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Narrative Review

Philosophical Issues and Psychological Variables that Influence the Determination of Opioid Effectiveness: A Narrative Review

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Background: The prescribing of opioids in the chronic pain setting is often based on the pharmacodynamics, pharmacokinetics, and pharmacogenetics of the drug obtained during development and clinical trials. However, the effectiveness of opioids varies widely and often appears to bear no relationship to the aforementioned variables. The impact of philosophical issues and psychological factors on determining how clinically effective opioid therapy is has often been over looked.

Objectives: This manuscript provides a selective review and narrative summary of the philosophical issues and psychological factors which can influence opioid effectiveness.

Study Design: A selective review and narrative analysis of the literature.

Methods: Experimental and clinical-based studies examining the impact of psychological factors on the effectiveness of opioids were extracted from the literature. Studies in which psychological factors were used as an independent variable were given preference.

Results: The philosophical issues reviewed include: (a) one's understanding of the nature of chronic pain, (b) the meaning of the score on the pain numerical rating scale (NRS), and (c) the selection of outcome measures. The psychological factors found to influence the effectiveness of opioids include: (a) role conditioning and learning, especially as they relate to conditioned analgesia, non-associative tolerance, and the nocebo effect, (b) dosing pattern, (c) patient specific factors, e.g., mood, overall psychological and neurocognitive status, (d) social variables, e.g., personal environment and the media, and (e) the dysfunctional endogenous opioid system and its relationship to various psychological disorders.

Limitations: This is a selective review of the literature. Some of the hypotheses presented have not been experimentally validated. The review includes animal, human, experimental, and clinical studies.

Conclusions: In general, the effectiveness of opioids may be influenced as much by the overall context in which they are used, including the physician-patient relationship as well as their pharmacological properties. Data obtained from short-term and well-controlled trials may not generalize to the clinical setting, which is often more complex and dynamic. Appreciating the impact of psychological factors may assist the clinician in proper patient selection, monitoring, and improved outcomes.

Key words: Psychological factors, philosophical issues, chronic pain, opioid therapy, effectiveness, conditioning, placebo, cognitive dysfunction

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The use of opioids in the treatment of chronic pain has increased significantly over the last 15 years, especially in the United States (1). The average daily morphine equivalent dose often approximates or exceeds levels which Ballantyne and Mao (2) described as 'high.' Despite the continued

use of opioids, the effectiveness of long-term therapy remains a source of considerable debate. Review articles differ in their conclusions. For example, a Cochrane review (3) concluded there was weak evidence suggesting that patients engaged in long-term opioid therapy experience clinically significant pain relief; improvement in function/quality of life (QoL) was inconclusive. Furlan et al (4) reported that opioids reduce both nociceptive- and neuropathic-related pain. Chou et al (5), however, stated the evidence to determine long-term effectiveness for improved function and pain relief was insufficient. They also noted that only 40/4209 (< one percent) of the studies reviewed met the criteria of 'long-term' (greater than 3 months duration), making the relevance of a large portion of opioid-related studies to the clinical setting very dubious.

This lack of a predictable clinical benefit of opioid therapy seems inconsistent, if not contrary, to expectations based on information from controlled clinical trials (6). Industry-based education regarding opioid pharmacology, prescribing, and guidelines rely heavily upon the information obtained during these clinical trials. However, there are number of philosophical issues and psychological factors capable of influencing the determination of how effective opioids are, which are not considered in these clinical trials or the outcome literature in general.

Philosophical issues include: (a) one's concept of pain (especially chronic pain), (b) the meaning of the pain numerical rating scale (NRS) score, (c) the relationship between statistical and clinical significance, and (d) the selection of outcome measure(s). The manner in which these issues are approached can impact the interpretation of the effectiveness of opioid therapy.

The role of psychological factors in opioid therapy may be underestimated. Generally, the interest has related to their use in the identification of patients at risk for aberrant drug behavior (7,8). Relatively little systematic attention has been given to the impact of psychological factors on patient responsiveness to opioids. In 1986, Portenoy and Foley (9) highlighted this point by noting that "…the efficacy of this therapy (opioids for noncancer chronic pain) and its successful management may relate as much to the quality of the personal relationship between physician and patient as to the characteristics of the patient, drug, or dosing regimen."

