

Opioid Dependence and Tolerance: Important Clinical Issues?

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Have the risks of opioid dependence or tolerance following therapeutic exposure to these agents been overestimated or underestimated? Since contemporary literature provides no definitive answer to this question, further study is required to more accurately define the problems. Nevertheless, the scientific community agrees on the fact that most patients do not develop a psychological dependence (addiction) on opioids or a tolerance to them as a result of taking opioids for analgesic purposes. This issue of *Anesthesiology Rounds* explores this question and the available research.

INTRODUCTION

While the use of opioids as a painkiller for cancer patients is widely accepted, there is still considerable reluctance to use this type of drug in other patient groups, especially those afflicted with chronic pain. This reluctance stems from fears that problems of drug addiction or tolerance might arise. Is there any truth to this? What are the chances of a patient developing these types of problems when prescribed opioids for therapeutic purposes? For many years, the risk was considered so high that opioids were only used with tremendous reluctance.¹ In the late 1980s, a diametrically opposed view emerged to counter what was referred to as the phenomenon of *opiophobia*.^{*} Internationally renowned experts in the field of pain treatment became fervent champions of opioids for pain relief not only in cancer, but also for chronic, noncancer pain on the grounds that problems of psychological dependence on opioids or opiate tolerance are rare, and the underuse of such drugs causes needless suffering for many patients.^{2,3} Moreover, recent American statistics point to a substantial increase in the rate of analgesic use for nonmedical purposes in the past decade.^{4,5} This phenomenon, which some considered alarming, received extensive media coverage, thereby forcing the pharmaceutical industry and scientific community to reexamine the prevalence of iatrogenic problems of opioid abuse and addiction. However, methodologically sound studies on this issue are lacking.

A PROBLEM OF TERMINOLOGY

Over the years, a great deal of confusion existed and still persists surrounding the terminology for the concepts of opioid dependence and tolerance.^{1,6,7} This confusion helps fuel concerns about opioids among patients as well as healthcare professionals, resulting in problems of undermedication and inadequate pain relief.

The term "dependence" has often been used indiscriminately to encompass the phenomena of physical dependence on opioids, psychological dependence (addiction), and tolerance. In the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV), tolerance and physical dependence are among the criteria used to diagnose a psychological dependence on a substance. In 1998, the American Society of Addiction Medicine specifically recommended against the use of these criteria to diagnose this type of problem in instances where opioids are used for the treatment of pain.⁸ In 2001, the American Society of Addiction Medicine, the American Pain Society, and the American Academy of Pain Medicine reached a consensus on definitions that distinguish psychological dependence, physical dependence, and tolerance in the case of opioids (Table 1).⁶ While these phenomena can coexist in the same individual, the presence of a physical dependence or tolerance does not mean there is a psychological dependence (addiction).^{2,6,7}

* The word is defined as "a fear of using opioids associated with a lack of knowledge about appropriate analgesic drug treatment complicated by an overwhelming fear of abuse and addiction."⁵

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TABLE 1: Opioid dependence and tolerance: Definitions⁶

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.

Tolerance: Tolerance is a state of adaptation in which exposure to a drug induces changes that results in a diminution of one or more of the drug's effects over time.

Psychological dependence (addiction): Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following:

- Impaired control over drug use;
- Compulsive use;
- Continued use despite harm; and
- Craving.

OPIOID DEPENDENCE

Nature of the problem

Psychological dependence (addiction) is a chronic neurobiological disorder that affects biologically and/or psychosocially vulnerable persons.^{7,9,10} However, we still do not know why some people develop this type of problem while others, exposed to the same substance, do not. A person who develops an addiction problem does not appear to do so as a result of simple exposure to a potentially addictive substance, but rather it involves a complex interaction of genetic, psychological, and environmental factors. The mechanisms underlying this interaction remains to be defined.¹⁰⁻¹³ Some people apparently have a genetic predisposition that favours the occurrence of an addiction problem to not just one, but a number of different substances (eg, alcohol, cocaine, etc.). Hence, based on current knowledge, someone with a history of alcohol problems and/or illicit drug abuse or dependence is considered more at risk than someone without that background. A family history of substance abuse could also be a risk factor.¹⁰ The presence of psychiatric comorbidities (eg, depression, personality disorders, etc.) is another factor that can be involved in abuse or addiction problems and boost an individual's risk of addiction.^{13,14}

