Adverse effects to opioids are usually dose related.[10,12] They affect mainly the gastrointestinal tract (nausea, vomiting and constipation), the central nervous system (sedation, dizziness, cognitive impairment, respiratory depression and myoclonus), the skin (pruritus) and the urinary tract (possible urinary retention).[10,12] Except for constipation, tolerance to these effects usually develops rapidly.[10,12] Thus, constipation should be treated prophylactically when strong opioids are used.[10] In addition to dietary advice, a peristaltic stimulant, such as senna, and/or a softening agent, such as docusate, can be recommended.[5,10] Patients who develop nausea and vomiting may be pre-

scribed antiemetics, e.g. low doses of haloperidol or metoclopramide.[5,10] In any case, a key principle for successful opioid therapy is to titrate carefully the dose against pain.[12]

Besides constipation, some patients experience other long-lasting adverse effects, including sedation. This may result in psychomotor impairment, which might account for the 60% increased risk of hip fracture found in the elderly receiving codeine or dextropropoxyphene.[22] Surprisingly, no association between opioid administration and falls has been reported, possibly because of methodological flaws in most studies.[22,23] The potential for persistent cognitive impairment is another important issue. Two small studies suggested that opioids did not alter functional capacity and indeed, could improve mood in patients with chronic noncancer pain.[24,25] Moreover, it was observed that pain relief was associated with improved performance in these patients.[26] Similarly, long term opioid therapy is viewed as fully compatible with normal functioning, including driving, in most patients with cancer pain.[8] Conversely, long term opioid use may cause subtle neuropsychological deficits which could interfere with rehabilitation, particularly in those patients concurrently receiving other central nervous system depressants.[8,10,27]

There is no good evidence that the overall incidence of adverse effects is different with different opioids at the same level of analgesia.[11,12] However, the incidence of specific adverse effects varies widely between drugs. For instance, pentazocine produces a relatively high incidence of κ-mediated psychomimetic effects, and myoclonus is most prominent with pethidine.[10,12] Repeated doses of dextropropoxyphene may induce hypoglycaemia and lead to naloxone-insensitive cardiac toxicity caused by the accumulation of its main metabolite, norpropoxyphene.[12] Furthermore, a patient may experience adverse effects with one agent and not with another at equipotent doses, and the individual responses cannot be predicted.[11] Subsequently, if problems are encountered with 1 drug, another should be tried.[12]

Other factors must be taken into account in choosing an opioid analgesic and its regimen. Special attention should be paid to elderly patients and those patients with compromised hepatic or renal function. General guidelines for reducing the risk of adverse events in these patients have been proposed recently.[28] First, lower initial doses and increased administration intervals compared with normal practice are recommended. Secondly, opioids with common specific (idiosyncratic) adverse effects such as pethidine (meperidine), pentazocine and dextropropoxyphene should be avoided. On the other hand, methadone kinetics appeared to be largely unchanged by renal insufficiency or cirrhosis.

1.3 Tolerance, Dependence and Addiction

Confusion about substance abuse terminology contributes to physicians' reluctance to prescribe opioids and patients' reluctance to use them.[10] Thus it must be emphasised that tolerance and physical dependence are biological phenomena that develop more or less with repeated use of all the opioids and do not imply abuse or addiction.[29]

1.3.1 Tolerance

Tolerance can be defined as the reduction in response to the drug after repeated administration or the need for higher doses to maintain a defined pharmacodynamic effect.[29]

As mentioned above, tolerance to most opioid adverse effects occurs rapidly. Conversely, clinical surveys have not shown the development of tolerance to analgesia to be a clinical problem.[8,30] In fact, most patients with noncancer pain can be maintained on stable doses of opioids over extended periods.[8] On the basis of animal studies, it may be hypothesised that chronic nociceptive stimulation acts to antagonise the development of tolerance to analgesia.[30] Apart from tolerance, a need for higher doses may reflect worsening pain or development of abuse behaviours.[8,26,31] Thus any dose escalation should be considered carefully. Interestingly, a recently published retrospective study of a cohort of patients with pain caused by defined rheumatic diseases indicates that dose escalations occurred in 32 out of 137 long term (≥3

months) users of codeine or oxycodone.[32] These dose escalations were temporary in 12 patients and persistent in 20.[32] Almost all were related to worsening of the underlying painful disorder or complication thereof.[32] They were unexplained in only 4 patients (3%) who also displayed abuse behaviours.[32]

