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RESEARCH ARTICLE

Opioids: Analgesia, Euphoria, Dysphoria, and Oblivion: Observations and a Hypothesis

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ABSTRACT

Introduction: In a previous paper, we inquired into the root causes of the two opioid crises our nation is facing, one evolved from the effects of political and psychosocial forces, one manufactured by the Centers for Disease Control and Prevention. This inquiry led us to suspect that the very different opioid consumption patterns of various groups of people were driven by very different motivations related to the opioid experience. Here we explore four potential motivations or disincentives: analgesia, euphoria, dysphoria, and the search for oblivion. We particularly focus on two populations more likely to be motivated by the search for oblivion: people addicted to opioids and terminal cancer patients, and the problem of tolerance.

Methods: Analytic review of the scientific literature.

Results and Discussion: Essentially all patients managed in American clinics, including many patients with cancer, are motivated by a simple desire for analgesia. A search for euphoria almost certainly motivates the population of people who use mind-altering drugs, including opioids, for recreation. Dysphoria is a feeling of unpleasantness associated with a particular opioid sufficient to motivate a patient to refuse the drug. It represents a common challenge in managing patients in chronic pain. The search for oblivion appears to be the primary motivation for people with opioid addiction. It may also be a motivating factor in certain patients with terminal cancer who suffer not just pain but also agonizing existential crisis.

Conclusion: A greater appreciation on the part of clinicians, scientists and policy makers of the different factors that motivate use of opioids could have major implications for how we handle different people consuming opioids. It could disabuse us of the suspicion that every patient in pain is seeking euphoria rather than analgesia and help us to understand their vanishingly small risk of drug abuse or addiction. It could lead to serious study of the mechanisms of dysphoria and the development of means to circumvent it. It could lead to improved approaches to patients with pain from terminal cancer and optimal strategies for dealing with the addiction crisis in the streets.

Keywords: opioids, analgesia, euphoria, dysphoria, oblivion, terminal cancer, opioid addiction

Introduction

There appears to have been very limited scientific interest in the nature of the opioid experience. However, if there are different opioid experiences, it would seem important, as a matter of science, clinical care, and public policy, to understand them. The neural basis for these experiences might also be very different, in which case very different approaches might be indicated to address the problems that might arise.

Over the past 15 years, the most prevalent view has been, to an ever-increasing extent, that there is but one experience: euphoria. The major focus of preclinical research has been on analgesia[1] but there has also been strong interest in neurobiological mechanisms of euphoria and addiction.[2]

Clinical research results and guidelines for treatment of chronic noncancer pain also reveal some competing concepts. The CDC guidelines heavily stress opioid use disorder (OUD), the modern term for addiction or imminent addiction.[3,4] They also feature the notion that illicit opioid use is consistently preceded by prescription opioid use, with the inference or claim that anyone prescribed opioids is stepping onto a slippery slope, implicitly driven by opioid-induced euphoria. Of course, there is strong evidence that the "prescription" opioids in question were almost entirely supplied by pill mills (terminated by the states by 2012)[5] and that further use of opioids after perioperative treatment with opioids is rare:[6] 0.6% incidence in the study of Brat et al.[7] The CDC Guidelines further reinforce the implicit euphoria concept by stressing the fact that the over 100 existing randomized controlled trials of opioids for chronic pain have failed to provide adequate evidence of analgesic efficacy. However, it has become evident that the relative lack of success of these trials reflects inadequate trial design.[8] Having presented these data, the authors of the Guidelines conclude that dosage up to 50 mg morphine equivalent/day (MMED) is acceptable (as if to say that a little bit of euphoria is all right) and that dosage higher than this is associated with diminishing returns and increasing mortality.

In what follows, we provide evidence that the concept of a singular experience of euphoria motivating all opioid use likely reflects a major and highly consequential oversimplification. A better understanding of the opioid experience in various populations might lead to different approaches to different populations that could be more effective both clinically and in dealing with the illicit opioid crisis.

A better understanding of one particular opioid side effect, tolerance, might also lead to significantly different treatment approaches. People addicted to illicit opioids and possibly some patients with cancer pain exhibit a propensity for developing tolerance — a need to continuously increase dosage to achieve the same effect — something that is rarely observed among patients treated for chronic noncancer pain, as noted over 30 years ago by Melzack[9] (see also[10-13]). This possible susceptibility to tolerance strongly suggests that another mechanism may be in play, such as pursuing the state of oblivion needed to escape intolerable physical and existential suffering.

