

Opioid tolerance and dependence : an inevitable consequence of chronic treatment ?

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Summary : Although opioids provide effective analgesia, largely unsubstantiated concerns about opioid-induced tolerance, physical dependence and addiction have limited their appropriate use. As a consequence, many patients receive inadequate treatment for both malignant and non-malignant pain. However, it has been shown that analgesic tolerance develops less frequently during chronic opioid administration in a clinical context than in animal experiments, and that instituting an appropriate dosing regimen can minimise withdrawal symptoms. Early studies had suggested that addiction might result from chronic opioid therapy, though more recent data indicate a low risk in patients with no history of drug abuse. New treatment regimens may also reduce the risk of tolerance, physical dependence and addiction. Long-acting preparations, such as transdermal fentanyl and possibly some forms of other slow release opioids, which maintain constant opioid concentrations in the plasma, minimise the occurrence of the 'between-dose' symptoms such as withdrawal and opioid-induced euphoria. This review discusses the development of tolerance, physical dependence and addiction during opioid therapy, and the influence of these factors on the choice of treatment.

Key words : Opioids ; Fentanyl ; Morphine ; Tolerance ; Physical dependence ; Addiction.

INTRODUCTION

Patients suffering from chronic debilitating pain constitute one of the most challenging treatment populations for the clinician. Chronic pain is a common cause of major disability and is experienced by one in five adult Americans (JORANSON and LIETMAN, 1994). Increasing recognition of the value of opioids in the management of both acute and chronic pain is evidenced by their position as the second and third steps of the World Health Organization (WHO) analgesic ladder, which was originally developed to help physicians prescribe appropriately when treating cancer pain (World Health Organization, 1996). However, despite considerable evidence supporting the efficacy and favourable safety profile of opioids across a range

of chronic conditions (MOULIN *et al.*, 1996 ; SWIFT and ROSZKOWSKI, 1998 ; MILLIGAN *et al.*, 2001), undertreatment of both malignant (ZENZ *et al.*, 1995 ; CLEELAND, 1998) and non-malignant pain (PORTENOY, 1990) frequently occurs. Such persisting, unrelieved pain represents a continuous source of frustration to the patient and their families as well as a considerable socio-economic burden (CLEELAND, 1984).

A number of barriers exist that have limited the appropriate use of opioids for analgesia. These include prohibitive regulatory guidelines, knowledge deficits regarding the opioid response to different types of pain, and historical societal mindsets (HILL, 1993). Prescribing reticence has been further compounded by concerns regarding the risks of opioid-induced tolerance, physical dependence and addiction. Early studies supported the notion that chronic opioid therapy leads to addiction (KOLB, 1925 ; RAYPORT, 1954). However, more recent data from retrospective analyses and randomised clinical trials indicate that this risk is low in patients with no history of drug abuse (MOULIN *et al.*, 1996 ; PORTER and JICK, 1980 ; TWYXCROSS, 1982 ; MCGIVNEY and CROOKS, 1984). It is anticipated that greater awareness of these positive data will result in opioid analgesia forming an integral part of the overall management of more patients suffering from chronic pain. Moreover, the use of opioid analgesia should have a clear position in the treatment algorithm for chronic pain.

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This article examines a broad range of preclinical and clinical data concerning the development of tolerance, physical dependence and addiction. The frequency and clinical significance of each is reviewed in the context of chronic pain, and consideration is given to the potential influence of the choice of opioid preparation on the development of these phenomena.