Repeated exposure to an opioid may confer tolerance not only to the drug being used but also to other opioids.[30] This effect, which is known as cross-tolerance, appears to be incomplete in both animals and humans.[30] Thus patients who have pain uncontrolled by a given opioid (e.g. morphine) in spite of intolerable adverse effects may be switched to an alternative opioid that provides a favourable balance between analgesia and adverse effects.[30]

1.3.2 Physical Dependence

Physical dependence is defined as the occurrence of a withdrawal syndrome following either abrupt dose reduction or administration of an antagonist.[10] It seems closely related to tolerance, since *N*-methyl-D-aspartate antagonists and nitric oxide synthase inhibitors that block tolerance to morphine in animals also block dependence.[12]

Physical dependence is not a clinical problem if patients are warned to avoid abrupt discontinuation of the treatment, a tapering regimen is used if drug cessation is indicated, and opioid antagonists are avoided.[10,30]

1.3.3 Addiction

Addiction is the main issue in opioid therapy for chronic nonmalignant pain. Unfortunately, the true extent of this problem cannot be assessed precisely. This results first from the lack of consensus about the definition of drug addiction. In this respect, it is agreed that the most important features are: (i) loss of control over drug use; (ii) compulsive drug use; and (iii) continued use despite drug-related harm to self or others.[8,10,27] In other words, the development of addiction is a psychological and behavioural process.[30] Secondly, the terms dependence, abuse and addiction have been used interchangeably, although they describe different problems.[27] Thirdly, the diagnosis of addiction is rarely straightforward so that it requires an astute assessment of the patient's behaviour, as discussed by Portenoy.[8] The complexity of this diagnosis is reflected in the term 'pseudoaddiction' that has been introduced to describe some types of abnormal behaviours developing as a consequence of inadequate pain management with opioids in cancer patients.[33]

The incidence of opioid addiction varied between 0 and 24% across observational studies in patients with chronic noncancer pain.[8,26,27,31] The gross discrepancies in these figures may be caused by population sample bias.[31] In this respect, the importance of situational factors and personality variables has been underlined.[8] Many addicted patients appeared to have had drug problems prior to the development of pain.[27] Relatively high prevalence of psychopathy has been observed among addict populations.[8]

Finally, special attention should be paid to patients with 'idiopathic' pain (without demonstrable organic pathology) and a high level of psychological distress or disability, previous overuse of medical resources, or overuse of drugs.[8,30] Conversely, clinical surveys and experience suggest the risk of addiction to be low among patients with organic pain syndromes and no prior history of substance abuse or psychiatric illness.[8,10] Nevertheless, the clinician must always consider the potential for addiction during the treatment of any patient.[8]

2. Opioids in Chronic Noncancer Pain

Reports of randomised, double-blind, controlled studies of opioids in chronic noncancer pain were identified through a systematic search consisting of electronic searching of Medline. Additional references were identified from reference lists of retrieved articles and reviews. Only publications written in English or French were retrieved.

2.1 Clinical Trials in Nociceptive Pain

Controlled studies were carried out mainly in patients with various musculoskeletal conditions. Two single dose studies were performed in patients

with rheumatoid arthritis.[34,35] One indicated that aspirin 650mg was the most effective analgesic amongst 5 drugs tested, with codeine 65mg and paracetamol 650mg intermediate between aspirin and dextropropoxyphene 65mg or placebo.[34] Pentazocine 50mg was also more effective than dextropropoxyphene or placebo, but not significantly so.[34] The second study showed that pentazocine 50mg and paracetamol 1g were intermediate in effectiveness between placebo on the one hand, and aspirin 600mg, aspirin 1g combined with codeine 16mg, or paracetamol 650mg combined with dextropropoxyphene 65mg on the other, these 3 treatments being about equally effective.[35]