The use of opioids for medical and nonmedical purposes

Recent studies have found a sharp rise in the use of opioids for medical and nonmedical purposes in the United States over the past decade. Thus, Joranson et al compared statistics collected from 1990 to 1996 in the American Automation of Reports and Consolidated Orders and the Drug Abuse Warning Network databases.⁴ They found an increase in the use of opioids for therapeutic purposes from 1990 to 1996, which suggests that the educational campaigns to improve the quality of analgesic practices have had some effect over the years. Yet, this rise in use was not

accompanied by a proportional increase in reports of opioid abuse cases when the figure was compared with the total number of abuse cases, regardless of the type of drug (licit or illicit) used during those years. The authors, therefore, concluded that an increase in the use of opioids for medical purposes is not necessarily accompanied by a rise in abuse cases. In a more recent report, however, Zacny et al challenged the conclusions in light of their examination of more recent statistics covering 1994 to 2001.⁵

The risks of developing an iatrogenic opioid dependence problem

Have iatrogenic opioid dependence problems been overestimated or, on the other hand, have they been underestimated? Unfortunately, we have few answers to these questions because of the problems of imprecision in terminology and a flagrant lack of scientific data. The type of population studied, the methodology used, the small size of the samples examined, and the length of the surveillance period are factors that can effectively contribute to an over- or underestimate of the real risk rates in various studies.

Risk overestimated

While there are still no properly tested instruments for diagnosing opioid addiction, the criteria used to define this type of problem have been considerably refined in recent years. Some studies, particularly those done prior to the 1990s, used criteria that no longer match those used today, which may have led to an overestimate of the prevalence rates.¹ Similar problems exist with recent studies based on the criteria of DSM III or IV. Strict application of these criteria can, in fact, result in an overestimate of addiction problems in a population of patients using opioids as painkillers because they include the criteria for physical dependence and tolerance.^{2,3,7}

The problem of overestimating risks can also result from the type of patients studied, for example, in studies conducted among patients undergoing treatment in a detoxification centre. These reports can suggest, at first glance, that there is a high risk of iatrogenic opioid addiction. In a study by Jamison et al, approximately 45% of the patients felt their addiction problem occurred after taking opioids to relieve pain.¹⁵ However, this 45% has as a denominator only patients participating in a methadone maintenance program at the same time who had a pain problem or not. More importantly, 78% of all the patients admitted to having an abuse problem with different substances almost their entire life. While interesting, the data collected from this type of patient group can not help assess the risk of iatrogenic addiction to opioids in the general population.

In addition, recent studies conducted among chronic sufferers that excluded patients with a history of alcohol or substance abuse reported low iatrogenic opioid abuse or addiction rates (0% to 2.7%).¹⁶⁻²⁰

Risk underestimated

Although during the 1990s, overestimates of iatrogenic opioid dependence problems and its perverse

effects on the treatment of pain were forcefully denounced, now the arguments put forward to justify that position are being challenged again. This is particularly true in cases where opioids are used to relieve chronic noncancer pain. One leading argument is that there is little scientific literature supporting the conclusion that the risk of iatrogenic opioid dependence is very low. One of the most commonly cited studies is by Porter and Jick, who found only 4 cases of iatrogenic opioid addiction in a population of 11,882 patients hospitalized for surgery or other medical reasons.²¹ Yet, this study was published under *Letters to the Editor* in the *New England Journal of Medicine*, where it comprised a single paragraph spanning a few lines. No details are provided about the methodology or criteria used to diagnose addiction. Further, the data were only collected during hospitalization, with no follow-up after the patients had been discharged. In addition, since the degree of exposure to opioids is not specified, for some patients it may have been very limited (eg, one dose).