In sum, we have identified three different opioid experiences: analgesia, euphoria, and oblivion, each of which almost certainly depends upon a different central nervous system mechanism and thus, likely calls for a different treatment approach. To these we add a fourth, dysphoria. We will detail these four experiences in the remainder of this paper.

Methods

This is an analytical review. Papers were identified from PubMed, reference lists in papers and books, and selectively, through Google search. Criteria for inclusion included relevance, methodological rigor, and completeness, transparency, and cogency of the results. Concurrence with results of other papers was not a selection criterion. Newspaper articles were selected on the basis of relevance, the standards of the journal and the consistency of the reporting with known events. Books were selected from reference lists and through Google search; some were known to the first author from leisure reading. All source materials were subjected to critical analysis and potential sources of weakness are identified in this paper.

Results And Discussion

OPIOID EXPERIENCES

Analgesia

The concept of pain as a source of suffering was perhaps best captured by Albert Schweitzer:[14]

> "We must all die. But that I can save a person from days of torture, that is what I feel as my great and even new privilege. Pain is a more terrible lord of mankind than death itself."

In 2011, the Institute of Medicine estimated that the annual cost to society of chronic pain, including post-operative pain, was $560–635 billion,[15] based on estimated health care expenditures and costs of lost productivity. Eighteen million American adults

experience moderate to severe chronic pain.[16] Treatment of pain has been associated with improvements in activities of daily living, reduced depression or improved mood, reduced fatigue, improved sleep, improved level of function, increased ability to work, increased enjoyment of life, and improved quality of life.[16] Although randomized controlled trials (RCTs) of opioids for chronic pain have, in aggregate, provided only modest and somewhat inconsistent support for their efficacy,[6] any clinician experienced in management of chronic noncancer pain can testify to their often dramatic efficacy, particularly for somatic pain.[17] Existing scientific data, coupled with this clinical experience, suggest that we are far beyond the point of equipoise (sufficient proof that it would be unethical to enter participants in a trial). However, it appears that, given the deep doubt created by the CDC 2016 Guideline and its 2022 revision, it will be necessary to conduct such trials. As we have noted, a trial design capable of providing the necessary proof now exists.[8]

In our 40 years of clinical experience, patients treated for chronic noncancer pain with opioids have repeatedly reported that they are mystified as to why anyone would take these drugs to "get high" as they experience no euphoria, only analgesia. In a randomized controlled trial (RCT) conducted in emergency department patients with severe, acute/subacute abdominal pain, the effects of intravenous (IV) lidocaine 120 mg were compared to those of 1 mg IV hydromorphone.[18] Hydromorphone was somewhat more effective at relieving pain than lidocaine (1.5 points on a 10-point analogue scale). The major determinant of feeling good, feeling "high," and feeling happy was degree of pain relief and the drug used had relatively minimal impact on the latter two measures once analgesic effect had been controlled for.

In another RCT comparing responses of patients with migraine seen in an emergency room to hydromorphone 1mg or prochlorperazine 25 plus diphenhydramine 25 mg IV, pain relief reported with prochlorperazine+diphenhydramine was actually slightly but not significantly greater than that achieved with hydromorphone,[19] undoubtedly because of the small dose of hydromorphone used. The investigators did not detect an independent association between hydromorphone and medication likeability, feeling good, or return visits to the ED. Headache relief was the sole driver of likeability and feeling good. Thus, clinical experience and controlled studies seem to strongly contradict the CDC argument. Patients in pain are seeking analgesia, not euphoria.

Euphoria

The experience of euphoria associated with certain mind-altering drugs, including opioids, has been detailed by Hart in his detailed description of people, including himself, who use these drugs for recreational purposes.[20] The epidemiology of this population has not been convincingly established. The potential for different opioids to elicit a euphoric effect is unknown. Genetic factors have a major influence on opioid dosing requirements. These factors include variations in hepatic metabolism,[21,22] receptor interactions,[23] and neural transmission.[24,25] To our knowledge, the effects of these factors on euphoric response is not known with any degree of certainty.