These data are in line with those of a systematic review of single dose double-blind controlled trials in postoperative pain, which showed that the analgesic efficacy of paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), especially ibuprofen, compares very favourably with that of weak opioids.[36] Furthermore, the analgesic effect of non-opioid analgesics appears to be only slightly increased by adding a weak opioid.[36-38]

However, it may be argued that single dose studies are inadequate to estimate the risk : benefit ratio of opioids in chronic pain conditions. A better analgesic effect may be achieved after repeated doses – a situation more in keeping with clinical practice.[34,37,39,40] Unlike single dose studies, multidose studies are reliable predictors of the most common adverse effects of a drug.[37] Therefore, double-blind randomised multiple dose trials will be reviewed briefly (table II).

2.1.1 Placebo-Controlled Trials of Opioids

A small short term study indicated that controlled-release codeine (200 to 400 mg/day) resulted in reduced pain and pain-related disability in patients with various chronic nonmalignant pain conditions.[41] Compared with placebo, there were more reports of adverse effects and treatment discontinuation due to adverse effects with codeine.[41]

A 4-week placebo-controlled study published in abstract form only concluded that controlled-release codeine produced clinically important improvements in pain, physical function, global status and sleep in patients with osteoarthritis of the knee and/or hip.[42] The frequency of constipation, nausea and sedation was higher with codeine than placebo, although overall adverse effect rates (not reported) and treatment discontinuation rates (36%) were similar.[42] In this study, the starting daily dosage of codeine was 100mg, increasing weekly to a maximum of 400mg.[42]

Unpublished data on file were reported to show the superiority of tramadol 50mg 3 times daily over placebo in 200 patients with moderate to severe pain due to osteoarthritis of the knee.[60] Based on these data and dose finding studies, it was suggested that tramadol 50mg 3 times daily is a suitable dosage for long term treatment in patients with chronic noncancer pain.[60] The effect of tramadol has also been evaluated in 42 patients with breakthrough pain from osteoarthritis while taking an NSAID.[43] An average dosage of tramadol 250 mg/day for 13 days appeared to be significantly more effective than placebo in reducing the severity of pain at rest. However, general severity of current pain and ability to perform activities of daily living were not significantly different with tramadol or placebo.[43] The incidence of constipation (45%), nausea (35%), drowsiness (25%) and vertigo (20%) were greater in the tramadol group than in the placebo group (0, 14, 14 and 5%, respectively).[43] Of note, there was a selection bias in this study, since only patients who were willing to continue tramadol after a non-blind phase were included in the subsequent double-blind placebo-controlled phase.[43]

There is only 1 double-blind placebo-controlled study investigating the long term use of opioids in chronic nonmalignant pain.[44] In this crossover study, patients with chronic regional pain of soft tissue or musculoskeletal origin who had not responded to codeine, NSAIDs and antidepressants received either sustained-release morphine at dosages up to 120 mg/day or benztropine over a period of 9 weeks. Benztropine was used as an active placebo because it mimics many of the possible adverse effects of morphine. After dose titration, the

mean daily dosage of morphine was 83.5mg. The major conclusion of this study was that oral morphine was of analgesic benefit with low risk of addiction, but did not confer any psychological or functional improvement. Furthermore, 15 patients out of 61 discontinued treatment during the titration phase, 11 of them during morphine titration. Vomiting, dizziness, constipation, poor appetite or nausea and abdominal pain were all significantly more frequent with morphine.[44] Finally, there was no significant difference in overall patient preference of morphine compared with placebo.[44]

2.1.2 Clinical Trials of Single Opioid Compounds

Single opioid drugs have been evaluated in patients with osteoarthritis.[45-48] Pentazocine (200 to 400 mg/day) and dihydrocodeine (120 to 240 mg/day) were found to provide similar degree of pain relief after 1 week of treatment.[45] However, 60 and 66% of patients, respectively, experienced typical opioid adverse events.[45]