Similar problems arise with the study by Perry and Heidrich that found no case of iatrogenic opioid dependence in a population of approximately 10,000 patients hospitalized at 93 burn treatment centres in the U.S.²² The study was confined to the nursing staff, usually, only in contact with the patients during their hospital stay, which once again limits the scope of the observations.

The findings of studies conducted among chronic sufferers where the main objective was not an examination of the problem of abuse or addiction, must be looked at with a great deal of caution.^{17,19,20} From a methodological standpoint, these studies were not designed to examine the issue. Hence, the risk that these studies underestimated the problem of iatrogenic dependence is not negligible.

Ignorance of the real risks and assessment of the benefits

Whether because of confusion in the terminology, flawed usage of DSM-III or IV criteria, or methodological shortcomings in the studies, this review of the scientific literature does not offer a precise figure on the prevalence of addiction problems in the general population, following the therapeutic use of opioids.^{1,7,23}

Nevertheless, there is a large body of literature pointing to the problems of undermedication and inadequate relief for patients whether suffering from acute or chronic pain. This situation is especially worrisome given the knowledge that poor pain control can have extremely damaging physical, psychological, social, and economic effects.^{2,23-25} Moreover, clinical experience suggests that inadequate pain relief and the accompanying symptoms can give rise to behaviour considered problematic in terms of opioid use, because it resembles the behaviour observed when there is a substance addiction problem. Thus, a patient may run out of opioids, turn up in the emergency room a few times, become demanding and even hostile, not because of an addiction problem, but rather because of insufficient pain relief or anticipation of the return of

intolerable pain.^{10,26} “Pseudoaddiction” is the term used to distinguish the distress and behaviour of trying to obtain medication that can result from inadequate relief.^{10,26} The most distinguishing characteristic of this syndrome is that the behaviour considered problematic vanishes with adequate relief from pain.

Even though the exact prevalence of iatrogenic opioid dependence problems is not known, experts in the field of pain treatment agree that, in patients with no risk factors, the odds of developing an abuse or addiction problem after taking opioids for analgesic purposes are slim. Although more studies are required to identify the type of patient or painful conditions most likely to benefit from opioid-based therapy, various organizations have issued guidelines designed to help clinicians select patients to ensure they receive the maximum available benefits from opioids.^{27,28}

Patients with a personal or family history of problems with alcohol or illicit drug addiction or abuse are considered at higher risk. The fact that a patient is at higher risk does not automatically rule out prescribing opioids for analgesic purposes, however, it becomes more important to treat existing comorbidities and ensure closer follow-up. The expertise of an addiction specialist on a multidisciplinary chronic pain treatment team can be valuable in some cases.^{10,23,27}

OPIOID TOLERANCE

Nature of the problem

The phenomenon of opioid tolerance as defined in Table 1, is often illustrated by a right shift in the dose-response curve, ie, by a gradual decline in the antinociceptive effect of the opioid following repeated administration. Therefore, a larger dose is necessary to achieve a similar analgesic effect.²⁹ Traditionally, this decline in opioid effect has been attributed to functional changes in the receptors (desensitization) that reduced the analgesic effectiveness of these substances. Recently, several studies conducted with animals suggested that repeated administration of an opioid could paradoxically give rise to the phenomenon of hyperalgesia by activating pronociceptive systems. A gradual decrease of the nociceptive threshold can be observed over a period of a few days following opioid administration on an intermittent or continuous basis. This reflects the phenomenon of hyperalgesia.³⁰⁻³² Furthermore, this “sensitization” to pain lasts several days after the administration of opioids is stopped.³² In addition, a study comparing different doses of fentanyl demonstrated that the extent (scope and duration) of the phenomenon depended on the dosage administered.³³ These studies seem to suggest that the phenomenon of “apparent” tolerance observed in animals cannot simply be explained by a loss of analgesic activity, as was traditionally imagined, but could mean a phenomenon of hyperalgesia induced by the opioids.³³⁻³⁵ A number of theories and models have been advanced to explain the phenomenon. Numerous studies indicate that activation of the NMDA receptors in the posterior column of the spinal cord plays a key role because administering antagonists of the receptors can block development of the