TOLERANCE TO THE PHARMACOLOGICAL EFFECTS OF OPIOIDS

Tolerance is a pharmacological phenomenon by which the magnitude of a drug-induced response decreases upon repeated administration of the drug (DOLE, 1972). Tolerance to the analgesic effects of opioids is characterised by an attenuation of analgesia over time, with progressive increases in dose required to maintain a given level of pain relief. This decreased antinociceptive effect upon chronic administration of opioids has been demonstrated in a number of animal studies (COCHIN and KORNETSKY, 1964; BROWN and GARRETT, 1972; MOULIN *et al.*, 1988; LOUIE and WAY, 1991). Although the mechanism by which tolerance occurs remains uncertain, a decrease in cell surface receptor numbers (downregulation), uncoupling of the receptor from its cellular effector systems, internalisation of the receptor from the cell membrane and anti-opioid neurochemicals, (such as cholecystokinin [CCK]) have been implicated (CHAVKIN and GOLDSTEIN, 1984; ROGERS and EL-FAKAHANY, 1986; CESSSELIN, 1995; KIEFFER and EVANS, 2002). Repeated administration of an opioid may also result in 'cross-tolerance', by which a diminished response is produced by other opioids administered subsequently (PARONIS and HOLTZMAN, 1992; SMITH and PICKER, 1998). However, this is not always the case (RIBA *et al.*, 2002), illustrating the complexity of the problem.

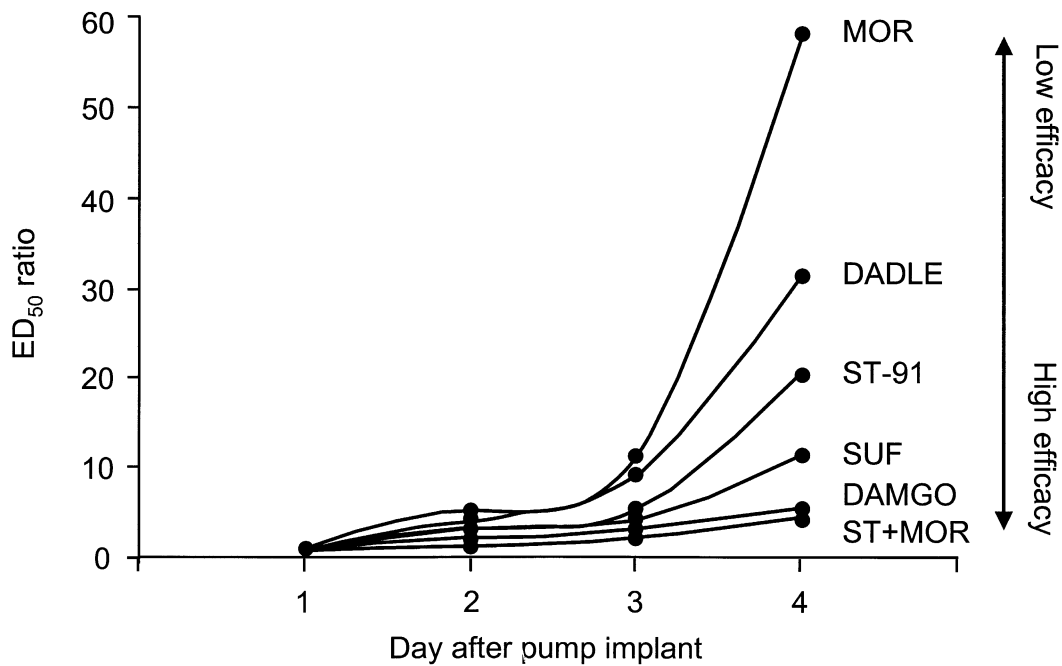
Is tolerance conferred by all opioids ?

The magnitude of an opioid-mediated response is determined by both its binding affinity – the strength with which the drug binds to its receptors, and its intrinsic efficacy – its ability to trigger a response when bound (NEGUS *et al.*, 1991) in addition to the mode of administration (intravenous vs oral), plasma concentration, dosing regimen, duration of action and fractional receptor occupation. It has been proposed that tolerance and cross-tolerance is conferred to different extents by equieffective