Another study compared tramadol 100mg 3 times daily with dextropropoxyphene napsylate 100mg (corresponding to dextropropoxyphene hydrochloride 65mg) 3 times daily in patients who reported moderate to severe pain of the hip and/or knee despite taking paracetamol (4 g/day) during a 1-week lead-in period.[46] At the end of the second week of opioid therapy, a significantly larger proportion of tramadol-treated patients had improvement on walking and during daily activities as compared with patients receiving dextropropoxyphene (about 70 and 50%, respectively). However, there was no significant difference between the 2 drugs with respect to mean pain relief as measured on a 10cm visual analogue scale (4.1 and 3.6cm, respectively). Both the incidence of adverse effects and the number of withdrawals due to adverse effects were significantly higher in the tramadol group.[46]

Tramadol 200 to 400 mg/day and ibuprofen 1.2 to 2.4 g/day were recently reported to be equally effective for symptomatic treatment of osteoarthritis.[48] Mean pain scores on a 10cm visual analogue scale were 7.22 and 7.29, respectively, at baseline, and 4.86 and 4.60, respectively, at the final visit (day 39). Again, the tramadol group experienced more adverse effects, including nausea (33 *vs* 9%), constipation (21 *vs* 8 %) and drowsiness (12 *vs* 4%).

2.1.3 Clinical Trials of Analgesic Combinations with Opioids

Opioids are widely used in combination with a non-opioid analgesic, especially paracetamol. The rationale for combining 2 differentially acting analgesics is the theoretical enhancement of efficacy.[39] Alternatively, such combinations may avoid increasing the dose of either drug alone and therefore may have a lower expected incidence of adverse effects.[39] To support these hypotheses, these combinations should be compared with any of the constituents alone.[39] Few trials have been conducted in this way.

A crossover study compared paracetamol 650mg, dextropropoxyphene napsylate 100mg and their combination (4 to 6 doses per day, each given for 2 days) against placebo in patients with chronic pain mainly related to musculoskeletal disorders.[49] In contrast with paracetamol, dextropropoxyphene was superior to placebo, and pain relief was better with the combination than with single entities alone.[49] However, there were no marked differences in the reported mean pain relief scores, suggesting no obvious differences in efficacy.[61]

A 1-week investigation found comparable pain relief in patients with back pain receiving 1 or 2 tablets of either paracetamol 500mg plus caffeine 50mg or paracetamol 400mg plus dextropropoxyphene 30mg, each 3 times daily.[50] Thus, it appears that the combination of small doses of dextropropoxyphene with paracetamol is no better than paracetamol on its own.[61]

The analgesic efficacy of ibuprofen 200mg plus codeine 30mg was reported to be significantly superior to that of ibuprofen 200mg alone which was, in turn, superior to placebo in patients with coxarthrosis pain who were given each of the 3 treatments as a total of 6 doses over 24 hours.[40] A significant difference in the analgesic effect was detected between codeine 60mg plus paracetamol 1g and paracetamol 1g alone, both 3 times daily,

Table II. Characteristics of double-blind randomised multidose trials in chronic nonmalignant nociceptive pain