Hart makes clear that many people can safely use these drugs for recreational purposes. However, as we have noted in an argument against legalization, everyone, regardless of their life situation, when faced with grave misfortune, overwhelming situational stress, personal loss, or existential crisis, is potentially susceptible to slipping from recreational use to abuse of mind-altering drugs, no less than with alcohol.[5]

Dysphoria

We operationally define opioid-associated dysphoria as any feeling of unpleasantness occurring despite very gradual titration and sufficiently severe for the patient to refuse to take the medication. It is most often described as "I just don't like the way I feel on this drug." However, dysphoria may include such symptoms as severe nausea or intolerable pruritis. We do not count such things as sedation or alteration of cognitive function, as these reflect problems with drug choice or dosage and are not acceptable in an outpatient non-cancer chronic pain population.

We have been unable to find any recent studies bearing on the epidemiology of opioid-associated dysphoria. In fact, it appears that this problem has not been seriously considered since the review paper by Cherny et al.,[26] largely focused on morphine associated side effects in patients with cancer. They reported a prevalence of nausea and vomiting of 15-30% and pruritis of 2-10%. They did not note dysphoria as we have defined it. Quang-Cantagrel et al.,[27] in a study of 86 patients with noncancer pain treated with opioids, found that the first opioid prescribed was effective for 36% of patients, was stopped because of side effects in 30%, and was stopped for ineffectiveness in 34%. The most common intolerable side effects were nausea/vomiting (40%), sedation (32%), and itching (24%). Dysphoria was not mentioned. Among the 25 patients who stopped the first opioid

because of intolerable side effects, 10 stopped the second opioid for the same reason. Sixteen patients (19%) did not find an effective opioid therapy. Our own experience with patients with chronic noncancer pain is that dysphoria is fairly common, it is usually drug-specific, and often a different opioid can be tolerated quite well; however, we concur with Quang-Cantagrel et al. that there exist patients who cannot tolerate any opioid.

As with euphoric responses, the extent to which genetic factors influence dysphoric responses has not, to our knowledge, been investigated. It is unknown whether concurrent use of other prescription drugs might increase the likelihood of a dysphoric response. Most importantly, the prevalence of a dysphoric response to all existing opioids is uncertain. This pan-dysphoric population presents a particular challenge to pain management.

Oblivion

Opioid use in some settings suggests an opioid experience quite different from euphoria or analgesia. Opioids are a major tool used in palliative care ("palliative sedation") to produce a state of oblivion that frees terminal patients from physical and existential suffering. There is a paucity of studies of the prevalence of existential suffering, at times unbearable, in terminal cancer patients. Estimates vary, largely in relation to methods of ascertainment.[28-30] Some studies have reported a frequency as high as 26%.[28]

The "rat park" experiments revealed that rats housed in isolation (a desolate condition for these highly social animals) will consume a substantial dosage of opioids if they are made available. In rats living in what have been called "rat parks" where they may interact with many peers in a quasi-natural environment, opioid consumption is markedly less.[31,32] Does this mean that rats enjoy their high to a greater extent when they live in isolation? These investigators raised the alternative possibility that rats housed in isolation use opioids to escape a highly noxious state, an opioid experience presumably quite different from euphoria or analgesia.

In a study of soldiers in Vietnam, it was found that 20% were addicted to heroin. However, when they returned home, only 5% of these people with addiction continued heroin use.[33,34] These results are reminiscent of the rat park data. Was the heroin induced euphoria really that much greater in Vietnam? Or is this an example of people using opioids to achieve oblivion to escape intolerable circumstances? We now have compelling evidence that the major driver of the illicit opioid crisis in this country is desperation and despair (see review[5]).

Illicit drug use

There is now abundant evidence, albeit not of the best quality, that oblivion is the state sought by those using illicit opioids as a means of escape from their lives of desperation and despair (reviewed[5]). People who use heroin and other addictive drugs for other than recreational purposes, given their generally dire state, plausibly also have an apocalyptic view that enhances risk taking behavior. The constant pursuit of their next dose also plausibly gives their lives a sense of purpose and occupies their time when they are not intoxicated.