TABLE 2: Summary of studies involving acute pain

| Authors | Type d'étude | No of patients per group | Type of surgery | Opioids administered during operations | Results |
|-------------------------------------|---------------------------|--------------------------|------------------------|--|---|
| Katz <i>et al</i> ⁵³ | Randomized clinical trial | 15/15/15 | Abdominal hysterectomy | Group 1: No opioids during operations; Group 2: 30 µg/kg alfentanil by induction followed by boluses of 10-20 µg/kg q 1h; Group 3: 100 µg/kg alfentanil by induction followed by a perfusion of 1-2 µg/kg/min stopped 30 min before the end of surgery | ↓ pain scores in Group 3 than in Group 1 (2h and 4h after surgery); ↓ morphine consumption in Group 1 than in Group 2 or 3 (0-2h after surgery) |
| Chia <i>et al</i> ⁵² | Randomized clinical trial | 30/30 | Abdominal hysterectomy | Group 1: 1 µg/kg fentanyl Group 2: 15 µg/kg fentanyl followed by a perfusion of 100 µg/hr | ↑ pain scores in post-op 4h and 8h after surgery in Group 2 than in Group 1; ↑ fentanyl consumption 0 – 16h after surgery in Group 2 than in Group 1 |
| Guignard <i>et al</i> ⁵¹ | Randomized clinical trial | 25/24 | Abdominal surgery | Group 1: perfusion of remifentanyl adjusted to autonomic response (average dose: 0.3 ± 0.2 µg/kg/min) Group 2: continuous perfusion of remifentanyl 0.1 µg/kg/min | ↑ pain scores in post-op in Group 1 than in Group 2; ↑ morphine consumption in post-op in Group 1 than in Group 2 |
| Cortinez <i>et al</i> ⁵⁴ | Randomized clinical trial | 30/30 | Gynecological surgery | Group 1: perfusion of remifentanyl (average dose: 0.23 ± 0.10 µg/kg/min) Group 2: No opioids during operations | No difference between the two groups in pain scores or morphine consumption in post-op |

phenomenon.^{33,34} An opioid occupying a μ receptor could paradoxically activate the NMDA receptor, thereby triggering a cascade of intracellular events. Protein kinase C (PKC) and nitric oxide are believed to have a central role in this process.³⁶

Spinal mechanisms are not the only ones cited to explain the phenomenon of tolerance. Numerous studies suggest that exposure to exogenous opioids could result in neuroplastic changes in supraspinal structures (eg, the rostral ventrolateral medulla, RVM), thereby triggering a (pronociceptive) facilitation process mediated by the descending modulating pathways. Cholecystokinin (CCK), known for its antiopioid properties, as well as dynorphin are apparently closely related to the development of this process,³⁵ which could favour the release of different excitatory neurotransmitters at the spinal level, including CGRP (calcitonin gene-related peptide).^{35,37} Interestingly, this model has a number of neurobiological and clinical similarities to the model of neuropathic pain where the role of NMDA receptors and supraspinal systems has been amply documented, and is often manifest through the phenomena of hyperalgesia or allodynia.^{33,36}

Opioid tolerance could also be explained by the bimodal activity of μ receptors, which traditionally have been perceived to act as inhibitors (μ receptor bound to protein $G_{i/o}$), thereby reducing neuronal excitability. Yet, research suggests

that μ receptors can also be excitatory (μ receptor bound to protein G_s). Under normal circumstances, their inhibitive activity is said to predominate and account for the antalgic effect of opioids. Still, the phenomenon of tolerance or hyperalgesia could be explained by an imbalance favouring excitatory activity, thereby antagonizing the antinociceptive effect. Preclinical studies indicate that, in these circumstances, minimal doses of naltrexone can prevent or even partially reverse morphine tolerance by selectively blocking the μ receptors in excitatory mode.^{38,39}