Reference	Design	Type of pain	Drugs	Duration	No. of participants	Analgesic efficacy	Adverse effects (% of patients)
Arkinstall et al.[41]	Crossover	Miscellaneous	CR codeine 200-400 mg/day *vs* placebo	1wk	46	CR codeine > placebo	15 *vs* 2[a]
Peloso et al.[42]	Parallel	OA (hip, knee)	CR codeine 318 mg/day *vs* placebo[b]	4wk	103	CR codeine > placebo	NR
Roth[43]	Parallel	OA	Tramadol 250 mg/day *vs* placebo[b]	13 days	42	Tramadol > placebo	NR
Moulin et al.[44]	Crossover	Miscellaneous	SR morphine 83.5 mg/day *vs* placebo[b]	9 wks	46	SR morphine > placebo	NR
Addis-Jones et al.[45]	Crossover	OA	Pentazocine 200-400 mg/day *vs* dihydrocodeine 120-240 mg/day	1 wks	76	Pentazocine = dihydrocodeine	60 *vs* 66
Jensen & Ginsberg[46]	Parallel	OA (hip, knee)	Tramadol 300 mg/day *vs* dextropropoxyphene napsylate 300 mg/day	2 wks	264	Tramadol ≥ dextropropoxyphene	55 *vs* 32, 36 *vs* 11[a]
Bird et al.[47]	Crossover	OA (hip,knee)	Tramadol 200 mg/day *vs* pentazocine 200 mg/day	2 wks	40	Tramadol > pentazocine	23 *vs* 28[a]
Dalgin[48]	Parallel	OA (hip, knee)	Tramadol (200-400 mg/day) *vs* ibuprofen (1.2-2.4 g/day)	39 days	292	Tramadol = ibuprofen	NR
Messick[49]	Crossover	Miscellaneous	Paracetamol (acetaminophen) 650mg (4-6 doses/day) *vs* dextropropoxyphene napsylate 100mg (4-6 doses/day) *vs* paracetamol 650mg + dextropropoxyphene napsylate 100mg (4-6 doses/day) *vs* placebo	2 days	32	Paracetamol + dextropropoxyphene > dextropropoxyphene > paracetamol = placebo	NR
Kuntz & Brossel[50]	Parallel	Back pain	Paracetamol 500-1000mg + caffeine 50-100mg, tid *vs* paracetamol 400-800mg + dextropropoxyphene 30-60mg, tid	1 wks	124	Paracetamol + caffeine = paracetamol + dextropropoxyphene	NR
Quiding et al.[40]	Crossover	OA (hip)	Ibuprofen 200mg (6 doses) *vs* ibuprofen 200mg + codeine 30mg (6 doses) *vs* placebo[c]	1 day	26	Ibuprofen + codeine > ibuprofen > placebo	19 *vs* 42 *vs* 23
Kjaersgaard-Andersen et al.[51]	Parallel	OA (hip)	Paracetamol 1g tid *vs* paracetamol 1g + codeine 60mg, tid	4 wks	158	Paracetamol + codeine > paracetamol (day 7)	7 *vs* 35 (day 7)[a]
Boureau & Boccard[52]	Parallel	RA	Paracetamol 500mg + codeine 30mg, tid *vs* placebo	1 wk	40	Paracetamol + codeine > placebo (days 3 to 7)	50 *vs* 30
Doyle et al.[53]	Crossover	OA	Paracetamol 650mg + dextropropoxyphene 65mg, tid *vs* ketoprofen 50mg tid	1 wk	72	Ketoprofen ≥ paracetamol + dextropropoxyphene	NR
Parr et al.[54]	Parallel	Joint pain	Paracetamol 1.95 g/day + dextropropoxyphene 180 mg/day *vs* SR diclofenac 100 mg/day	4 wks	846	Diclofenac > paracetamol + dextropropoxyphene	11 *vs* 10[a]
Lloyd et al.[55]	Parallel	OA (hip)	Paracetamol 650mg + dextropropoxyphene 65mg, tid or qid *vs* CR dihydrocodeine 60-120mg tid	2 wks	86	Dihydrocodeine ≥ paracetamol + dextropropoxyphene	9 *vs* 40[a]

Rauck et al.[56]	Parallel	Miscellaneous	Paracetamol 1.4 g/day + codeine 141 mg/day *vs* tramadol 244 mg/day[b]	4 wks	390	Paracetamol + codeine = tramadol	10 *vs* 19[a]
Müller et al.[57]	Crossover	Back pain	Paracetamol 1g + codeine 60mg, tid *vs* tramadol 100mg tid	1 wk	55	Paracetamol + codeine = tramadol	69 *vs* 69
Thurel et al.[58]	Parallel	Back pain	Paracetamol 1.5 g/day + codeine 90 mg/day *vs* paracetamol 1.6 g/day + dextropropoxyphene 120 mg/day	2 wks	50	Paracetamol + codeine = paracetamol + dextropropoxyphene	8 *vs* 16
Boissier et al.[59]	Parallel	OA (hip, knee)	Paracetamol 3 g/day + codeine 180 mg/day *vs* paracetamol 2.4 g/day + dextropropoxyphene 180 mg/day	1 wk	141	Paracetamol + codeine = paracetamol + dextropropoxyphene	38 *vs* 13[a]

a Percentage of patients discontinuing treatment due to adverse effects.

b Mean dosages (dose titration).

c The interval between first and second doses was 6 hours and 4 hours thereafter.