The present article will discuss the relationship between the philosophical issues and opioid effectiveness. It will also provide a narrative review of the literature designed to illustrate the influence of psychological processes (e.g., conditioning and learning), states (e.g., mood), characteristics (e.g., distress intolerance), and disorders (e.g., cognitive dysfunction, psychopathology) on the effectiveness of opioids. Articles from the animal, human-experimental, and human-clinical literature have been selected to demonstrate particular points. The heterogeneity of the literature does not lend itself to a systematic review with a meta-analysis. Furthermore, although some studies used psychological factors as independent variables, this is the exception rather than the rule when examining the effects of opioid therapy in the chronic pain setting. Understanding how these variables influence the patient's response may provide researchers and clinicians with a broader framework for understanding the clinical pharmacology of opioid therapy, interpreting inconsistent outcomes, and improving outcomes.

Terminology and Background

Opioids can be examined from a number of different perspectives. Pharmacokinetics involves the study of the movement of drugs in the body, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion; what the body does to the drug. Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of their actions; what drugs do to the body. Pharmacogenetics relates to the investigation of inherited genetic differences in drug metabolic pathways (10). Psychopharmacology is the study of the effect of drugs on the mind and behavior, and behavioral pharmacology is the study of the physiological and behavioral effects of drugs on the mood and the mind. Efficacy relates to how well a drug works under ideal conditions (i.e., controlled clinical trial), while effectiveness relates to its performance in a general clinical or 'real world' setting.

Observations in the clinical setting often vary from those in phase-3 type clinical trials (11,12). These differences may be accounted for by a number of factors. First, much of the information provided to the practicing clinician is that which the Food and Drug Administration (FDA) has authorized. This information relates primarily to the pharmacokinetics, pharmacodynamics, and pharmacogenetics of the drug obtained in phase 1, 2, and 3 investigations. Second, the FDA only requires a 12-week exposure to the drug (opioid) under study (13), while opioid therapy in the clinical setting is often

maintained for years. And third, changes in the NRS score are considered the primary outcome, whereas the emphasis of therapy in the clinical setting may be on outcomes other than subjective pain relief.

Assessing Efficacy and Effectiveness

Accepting the NRS as the proxy for the patient's subjective experience of chronic pain has the effect of rendering it a primary indicator of treatment effectiveness. Pre-clinical studies are frequently conducted in an experimental or acute setting, and the trial itself is acute (relatively short-tem). Secondary outcome measures, e.g., mood, function, QoL, etc., are only reported if the primary outcome is statistically significant. The implied assumptions are that (a) a subjective reduction in pain is the most important goal and foreshadows changes in secondary outcomes and (b) one can generalize the results from the acute/experimental model to the long-term clinical setting.

This approach begs the question as to the relationship between clinical and statistical significance. Depending upon the homogeneity of the sample, a reduction as small as one point on a 0 – 10 NRS could be found statistically significant. Yet, this could be clinically meaningless. Indeed, there is a growing realization that improvement in function may be a more relevant metric in determining the benefit of opioids in the chronic pain situation (14-16). The exact amount of reduction in the NRS score required to be clinically meaningful may not be the relevant question in the clinical setting. In fact, simply establishing cut-off scores for determining pain of 'mild,' 'moderate,' or 'severe' intensity has proven to be difficult (17).

The NRS itself can be affected by a number of psychological variables which bear no relation to the pharmacokinetics or pharmacodynamics of the drug, including perceived consequences (18), mood (19), gender of the experimenter/clinician (20), and presence of a reinforcing spouse (21). Even the use of certain language to describe a potentially painful stimulus can influence the report of pain and its intensity. The use of the term 'pain' in place of 'cold sensation' (22) or 'you will feel a bee sting' in place of 'it will numb the area' (23) has been shown to increase the reported intensity of pain.