As is often the case, novelists are ahead of scientists in characterizing the particular opioid experience associated with use of illicit drugs. Physician-author Abraham Verghese uses the term oblivion to describe the state sought by a protagonist who resorts to eating opium in the wake of the particularly gruesome accidental death of his young son and the immediate departure of his wife, whom he adores — events for which he harbors a deep conviction that he is responsible.[35] Gregory David Roberts, in the semi-autobiographical *Shantaram*,[36] describes in detail the actual experience of the principal character as he resorts to heroin in the wake of complete collapse of his entire complicated life:

> "Heroin is a sensory deprivation tank for the soul. Floating on the Dead Sea of the drug stone, there's no sense of pain, no regret or shame, no feelings of guilt or grief, no depression, and no desire. The sleeping universe enters and envelops every atom of existence. Thoughts drift like ocean weeds and vanish in the distant, grey somnolency, unperceived and indeterminable. The body succumbs to cryogenic slumber: the listless heart beats faintly, and breathing slowly fades to random whispers. Thick nirvanic numbness clogs the limbs, and downward, deeper, the sleeper slides and glides toward oblivion, the perfect and eternal stone."

Accounts in the lay press are generally congruent:

> "I would feel a distinct heaviness throughout my body that was similar to when a person is extremely tired after a long day. That heaviness resembled a fatigue in which it was difficult to keep my eyes open. It was a comfort with whatever was going on

around me: a blissful oblivion, even to incredibly dangerous situations."[37]

"When someone first uses heroin, the high is often pleasurable. A rush of euphoria and a false sense of well-being can also come with a relief of pain, anxiety and depression. A heroin high can feel like an escape, and is often used as a recreational drug or a method of self-medication. Other feelings often associated with a heroin high include a sense of safety and well-being, despite the actual surroundings or environment…People who experience a heroin high may also feel warmth, relaxation and coziness."[38]

"Right after you take heroin, you get a rush of good feelings and happiness. Then, for several hours, you feel as if the world has slowed down. You think slowly and may walk slowly. Some users say you feel like you're in a dream."[39]

"You'll probably first notice a rush of euphoria. Some people describe this as a warm, relaxed feeling, like resting on a cloud."[40]

"The rush from intravenous heroin use lasts about 2 minutes. Intravenous users have likened the rush to an orgasm in terms of pleasure. As heroin travels through the bloodstream, the high lasts for 4 to 5 hours. The general effects of using heroin include: contentment, reduced anxiety, relieved tension, drowsiness and apathy."[41]

The results of scientific studies bearing on this issue[42-45] have been broadly congruent with the descriptions above, though not as eloquent.

Treatment of cancer pain

Cancer is often associated with both extreme pain and dire existential threat. Pain may be controllable but existential threat likely poses a greater treatment challenge and could plausibly lead patients to seek oblivion. Unfortunately, the evidence that has emerged from clinical trials, for the most part, does not lead to any firm conclusions. The nature of a patient's desired outcome seems never to have been a source of interest. The closest we come is old studies, which showed that by the time of approaching death, the prevalence of depression, intense sadness, psychomotor retardation, and dull affect had markedly increased.[46] The results of more recent clinical studies of cancer patients in great pain are deeply flawed by the failure to define what is meant by "tolerance" or "refractory pain."

Tolerance

Illicit opioid use appears to be defined by repeated cycles of steadily increasing doses as tolerance develops, interspersed with periods of abstinence (e.g., during medically assisted treatment in rehabilitation), during which tolerance resolves, followed by relapse.[47] The loss of tolerance during abstinence is largely responsible for the increased mortality following relapse.[47] The mortality of prisoners with a history of opioid abuse is elevated during the week after being freed from incarceration,[48] likely reflecting a tendency to return to the doses used when tolerant.

A recent systematic review of trials of intrathecal opioid treatment in patients who had developed "tolerance" or "refractory pain" revealed that no study has provided an adequate operational definition of these terms.[49] Both tolerance and refractory pain are often defined simply as failure to respond to any of what are deemed aggressive opioid regimens: typically, 200-400 mg morphine equivalents/day (MMED). No mention is made of dose requirements that increased over time. In one study,[50] to be eligible for intrathecal therapy, patients had to have a pain score of above 50mm on a 100mm visual analogue scale. Clinical experience suggests that 50mm corresponds to moderate discomfort most of the time. There are many studies in the literature reporting dosage up to 2000 MMED.[51]

It would seem that *a better definition of refractory pain* would be "pain that remains inadequately controlled despite fully adequate treatment of depression and sleep disorders, trials of multiple opioids titrated to the maximum dose possible without causing intolerable side effects, and vigorous trials of treatments for neuropathic pain, to the extent that such pain exists." Tolerability is a relative term. The development of even mild impairment of cognitive function relatable to opioids in patients who lead fully functional lives would be unacceptable. On the other hand, even moderate degrees of sedation, as routinely sought in hospices, may be quite acceptable if not rewarding to the patient in excruciating physical or existential pain in the last stages of life.