CR = controlled release; **NR** = not reported; **OA** = osteoarthritis; **qid** = 4 times daily; **RA** = rheumatoid arthritis; **SR** = sustained release; **tid** = 3 times daily; **>** indicates significantly better than; ≥ indicates significantly better than or nonsignificantly different, depending on the efficacy endpoint considered ; **=** indicates a nonsignificant difference.

only in the first week of a 4-week study conducted in patients with chronic pain due to osteoarthritis of the hip.[51] This was presumed to result from a development of tolerance to codeine after the first week of therapy.[51] Alternatively, this may be due to spontaneous subsidence of hip pain, which may explain why the proportion of paracetamol-treated patients reporting pain relief increased progressively as the trial proceeded.[62] Other striking features of that study were the high rates of adverse events (87%) and adverse effects causing withdrawals (35%) during the first week in those patients treated with the combination compared with paracetamol alone (38 and 7%, respectively).[51]

The remaining studies do not provide further information on whether such combinations are any more effective than any of the constituents alone. Paracetamol 500mg plus codeine 30mg 3 times daily was shown to produce a significant improvement in pain and disability scores relative to placebo from the third to the seventh (last) day of treatment in patients with rheumatoid arthritis taking regular anti-inflammatory therapy.[52] NSAIDs were reported to be at least as effective as paracetamol combined with either codeine or dextropropoxyphene in relieving joint pain of various aetiologies.[53,54] Even single opioids, such as controlled-release dihydrocodeine[55] and tramadol,[56,57] may be as effective as paracetamol combined with dextropropoxyphene or codeine. Finally, 2 controlled studies of preparations combining paracetamol and a weak opioid suggested that the incidence of adverse effects depended primarily on the daily dosage of the opioid.[58,59]

2.2 Clinical Trials in Neuropathic Pain

For a long time, it was considered that neuropathic pain is intrinsically refractory to opioid analgesics. However, this dogma was poorly substantiated by scientific evidence.[10] Consistent differences in responsiveness to opioids depending on the pathophysiology of chronic pain states have been observed only rarely.[63,64] Based on the response to test infusions of 15mg of morphine, it was claimed that, in contrast to nociceptive pain, idio-

pathic (i.e. with no or little demonstrable pathology) and neuropathic forms of chronic pain are opioid-insensitive.[63] Unfortunately, there was a major selection bias in that study since the patients with neuropathic pain had all previously undergone unsuccessful opioid therapy.[64] A single 120mg dose of codeine was reported to be ineffective in patients with post-herpetic neuralgia.[65] As intravenous morphine (0.3 mg/kg bodyweight) was found to reduce the affective but not the sensory dimension of peripheral or central neurogenic pain, it was hypothesised that opioids would be taken primarily for their mood changing effects.[64] Conversely, a similar dose of intravenous morphine was shown to produce significant pain relief relative to placebo in patients with postherpetic neuralgia.[66]

To reconcile these contradictory findings, it was presumed that some neuropathic pains are truly opioid resistant, whereas others are not.[66] This was substantiated by a 6-week randomised, double-blind, placebo-controlled study indicating that tramadol at an average dosage of 210 mg/day was significantly more effective than placebo for treating the pain of diabetic neuropathy.[67] Whether these data reflect the ability of tramadol to activate monoaminergic spinal inhibition of pain rather than its opioid agonist properties is unknown. Of interest, intravenous dose titration of fentanyl provided equal relief of pain intensity and pain unpleasantness in patients with noncancer neuropathic pain of various aetiologies, suggesting that any type of neuropathic pain may be responsive to opioids.[68] The mean infused dose of fentanyl was equivalent to the analgesic effect of morphine 70mg.[68]