doses of different opioids, with high intrinsic efficacy agents, such as fentanyl and its derivatives, being associated with less development of tolerance than opioids with a lower intrinsic efficacy (PARONIS and HOLTZMAN, 1992; STEVENS and YAKSH, 1989a; STEVENS and YAKSH, 1989b). For example, STEVENS & YAKSH (1989b) found that, although tolerance developed to all the opioids tested, the magnitude of tolerance was less for the high intrinsic efficacy opioids, sufentanil and DAMGO (D-Ala²-MePhe⁴-Gly-ol⁵-enkephalin) than for the lower intrinsic efficacy opioids, morphine, DADLE (D-Ala²-D-Leu⁵-enkephalin) and ST-91 in rats (Fig. 1). This differential behaviour has been attributed to the different degrees of receptor occupancies exhibited by the various agents, with the prediction that a high efficacy opioid will leave a larger number of receptors in the non-tolerant state (STEVENS and YAKSH, 1989a). This postulated inverse correlation between the degree of tolerance and intrinsic efficacy of opioid analgesics has led to the suggestion of a preferential role for high-efficacy agents in chronic opioid administration (SOSNOWSKI and YAKSH, 1990).

The relationship between opioid administration and the development of tolerance may prove to be more complex, with the observations that, while fentanyl was associated with less tolerance than morphine upon continuous infusion, no difference was found after intermittent dosing (DUTTARROY and YOBURN, 1995) and that continuous infusion of the high potency mu receptor agonist remifentanyl is associated with a very rapid onset of tolerance (less than 3 hours) (VINIK and KISSIN, 1998). The dose of opioid administered may also be important, as studies in rats and humans have demonstrated that tolerance develops more rapidly when larger doses are given (MARSHALL *et al.*, 1985; KISSIN *et al.*, 1996; FENNESSY and RATTRAY, 1971). In addition, data from recent animal studies suggest that while systemic fentanyl administration (4 doses over 1 hour) may initially result in acute antinociception for 1-5 hours, hyperalgesia then occurs, which can last for several days (CELERIER *et al.*, 2000), and the higher the dose of fentanyl used, the greater the resultant hyperalgesia. The hyperalgesic effects of fentanyl have also been observed in humans (CHIA *et al.*, 1999), but not all opioids have been seen to produce this effect (KATZ *et al.*, 1996).

An additional factor that may affect the action of opioids is the clinical setting of the pain. Observations from animal models of both acute and chronic pain showed no tolerance to develop to opioid-induced analgesia when administration was



Mor : morphine ; DADLE : D-Ala²-D-Leu⁵-enkephalin ; Suf : sufentanil ; DAMGO : D-Ala²-MePhe⁴-Gly-ol⁵-enkephalin.

Fig. 1. — Generalised model of dose-ratio shift during continuous intrathecal infusion (STEVENS and YAKSH, 1989b)

accompanied by nociceptive stimulation (COLPAERT *et al.*, 1978 ; COLPAERT, 1979). The authors postulated that tolerance to the analgesic action of a drug does not occur if its time course and intensity of action corresponds to the time course and intensity of pain (COLPAERT *et al.*, 1978 ; COLPAERT, 1979). This might explain why addicts using opioids in the absence of pain develop tolerance, whereas many cancer patients can be maintained on constant oral doses of morphine for months. If these patients do require an increase in dose, it has been proposed that this is linked to disease progression (SCHUG *et al.*, 1990), though this is not easy to prove in clinical practice.

The clinical relevance of opioid-induced tolerance

The phenomenon of tolerance becomes even more complex in the clinical setting. 'Genuine' pharmacological tolerance must be differentiated from increasing nociception, changes in the affective state of the patient, or underdosing – all of which may result in an increased dose requirement (PORTENOY, 1996 ; PORTENOY and SAVAGE, 1997). Indeed, it has been proposed that the predominant rationales for increasing doses of opioid analgesics are a change in the underlying pain state as precipitated by disease progression (PAYNE and FOLEY, 1984 ; GOURLAY *et al.*, 1986 ; FOLEY, 1991 ; COLLIN *et al.*, 1993) or prior opioid medication. These

hypotheses are supported by evidence suggesting that analgesic tolerance occurs at a low frequency (0–6%) in patients with chronic pain of non-malignant origin (MEDINA and DIAMOND, 1977 ; PERRY and HEIDRICH, 1982 ; WINKELMULLER and WINKELMULLER, 1996). Regular dose escalation has been shown to be uncommon in this patient population during long-term treatment, with doses remaining stable after initial upward titration to achieve adequate analgesia (MILLIGAN *et al.*, 2001 ; FRANCE *et al.*, 1984 ; PORTENOY and FOLEY, 1986 ; ONOFRIO and YAKSH, 1990 ; SCHUG *et al.*, 1992). This viewpoint seems to be confirmed by a long-term evaluation of transdermal fentanyl for the treatment of neuropathic pain, where DELLEMIJN *et al.* (1998) found no tolerance to develop in patients (n = 48) at 12 weeks and only one case at 2-year follow-up.