We suggest that a *better operational definition of tolerance* in cancer populations would be "pain that steadily increases in severity and the increase cannot be reasonably explained by disease progression, such that continual upward dosage titration is needed."

According to Mercadante,[49] the incidence of tolerance is 10-20%. The empirical basis for this figure is uncertain. In older studies[46,52,53] (see also references they cited), investigators concluded that the modest changes in opioid dosage made over time were all driven by disease progression and that dosage requirements actually decreased when other means were found for relieving pain. On the other hand, Schug et al.[52] documented a morphine dose range of 5-1,900 mg/day. The highest number does raise a question of tolerance effects, although it might just reflect genetic factors. There are also case reports that strongly suggest development of tolerance.[54] Further studies, modeled on the investigation of Collin et al.[46] and recruiting much larger numbers of participants, would help to resolve the drug tolerance vs. progressing disease question.

Conclusion

Our hypothesis that the development of tolerance is uniquely associated with the search for opioid-induced oblivion remains viable but available scientific evidence is insufficient to determine its validity. Rather, our attempt to build a case for this hypothesis has revealed some serious gaps in the scientific literature. Most particularly, there has been very little scientific interest in the actual opioid experience in all the various circumstances in which opioids are used. Many investigators seem to have blithely assumed that all opioid users are seeking euphoria, as with recreational drug users. Clearly this is not the case, for example, in patients in severe pain who are solely seeking analgesia, as elegantly demonstrated by Ochoa and colleagues[18] and Friedman et al.[19] Clearly, replication of these results is needed.

Among illicit opioid users, we certainly cannot expect the eloquence of Gregory David Roberts (*Shantaram*) in describing the heroin experience. However, more qualitative research in this area could certainly be informative. Epidemiologic research is also needed.

The mindset and wishes of patients with chronic cancer pain are almost entirely opaque for lack of scientific inquiry. This is a potentially important issue for their care. Some patients are simply seeking analgesia. They would likely deplore any alteration in cognitive function and this might translate into a choice of earlier use of intrathecal delivery of analgesics when a suitably titrated oral, subcutaneous, or intravenous regimen cannot achieve adequate control of pain. Others may in addition be seeking something closer to oblivion and may elect to take doses that provide some measure of oblivion. Presently, patients may not be given that choice because clinicians have not explored their mindset. This lack of qualitative inquiry into the mindset of patients with cancer pain is compounded by the rather modest upper limits of opioid doses commonly used to treat these patients, the apparent lack of attention to important comorbidities like depression and insomnia, and the nebulousness of operational definitions of refractory pain and tolerance. Tolerance is said to develop in 10-20% of these patients[49] but the older studies that have explored this issue have concluded, with good evidence, that increases in dosing requirements are entirely driven by disease progression. Collin and colleagues have provided the model experimental design.[46] Further studies are warranted.

The challenge of determining the mix of desire for analgesia and desire for oblivion in cancer patients could potentially be addressed by palliative care clinicians and hospices, provided it were universally available. Unfortunately, the most recent data available (published in 2016) indicate that in the year 2015, only 27% of patients had discussed end of life care with physicians.[55] Unfortunately, we were unable to track down more recent data. There are also significant disparities related to race and ethnicity in the rates at which palliative care services are actually received.[56]

There is no such thing as palliative care for people with addiction. Rather, we need to address the factors in their lives that led them to their relentless quest for oblivion: serious mental health problems, often physical pain, isolation, and hopelessness (reviewed[5]). This constitutes an enormously greater challenge than simply deterring people from a quest for euphoria.

Conflicts of Interest

Neither of the authors has any conflicts of interest bearing on this manuscript.

Author Contributions

†SEN was primarily responsible for the literature review, the analyses, and writing the paper.

†RAL and SEN have engaged in an intensive collaborative effort since 2016 to understand the scientific evidence bearing on the prescription opioid crisis, to provide a clinical guideline for management of chronic pain, to understand the fundamental causes of the current crisis in clinical pain management and illicit opioid use, and to propose solutions to these crises. The current manuscript reflects, in substantial part, ideas

generated over the years in this intense dialogue. RAL also critiqued the final draft.

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Data Availability

This paper consists solely of an analytic review and no data were independently collected.

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