Finally, the question of whether or not neuropathic pain is opioid responsive cannot be settled by investigations employing 'usually effective' fixed doses of opioids.[69] Opioid responsiveness must be evaluated by measuring the response to escalating doses until adequate analgesia is obtained or intolerable adverse effects occur despite routine measures to control them.[69] As such, opioid responsiveness was shown to be a continuum, rather than a quantal, yes or no, phenomenon.[69]

In summary, pain mechanism alone does not accurately predict analgesic outcome from opioid therapy, although nociceptive pain is more likely than neuropathic pain to show a good response.[69-71]

2.3 Observational Studies

Even well-controlled clinical trials have major limitations that have already been emphasised.[8,66] First, they do not resolve the issue of the long term efficacy and safety of opioids. Secondly, they would not detect infrequent or late adverse effects. Thirdly, their results may not always be generalisable to individual patients. Thus, observational studies might provide a realistic means of assessing the long term outcome of opioid therapy in chronic nonmalignant pain.

The published surveys have been reviewed by different authors in recent years.[8,27,72] On the basis of the available literature and own clinical experience, Schofferman[27] came to the conclusion that opioid therapy made many, if not most, patients worse. Portenoy[8] stressed the troubling contradictory findings of these surveys. Some reported a favourable outcome in a majority of patients, whereas others described heightened pain and functional impairment, neuropsychological toxicity and prevarication about drug use in most patients receiving long term opioid therapy. Accordingly, a meaningful number of patients felt better after opioids were withdrawn. Jamison[72] conceded that these reports do not allow any definite conclusion to be drawn, especially since all were subject to referral and observer biases as well as selection bias. Furthermore, these discrepant findings may be the result of the wide diversity of the populations studied, the drugs and dosages employed, and the outcome measures used.[27]

However, there is general agreement that a subset of patients with chronic nonmalignant pain may benefit substantially from opioids.[8,27,72] This is supported by a survey on patients' perception of the effects of opioid therapy for noncancer pain.[73] Over 80% of the patients felt that opioids are at

least moderately beneficial in relieving their pain although the efficacy tended to decline over time.[73] However, the majority of the patients expressed some fear of addiction or dependence.[73]

3. Overall Risk-Benefit Assessment

Taken together, the available data indicate that outcomes associated with opioid therapy vary markedly across patients with chronic noncancer pain. Although pain characteristics alone do not fully predict the response to opioids, neuropathic pain appeared to be associated with a reduced likelihood for a favourable response compared with nociceptive pain.[8,10,69-71] Furthermore, there is little evidence that patients with psychogenic pain constitute a target group for opioids.[63,64] Accordingly, it was claimed that patients with poorly defined peripheral stimulus, or with pain and disability far out of proportion to the structural disease, are the least likely to gain benefit from opioid analgesics.[27] This does not preclude the possibility of a favourable response in any individual case.[8]

With regard to analgesia, usual doses of weak opioids alone did not appear to be better than non-opioid analgesics, at least in chronic pain related to musculoskeletal disorders.[36,48,49] Furthermore, some combination products containing paracetamol plus a weak opioid generated disappointing results.[50,61] This is probably due to the low dose of opioid in these formulations, since an additive effect may be obtained only if appropriate doses of both compounds are used.[39] Overall, opioids were shown to relieve chronic noncancer pain of various aetiologies. Inconsistent findings have been reported with respect to functional improvement.[41,43,44,52,74] Whether opioids may yield additional positive outcomes in these patients, in terms of reduced distress and depression, greater possibility of re-employment and decreased use of the healthcare system, is disputed.[9]

Clinical trials showed that opioid therapy was generally associated with relatively high rates of gastrointestinal and central nervous system adverse effects and withdrawals due to adverse effects. This may partly be explained by the lack of dose titration in most studies. In practice, the initial dosage of opioids should be rather low, especially in the elderly, followed by dosage adjustment according to the patient's individual requirement.[10,28,53,54]