In contrast to analgesic tolerance, tolerance to opioid-induced side effects is a desirable consequence of long-term treatment facilitating upward dose titration, as necessary, to attain satisfactory pain relief (PORTENOY and SAVAGE, 1997). For example, tolerance rapidly develops to respiratory depression with repeated opioid administration, such that the risk of respiratory depression in patients receiving chronic treatment is very low (HILL, 1993). Tolerance develops at different rates for each opioid-induced side effect, with the incidence of respiratory depression, sedation and to

Table I

Relative potency estimates (95% confidence limits) of opioids in rats administered either butorphanol 3.0 mg/day (n = 6) or butorphanol 30 mg/day (n = 6) for 6 weeks (SMITH and PICKER, 1998). Comparisons were made from the dose-effect curve for each opioid as determined both before and after chronic butorphanol administration

	Relative potency before and after chronic treatment with butorphanol 3.0 mg/day	Relative potency before and after chronic treatment with butorphanol 30 mg/day
Butorphanol	14.88 (3.70-70.15) ^a	54.58 (20.24-139.59) ^a
Buprenorphine	5.17 (2.46-10.45) ^a	11.72 (5.50-25.69) ^a
Morphine	2.26 (1.56-3.32) ^a	2.31 (1.40-3.79) ^a
Fentanyl	1.74 (0.89-3.98)	2.51 (1.24-4.84) ^a
Sufentanil	1.06 (0.41-2.20)	2.90 (1.31-6.29) ^a

^a p < 0.05

some extent nausea and anorexia decreasing rapidly over time, whereas opioid-induced constipation frequently persists (HILL, 1993).

Physical dependence

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (SAVAGE *et al.*, 2002). Despite persistent confusion and historical overlap in the nomenclature of these two syndromes, physical dependence does not equate with opioid addiction (World Health Organization, 1973), which is characterised by the impaired control over drug use, compulsive use, continued use despite harm, and craving (SAVAGE *et al.*, 2002).

Does physical dependence correlate with opioid-induced tolerance ?

Dissociation between the development of opioid-induced tolerance and physical dependence has been observed in a number of *in vivo* studies (SMITH and PICKER, 1998 ; JOHNSON and DUGGAN, 1984 ; RAHMAN *et al.*, 1994). Typically these studies report the development of dependence in the absence of tolerance (JOHNSON and DUGGAN, 1984 ; RAHMAN *et al.*, 1994), though SMITH and PICKER (1998) observed tolerance induced without physical dependence on administration of low doses (3.0 mg/kg) of butorphanol in rats (Table I). In the same study, however, both physical dependence and tolerance occurred in rats receiving high doses (30 mg/kg) of butorphanol, as evidenced by enhanced sensitivity to the rate-suppressing effects of the

mu-opioid antagonist, naloxone, and a time-dependent weight loss.

These data indicate that tolerance not always correlate with physical dependence, and suggest that different cellular adaptations are responsible for the development of each phenomenon (SMITH and PICKER, 1998). Although it has been suggested that opioids with a lower intrinsic efficacy produce less physical dependence (COWAN *et al.*, 1977), this observation has not been confirmed.

The clinical relevance of physical dependence

Rapid withdrawal of opioid therapy can result in a spectrum of withdrawal symptoms, including pain, insomnia, tachycardia, tachypnea and diarrhoea (PORTENOY and SAVAGE, 1997), which, unlike withdrawal from alcohol or sedatives, rarely have any life threatening consequences. Although the time-course and minimum dosing regimen associated with the development of physical dependence is currently unknown, a withdrawal syndrome can occur after even brief use (more than 48 hours) (SEES and CLARK, 1993). Physical dependence should, therefore, be presumed to exist when opioid therapy is administered for more than 48 hours (though not all patients on regular opioid therapy develop physical dependence) (PORTENOY, 1990 ; SEES and CLARK, 1993). The likelihood of experiencing withdrawal symptoms from opioids can be minimised by the regular administration of adequate doses that must be gradually tapered until discontinuation of therapy becomes indicated (HILL, 1993 ; PORTENOY and SAVAGE, 1997).