In addition, there appears to be a functional disconnect between self-reported pain intensity and other outcome domains (24,25) including patient satisfaction (26-28). For example, Rowbotham et al (29) found that while one group of patients had a significantly greater reduction in NRS scores than the other, both groups showed similar improvements in sleep, mood, and function. Furthermore, positive outcomes without a reduction in pain intensity have also been reported (30-32).

Despite reporting significant levels of pain and the relative lack of changes in mood and function, Comley and DeMeyer (27) noted that 90% of the patients studied stated they were satisfied with their pain management. Satisfaction appeared to be determined by the perceived effectiveness of medication, independent of pain intensity, and communication with the clinician. Also, pain ratings at the time that satisfaction was measured had a greater influence on satisfaction levels than ratings obtained at an earlier time (33).

Backonja and Farrar (34) conducted a survey of practicing clinicians and reported that the NRS was used by 68% of the responders at the time of the initial visit, but by only 42% at each follow-up visit. The most common reason for using the NRS was to justify prescribing analgesics. The authors commented that "… the complexity of the human pain experience reminds us that we neither have a clearly articulated nor widely accepted statement about what the pain intensity ratings represent." A number of clinicians indicated they did not pay attention to or use pain intensity scores. Instead, they considered function and how the patient was doing overall.

The argument could be made that since pain is defined as a 'sensory and emotional experience' (subjective) (35), and given the acceptance of the NRS as a proxy for that experience, that a reduction in pain intensity meets the criteria for effectiveness. However, the most salient feature of chronic pain may be its impact on the patient's function and QoL. The growing emphasis on function as the primary outcome (14,15) in chronic pain reflects the realization that variables other than the NRS may be more relevant. This emphasis on function was echoed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) when they recommended focusing on outcomes "…that individuals experiencing chronic pain consider important in evaluating the consequences of their condition (36)."

Likewise, Deyo et al (37) have suggested that chronic low back pain patients be stratified according to the impact of pain on their mood, sleep, function, etc., in addition to pain intensity. The importance of considering function/QoL in addition, if not in place of, pain intensity is revealed by Reitsma et al (38). They reported a large variation among individuals reporting

chronic pain in regards to its impact on functioning. Therefore, patients with comparable levels of chronic pain intensity may have very different levels of functioning and respond differentially to opioids. In the case of higher functioning patients, the goal of treatment may be the 'ease of functioning' (39) rather than increased functioning or a reduction in NRS scores.

In summary, the effectiveness of opioids in the clinical setting can be judged by a change in any number of potential outcome variables including NRS, function, QoL, patient satisfaction, among others. Our philosophical approach to chronic pain, its assessment, and what constitutes meaningful clinical outcomes will determine which outcome variable is chosen and therefore, how we interpret the effectiveness of opioids. For example, there appears to be a relatively low correlation among NRS scores, patient-reported function, and patient satisfaction. The continued emphasis on the NRS appears to be incomplete as well as inadequate and perpetuates the notion of 'pain' as a symptom and pain intensity as the primary determining factor of all other associated psychological/functional abnormalities.

There are several alternatives. The use of a 'global satisfaction rating' has been found to incorporate a broader and more individualized array of outcomes other than pain intensity or change in pain intensity (28). Helping patients to select 3 – 5 reasonable goals, which may or may not include a reduction in pain intensity, and focusing on these as a measure of treatment effectiveness is consistent with many opioid prescribing guidelines. Finally, engaging the patient in the process of identifying what they believe needs to be done to bring about a reduction in their pain intensity other than, or in conjunction with, medication, e.g., stress management, exercise, weight reduction, smoking cessation, etc. This shares the responsibility for the outcome of treatment and distracts from an over-reliance on opioid medications.

Approach to Chronic Pain

The concept of chronic pain continues to evolve. While processes such as transduction and transmission remain important, there is a heightened recognition of chronic pain as a complex disease process. Deyo et al (37) noted "There is growing evidence that low back pain like other chronic pain conditions can progress beyond a symptomatic state to a complex condition involving persistent anatomical and functional changes in the central nervous system." Similarly, Fillingim et al (40) stated that "… a revolutionary approach to chronic pain taxonomy might completely abandon current diagnostic labels and approaches based on anatomical structure and organ systems in favor of an approach that prioritizes the neurobiological mechanisms underlying chronic pain disorders." Therefore, chronic pain should not be viewed as simply an extension of acute pain, but as an outgrowth of the processes of chronification involving, at least in part, a transitioning from a sensory to an affective system (41).