Aside from these few models, many other substances or receptors could equally be involved in the development of tolerance. Studies suggest that delta receptors, as well as “antiopioid” peptides such as neuropeptide FF and nociception might take part in the process. The endocytosis of μ receptors may also play a role. However, the connections between these different proposed mechanisms remain to be worked out.²⁹

Risks of developing an opioid tolerance problem

In humans, sustained use of an opioid builds up tolerance against most of the nonanalgesic effects of this drug family (nausea, drowsiness, respiratory depression, etc.). Constipation alone appears to evade the phenomenon. What about the analgesic effect? Is the phenomenon of toler-

ance found in certain patients? This question remains controversial and less well documented than among animals. The few observational studies on this problem with cancer patients report that most required only moderate increases in opioid dosages in the course of their illness.⁴⁰⁻⁴⁴ The progress of the disease is considered the main factor leading to increased medication with these patients.⁴³⁻⁴⁵ The data is also very sparse in the case of patients suffering from chronic noncancer pain. A number of studies have been done over a short time span and/or with a limited number of patients. Those that tracked patients over a longer period often had rather high dropout rates, thereby limiting the scope of their findings.⁴⁶ Nonetheless, the available data suggest that, for most patients, the opioid dosage required to relieve pain remains relatively stable over time.^{18,47-50} Recently, several researchers have examined this question in the context of acute pain by comparing different dosages of opioids administered to surgery patients during operations (Table 2). While the studies by Chia et al and Guignard et al,^{51,52} suggest that tolerance and even hyperalgesia can develop rapidly following the administration of high doses of opioids during operations, other studies have yet to confirm these findings.^{53,54}

While it is difficult to draw clear conclusions based on the data compiled from humans, nevertheless, it appears that "tolerance" can occur in some situations, but the extent and frequency of the problem seem far less pronounced than with animals. What accounts for this difference? A few explanations can be proposed; for example, in the preclinical studies, most animals were subjected to brief nociceptive stimuli (provoked pain), whereas in a clinic, the pain experienced is usually continuous. Moreover, the dosages administered to animals in these studies were often, proportionally, much larger than those normally used to relieve human pain. Therefore, hyperalgesia in animals might be related to similar observations in patients receiving high doses of opioids systemically or spinally, or whose dosages have been sharply increased. In a clinical setting, this "paradoxical" pain often manifests itself as allodynia, diffuse hyperalgesia, and myoclonus. Typically, in this situation, continuing to increase the dose of opioids merely exacerbates the problem.⁵⁵

At present, a number of questions related to tolerance remain unanswered at the clinical level. Is it a rare or common phenomenon? Can it occur subclinically in some patients? Can it arise regardless of dosage or the type of opioid used? Are there significant individual differences? How do we recognize the problem? At times, it can be very difficult to determine whether the increased pain felt by the patient is secondary to the problem of tolerance or due to actual intensification of the pain.

If, in the course of treatment, a problem of tolerance is suspected, the first step is to increase the dosage while ensuring that optimal use is made of other therapeutic procedures that can help relieve pain.⁵⁶ However, if the necessary doses escalate, a change in opioid⁵⁶ can be tried because clinical experience suggests that cross tolerance among the various opioids can be incomplete. In some clinical situations, adding small doses of NMDA receptor antagonists can be considered, although to date the clinical results remain mitigated.^{57,58} The addition of low doses of μ receptor antagonists could be a theoretically interesting option,⁵⁹ although postoperative studies have reported conflicting results. Clinical studies are now underway to assess the efficacy of this type of strategy with patients taking opioids over an extended period.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Opioids represent the drug of first choice for relieving moderate to severe pain and the risks of causing dependence or tolerance problems should not be considered obstacles to their use. Even though opioids are very attractive as analgesic agents, they still do not represent a panacea in the context of chronic noncancer pain. Given the physiopsychopathology and complexity of the problems of chronic pain, a multimodal approach is still considered the best means of diagnosing and treating this type of problem.

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