Patients may experience intermittent withdrawal symptoms between doses of short-acting opioid preparations (JAFEE, 1985), resulting in a potentiation of their perception of pain (BRODNER AND TRAUB, 1978 ; SAVAGE, 1993). Consideration should therefore be given to the use of longer-acting opioids, such as slow-release morphine and transdermal fentanyl, which confer more constant plasma concentrations of drug (PAPPAGALLO and HEINBERG, 1997). Furthermore, as mixed agonist-antagonist opioids (e.g. buprenorphine, butorphanol and pentazocine) can antagonise the effects of full mu agonists, such as fentanyl, morphine and oxycodone, and precipitate a withdrawal syndrome (PAPPAGALLO and HEINBERG, 1997), concurrent use of these agents should be avoided.

Adherence to these recommendations means that the development of opioid-induced physical dependence need not interfere with the provision of effective therapy.

ADDICTION

Opioid addiction is distinct from the neuro-adaptive processes of tolerance and physical dependence. Although variously defined, addiction is most correctly regarded as a consequence of the inherent reinforcing properties of a drug, in combination with predisposing social, psychological and physiological triggers (PORTENOY, 1996). Indeed, the consensus statement from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine characterises addiction as 'behaviours that include one or more of the following : impaired control over drug use, compulsive use, continued use despite harm, and craving' (SAVAGE *et al.*, 2002). Although opioids are recognised as possessing reinforcing properties, this characteristic alone is insufficient to result in abuse as, in isolation, it is neither self-destructive nor socially harmful (LEWIS, 1985). The terms addiction and psychological dependence are sometimes used interchangeably, though the latter is more correctly viewed as one facet of addiction, covering the psychic element of compulsive use but not the behavioural phenomena (PORTENOY, 1990).

In vivo assessment of addiction

Conditioned responses to opioids that may both perpetuate opioid consumption and increase the likelihood of continued use have been demonstrated in a number of animal studies (LYNCH *et al.*, 1976 ; BRADY and HOLTZMAN, 1980). However, such observations have not been consistently reproduced (JURNA *et al.*, 1992), and it has been suggested that the presence of pain may reduce the addictive properties of opioids (LYNESS *et al.*, 1989). Indeed, arthritic rats have been shown to consume significantly less morphine than their pain-free littermate controls, with subsequent dissipation of the pain being associated with an increase in opioid intake (LYNESS *et al.*, 1989).

A reliable test of the addictive potential of opioid analgesics would provide an important pre-clinical indication of the likely clinical and social safety of each agent. PCHELINTSEV *et al.* (1991) proposed that the ratio of an opioid's analgesic efficacy to its reinforcing effects constitutes a measure of the drug's addictive index. The authors calculated the addictive indices of a range of opioids administered subcutaneously to rats, using the writhing test to assess analgesic efficacy and the conditioned place preference paradigm to assess reinforcing

behaviour. Despite their known disparate analgesic efficacies, comparable addictive indices were determined for the widely used opioids buprenorphine, fentanyl and morphine. These results, obtained in animal experiments, are suggestive of a correlation between opioid analgesia and addictive potential, and do not confirm the earlier findings, obtained in human addicts, of a lower propensity for addiction for partial agonist opioids, such as buprenorphine (JASINSKI, 1979).

Does opioid addiction occur in the clinical setting of chronic pain ?

Accurate assessment of the incidence of opioid addiction in clinical practice has been impeded by inconsistencies in definitions and terminology (PORTENOY, 1990). Such confusion may have contributed to the stigma that remains attached to a more liberal use of opioids. The undertreatment of patients with chronic pain of both malignant (ZENZ *et al.*, 1995 ; CLEELAND, 1998) and non-malignant origins (PORTENOY, 1990) was, and still is, a consequence of this.