Rather than chronic pain being interpreted and treated as the symptomatic expression of the activation of the peripheral nociceptive system, whose intensity is influenced by psychological factors, these psychological factors become aspects of chronic pain itself. Therefore, chronic pain is approached by deconstructing it into its component parts (mood, function, sensory, social, etc.) and implementing the appropriate intervention. One would not expect that merely prescribing insulin to a diabetic would alter their eating pattern. Similarly, to the extent that depression, social isolation, deconditioning, and poor motivation represent key aspects of a given patient's chronic pain, it would seem illogical to assume that prescribing an opioid would produce a substantive change; chronic pain is not an opioid deficiency. Opioids may be a tool to assist the patient in achieving other goals, and their effectiveness should be judged accordingly. Therefore, the clinician's approach to chronic pain, i.e., a sensory-based symptom versus a complex disease process may well influence when, how, and for how long opioids are used and the manner in which effectiveness is determined.

Role of Conditioning and Learning

The principles of conditioning and learning have been applied to understanding how environmental cues, associations, and consequences can influence the customary activity of opioids. The Pavlovian classical conditioning paradigm, for example, has been used to demonstrate that associating morphine with a neutral olfactory stimulus resulted in a morphine-like conditioned analgesic response to the olfactory stimulus after only 4 pairings (42). Duncan et al (43) demonstrated conditioned spinothalamic activity to a visual stimulus used to cue the onset of an experimental trial. Siegel et al (44,45) interviewed a group of heroin addicts that survived an unexpected overdose and found that the overdose was associated with the use of a similar amount of drug but in an unfamiliar environment, suggesting the lack of generalization of tolerance. Siegel and Ramos (46) have demonstrated this phenomenon

of situational tolerance in the lab. These observations illustrate that both the effects of opioids and the physiological process that they are assumed to impact can be conditioned to otherwise neutral environmental cues.

Siegel et al (45-47) also described the role of self-administration cues (SACs) and drug onset cues (DOCs) in the development of tolerance. SACs refer to exteroceptive and interoceptive cues incidental to self-administration of a drug, and DOCs refer to the exteroceptive and interoceptive cue incidental to the onset of a drug effect. SACs and DOCs are capable of eliciting a conditional compensatory response (CCR) which mimics the compensatory response unconditionally elicited by a drug itself. That is, after a series of pre-drug pairings, the body responds to the non-drug as if the actual drug was being administered. These CCRs represent the homeostatic activity of a complex adaptive system and may attenuate the effects of the drug and contribute to tolerance.

Because the DOCs elicit CCRs which can attenuate the drug effect, tolerance is greater when assessed in the presence of drug-associated cues than in a novel situation. Animals that self-administer a drug by making a designated response (e.g., pressing a lever in an operant conditioning chamber) were found to be more tolerant to the drug than were yoked animals that received the same drug doses at the same time, but not contingent on their behavior. Self-administering individuals displayed more tolerance and more withdrawal symptoms than passive receipt individuals when the instrumental response no longer leads to pharmacological reinforcement. They also demonstrated that when a smaller dose of morphine (4 mg/kg) reliably preceded a larger dose (12 mg/kg), the smaller dose came to function as a cue for the larger dose/drug effect of the opioid and influenced the development of morphine tolerance (48).

In summary, repeated administration of an opioid in the presence of specific environmental cues can induce tolerance specific to that setting (associative tolerance). Prolonged or repeated administration of an opioid without consistent contextual pairing yields non-associative tolerance. Microinjection of the cholecystokinin-B antagonist into the amygdala blocks associative tolerance (48) but does not influence non-associative tolerance, indicating the presence of 2 different mechanisms of action.