Equi-analgesic doses of different opioid drugs appear to be associated with roughly similar incidences of adverse effects. However, some compounds, such as pentazocine and pethidine, should be avoided because of specific adverse events.[11,12] Other factors may influence opioid selection, including pain intensity, previous opioid exposure and the presence of coexisting disease.[10,12,71] The initial treatment of patients with moderate pain may be a combination product containing paracetamol and an opioid. The dosages of these combination products can be increased until the maximum daily dosage of the non-opioid analgesic is attained; beyond this, the opioid contained in the combination product could be increased as a single agent.[10] The individual variability in the response to different opioids should also be considered. In this respect, it is important to review the response to previous trials of opioid therapy and prescribe the compound that was effective and well tolerated in the past.[10]

Based on survey data, the illicit use and/or diversion of prescription drugs appears to be uncommon in patients taking opioids for chronic noncancer pain.[8,27] Furthermore, tolerance seldom causes difficulties.[8,27,30,75] The risk for drug addiction is generally considered to be low, but it remains poorly defined.[8,27,30] All in all, there is general agreement that a subset of patients with chronic noncancer pain can benefit from the use of opioids without requiring rapidly escalating doses or developing intolerable adverse effects or addiction.[8,27,72,74,75]

Although further studies are needed to clearly identify those patients who are suitable for this form of therapy,[9] prescribing guidelines have already been proposed to assist practitioners in selecting the appropriate patients and ensuring the maximum benefit from opioids.[1,8,27,74,75] Their

major recommendations may be summarised as follows.[8,74]

(i) Before considering opioids, the patient's overall health should be assessed and all reasonable attempts should be made to achieve a diagnosis for the cause of pain, including nociceptive, neuropathic and psychological contributions. A thorough history of previous treatment options is essential to be sure that the patient underwent adequate trials of pain management.

(ii) Opioids should be intended for patients who are psychologically stable. A psychological assessment is essential for patients with poorly defined pathology, younger age, high levels of distress, or previous or ongoing substance abuse. These patients should ideally be referred to a multidisciplinary pain management centre before prescribing opioids.

(iii) The prescribing physician should have an established relationship with the patient. Physician and patient must agree on the goals of the treatment before opioids are prescribed. The indications for the cessation of treatment with opioids should be specified from the outset.

(iv) Patients should be fully informed of the possible consequences of opioid therapy, including the likelihood of physical dependence, the potential for cognitive impairment and other common adverse effects, the risk of addictive behaviour and the potentiating effects of opioids on the sedative effect of other compounds. Written informed consent from the patient has been advocated before starting treatment with opioids.

(v) A trial of therapy, with goals and end-point agreed between patient and physician, should precede any decision to prescribe opioids in the long term. Failure to achieve at least partial analgesia with the equivalent of moderate dosages of morphine and the occurrence of intolerable adverse effects that outweigh the analgesic benefit should be viewed as contraindications to further long term opioid treatment. Similarly, opioid-naive patients whose dosage rapidly escalates within a month of starting treatment may be considered inappropriate for long term treatment.

(vi) Regular monitoring is essential in patients who are prescribed opioids on an ongoing basis. Initially, patients should be reviewed frequently by the prescribing physician. At each visit, assessment should specifically address the degree of analgesia (comfort), the level of function, the adverse effects and the existence of aberrant behaviour. In the case of major aberrant behaviour, the appropriateness of opioid use should be seriously reassessed.

4. Conclusion

Chronic noncancer pain is a complex entity that requires a treatment plan tailored both to the individual and to the presenting problem. Although analgesic medications are only part of this treatment, they are of primary importance. In view of the limited number of analgesics and the interindividual variability in response to a given compound, the use of opioids must frequently be considered. However, opioids appear to be beneficial only in selected patients.Therefore, the proposed prescribing guidelines (section 3) for opioids in chronic noncancer pain are useful tools for the clinician. Further studies are needed to assess the effectiveness and applicability of these guidelines.

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