Addictive problems associated with the clinical use of opioids must be differentiated from other aberrant drug-seeking behaviours. The term 'pseudoaddiction' has been applied to behaviours reminiscent of those displayed by addicts, but occurring as a consequence of the undertreatment of pain that may result, for example, from inadequate opioid doses or excessive dosing intervals (WEISSMAN and HADDOX, 1989). Such pseudoaddictive behaviour, while undesirable, may be regarded as both an appropriate and inevitable reaction to suboptimal pain management that also has significant deleterious effects on patients' quality of life (PORTENOY, 1990 ; CLEELAND, 1984). In contrast, several studies have demonstrated that long-term opioid treatment employing adequate doses enhances the quality of life of this patient population (MILLIGAN *et al.*, 2001 ; WINKELMULLER and WINKELMULLER, 1996 ; DELLEMIJN *et al.*, 1998 ; ROTH *et al.*, 2000 ; PELOSO *et al.*, 2000), and improves patient functioning (FRANCE *et al.*, 1984). However, MOULIN *et al.* (1996) reported no improvement in functioning in patients with chronic non-cancer pain after treatment with morphine. It should also be noted that opioid use has been associated with impairment of cognitive function in patients with cancer pain (BRUERA *et al.*, 1989) and studies in both animals and humans have shown that chronic opioid use may influence endocrine (ABS *et al.*, 2000) and

Table II

Medical use and abuse of selected opioid analgesics between 1990 and 1996. Medical use data were obtained retrospectively from the Automation of Reports and Consolidated Orders System, and abuse data from the Drug Abuse Warning Network (JORANSON *et al.*, 2002)

	Fentanyl	Hydromorphone	Meperidine	Morphine	Oxycodone
Percent change in medical use	↑ 1167.88	↑ 19.31	↓ 35.28	↑ 59.37	↑ 22.76
Percent change in abuse	↓ 59.32	↓ 15.18	↓ 39.63	↑ 3.22	↓ 29.52

immune functioning (BRUERA *et al.*, 1989 ; PALM *et al.*, 1998 ; PAGE *et al.*, 1993).

'True' opioid addiction must also be differentiated from other appropriate patient reactions resulting from the effective management of their pain. For example, the emotional relief experienced by patients following the alleviation of their pain may be misinterpreted as 'euphoria' (HILL, 1993), and the improved quality of life conferred by opioid treatment leading to the desire to continue therapy may be misconstrued as 'opioid dependence'. It is interesting to note that opioids, or at least morphine, while not relieving the sensory components (pain intensity as measured by a visual analogue scale [VAS]) of some pain syndromes, may attenuate the psycho-emotional suffering (as measured using the McGill Pain Questionnaire) (JAFFE and MARTIN, 1975). This may explain why some patients report no improvement of their pain but continue to take the opioid medication. It also demonstrates how difficult it is to discriminate between opioid responders and non-responders when using simple screening tools such as VAS scores.

Traditional fears regarding the long-term use of opioid analgesics for chronic pain have resulted from non-randomised, retrospective clinical trials that purported poor efficacy combined with high levels of addiction in opioid recipients (PORTER and JICK, 1980). However, when defined correctly as a combination of aberrant drug-related behaviours and psychological dependence, the incidence of addiction seems low in patients with no prior history of addiction (PORTENOY, 1990). For example, in a retrospective analysis of 11,882 hospitalised patients who received at least one opioid preparation, only four cases of addiction were reported in patients with no such history (PORTER and JICK, 1980). These data are supported by numerous other studies of long-term opioid use in patients suffering from cancer or chronic non-malignant pain (MOULIN *et al.*, 1996 ; MEDINA and DIAMOND, 1977 ; PERRY and HEIDRICH, 1982 ; PORTENOY and FOLEY, 1986 ; DELLEMIJN *et al.*, 1998 ; TAUB, 1982 ; FOLEY,

1985). However, as some of these studies were conducted in the hospital setting, it is reassuring that a 25% decrease (5.1% in 1990 vs 3.8% in 1996) in the proportion of reports for opioid abuse relative to total drug abuse reports was calculated in a retrospective evaluation of the medical use and abuse of opioids in the USA over the period 1990 to 1996 (JORANSON *et al.*, 2000). This reduction occurred despite a substantial overall increase in the clinical use of these agents, indicating that the recent trend of increasing medical administration of opioid analgesics is not contributing to increases in opioid abuse. Table II presents the trends over this period in medical use and abuse of five specific Schedule II opioids commonly used as analgesics. The most substantial increases in use were seen for fentanyl and morphine, while the use of meperidine decreased. The number of abuse mentions for fentanyl, hydromorphone, meperidine and oxycodone decreased during the study period, whereas abuse mentions for morphine increased slightly, by 3.2% (JORANSON *et al.*, 2000). The most recent data from the USA does however demonstrate an increase in opioid abuse, and in particular abuse of oxycodone (Substance Abuse and Mental Health Services Administration, Office of Applied Studies, 2002). Emergency department mentions for oxycodone increased from 5,012 in 1997 to 10,825 in 2000 (Substance Abuse and Mental Health Services Administration, Office of Applied Studies, 2002). This finding highlights the fact that the form of delivery and availability are important aspects in abuse.

A wealth of data therefore suggests that opioid addiction poses a low hazard when these agents are administered appropriately to carefully selected patients. This should not mean that opioid addiction should no longer be a concern for the health professional and regulatory bodies. Screening patients for addiction risk, regular monitoring and special attention to patterns of prescribing requests are and remain necessary measures in decreasing the risk of misuse of the opioids in society. However, efforts to stop addiction should

not interfere with prescribing opioids for pain management. The development of formulations that make opioid misuse more difficult, such as transdermal preparations which are harder to abuse and to sell than pills, may further demystify opioid addiction in society. Co-administration of N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine, dextromethorphan and amantadine have been shown to delay the development of tolerance and hyperalgesia (FISHER *et al.*, 2000), and can inhibit some of the symptoms of opioid withdrawal (HERMAN *et al.*, 1995; BISAGA and POPIK, 2000). However, NMDA receptor antagonists have variable tolerability profiles, and ketamine has been associated with feelings of unreality and uneasiness, dissociation, and other psychological effects. Development of subtype-selective NMDA receptor antagonists may reduce toxicity (FISHER *et al.*, 2000).

INFLUENCE OF TOLERANCE AND DEPENDENCE ON TREATMENT CHOICE

The experimental and clinical pharmacology of opioids appear to differ, and it is increasingly accepted that different opioid-mediated responses are exhibited in the presence and absence of pain (MCQUAY, 1999). Indeed, pain appears to act as a natural 'antagonist' to the pharmacological effects of opioid analgesics, reducing the incidence of both tolerance and addiction (COLPAERT *et al.*, 1978; COLPAERT, 1979).

Should analgesic tolerance or increased nociception occur in the clinical setting, it is important that these effects can be effectively counteracted by increasing the dose of the opioid. Unlike partial opioid agonists (e.g. pentazocine and buprenorphine) which appear to exhibit an analgesic plateau or 'ceiling effect' at higher doses (WANG *et al.*, 1993; WALSH *et al.*, 1994), full agonists (e.g. morphine and fentanyl) can undergo unlimited dose escalation and thus provide greater clinical flexibility (SCHUG *et al.*, 1991). However, as discussed earlier, dose escalation not matching pain requirements, may facilitate tolerance development. It should also be noted that high doses of morphine are associated with sporadic hyperalgesia and myoclonus, which is often the result of secondary effects, possibly by the accumulation of the morphine metabolite, morphine-3-glucuronide. The development of analgesic tolerance may also be counteracted by opioid rotation, a procedure that has been successfully employed in patients with both cancer pain

(MERCADANTE, 1999) and chronic non-cancer pain (THOMSEN *et al.*, 1999). A change of opioid therapy may establish a more favourable analgesic/side-effect profile, probably as a result of differences in analgesic efficacy and asymmetrical cross-tolerance between opioids favouring analgesia over adverse events (MERCADANTE, 1999; THOMSEN *et al.*, 1999). Indeed, it has been shown that rotation from a short-acting opioid to a long-acting agent in order to minimise the risk of tolerance and withdrawal symptoms enhances the analgesic response, though dose titration may be required (THOMSEN *et al.*, 1999). However, the need for large, well-controlled randomised trials to determine the clinical value of changing the opioid used rather than the route of administration has been highlighted (MCQUAY, 1999).

As tolerance to the constipatory effects of opioids occurs slowly compared with other adverse events, and frequently persists during the course of treatment, consideration should be given to the use of more potent opioids that may be associated with a lower incidence of constipation due to the lower doses administered. For example, several trials have shown transdermal fentanyl to be associated with less constipation than slow-release morphine (MILLIGAN *et al.*, 2001; AHMEDZAI and BROOKS, 1997; PAYNE *et al.*, 1998), a possible consequence of the relative lipophilicities of these two drugs favouring the superior central penetration of fentanyl (PETERSEN and FUJIMOTO, 1983).

Long-acting preparations, such as sustained-release morphine or transdermal fentanyl, obviate the peaks and troughs in plasma drug levels that occur with shorter-acting opioids and would be expected to confer a number of advantages. The more constant plasma concentrations associated with these formulations minimize the occurrence of between-dose withdrawal symptoms and reduce the incidence of opioid-induced euphoria that may contribute to the reinforcing psychological effects of opioids (PAPPAGALLO and HEINBERG, 1997). Furthermore, the concomitant use of selective mu opioid agonists and mixed agonist-antagonists should be avoided, as the latter can antagonise the effects of mu agonists or precipitate withdrawal symptoms (PAPPAGALLO and HEINBERG, 1997).

CONCLUSIONS

Historical perceptions regarding the development of tolerance, physical dependence and addiction are slowly being overturned with increased

understanding of their occurrence in the clinical setting and clarification of terminologies used. Tolerance and physical dependence are manifestations of the neuroadaptations associated with the chronic use of opioids. Both processes are completely dissociated from the occurrence of opioid addiction. Analgesic tolerance occurs infrequently with the chronic use of opioids and can be readily managed, whereas the development of tolerance to opioid-induced side effects should be viewed as a positive phenomenon. As the likelihood of tolerance can be reduced by using the lowest opioid dose capable of maintaining analgesia and occurrence of withdrawal symptoms can be minimised by instituting an appropriate dosing regimen, the development of tolerance and physical dependence need not impact on the provision of effective pain management.

Opioid addiction is statistically unlikely to occur in many patients receiving opioid-mediated analgesia (PORTENOY, 1996). Increasing data from randomised, blinded and prospective trials suggest that chronic opioid administration does not lead to psychological dependence or addiction in patients with no prior history of substance abuse (MOULIN *et al.*, 1996 ; DELLEMIJN *et al.*, 1998). Nevertheless, as a prior history of drug abuse or severe personality disorders are potential risk factors for the development of iatrogenic addiction, opioid treatment should be undertaken cautiously in this minority of patients (PORTENOY, 1996).

The traditional barriers imposed by politics, prejudice and ignorance upon the prescription of opioids for long-term analgesia in patients refractory to non-opioid therapy are being gradually eroded. The resultant change in practice is a consequence of the increasing clinical data supporting the role of the long-term use of these agents. A more open attitude toward the use of opioids in the management of chronic pain is reflected by the publication of a Joint Consensus Statement from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine that challenges the commonly held misperceptions regarding the use of opioids in chronic pain (SAVAGE *et al.*, 2002).

The available literature seems to support the hypothesis that, when prescribed for the right patients, the long-term use of opioids does not necessarily result in problems of tolerance, physical dependence and addiction. Careful consideration of the choice of opioid and the route of administration, coupled with judicious use in carefully selected patients, provides effective analgesia with

a low risk of addiction. In those patients that are responsive to opioid therapy, effective analgesia, in turn, provides an enhanced quality of life, restored patient functioning and a reduction in the associated socioeconomic burden.

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