The above observations have several clinical implications. When patients indicate that a certain color, size, or shape of a drug has a superior effect to another, although the chemical contents are very much alike, they may be reporting the effect of SACs and DOCs. This may also have implications for the use of short-acting (SA) drugs, which have very detectable DOCs, in combination with long-acting/controlled-release/sustained-release (LA; CR; SR) agents to address 'breakthrough' pain (BTP). That is, the SA agents, by virtue of the more salient DOCs, could facilitate the development of tolerance to the LA agents. In the setting of intrathecal (IT) opioids, the use of SA agents, especially on a daily basis, could compromise the effect of the IT opioid through the CCR response elicited by the SACs and DOCs. This may be seen clinically by what appears to be a rapid developing tolerance or loss of efficacy over a relatively brief period of time. Alternatives to the use of SA opioids for BTP will be discussed below.

Rowbotham et al (32) examined the effectiveness of levorphanol in a group of patients with neuropathic pain. The patients underwent 8 weeks of treatment. They were randomly assigned to the 'high' strength (HS) (0.75 mg/pill) or 'low' strength (LS) (0.15 mg/pill) group and allowed to self-titrate up to a maximum of 21 pills per day. On average, the patients in the LS group took 50% more pills per day (18.3 vs. 11.9), but their total dosage was some 70% less (2.7 mg vs. 8.9 mg) per day. Although the reduction in pain intensity was greater in the HS group compared to the LS group (36% vs. 21%), there were no differences between the 2 groups in the improvement of affective distress, sleep, and interference with functioning.

The study suggests that there may be a ceiling to the number of pills patients find acceptable or necessary, which is unrelated to the total opioid load. Furthermore, despite a vast difference in the total daily dose and less reduction in pain intensity, those taking a larger number of pills had similar improvement in measures of mood, function, and sleep, indicating the psychological impact of taking a given number of pills over and above that attributable to the actual dosage. This may be another example of the effect of SACs.

Placebo Effect

The notion of a placebo as an inert or innocuous substance used in controlled experiments to assess efficacy of other drugs has been replaced. The contemporary approach views the placebo as a treatment with no specific therapeutic action and the placebo effect as the outcome following its administration (49,50). The placebo effect is a psychobiological phenomenon. The effects following administration of a placebo are due

to the psychosocial context surrounding the therapy (i.e., 'contextual sensitive treatment'). A positive psychosocial context may induce a placebo effect, whereas a negative context may lead to a nocebo effect.

The placebo analgesic effect is often mediated by the endogenous opioid system, while the nocebo hyperalgesia effect is mediated by anxiety-induced activation of the cholecystokinin system.

Contrary to conventional wisdom, Kaptchuk et al (51) demonstrated that there was no need for deception when administering a placebo. Their study involved 80 women with irritable bowel syndrome (IBS). The patients were randomized to either (a) open-label placebo pills presented as "…placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes," or (b) a no-treatment control group involving similar quality of interaction with providers but without information about the placebo effect.

The patients in the first group were informed that the placebo pill was an inactive substance like a sugar pill and contained no medication. The experimenter also read a 15-minute prepared script which incorporated the following 4 discussion points: 1) the placebo effect is powerful, 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, and 4) taking the pills faithfully is critical to the patients in the open-labeled group.

The open-label placebo group showed a significantly higher mean global improvement score, reduced symptom severity, and adequate relief. Similar to Portenoy and Foley (9), Kaptchuk et al (51) concluded that "…patients given open-label placebo in the context of a supportive patient-practitioner relationship and a persuasive rationale had clinically meaningful symptom improvement."

The magnitude of the placebo response appears to be increasing with time (52-54). A recent report examined the randomized controlled trials (RCTs) relating to drugs used to treat neuropathic pain from 1990 to 2013. The placebo response increased considerably during this time period. The effect was most strongly noted in studies conducted in the US (54). The effect seemed more pronounced in longer trials. The authors speculated that longer trials may provide more opportunities for greater social support, staff attention, and education.

The notion of the placebo effect as a contextual, sensitive treatment adds a new dimension to the clinician-patient interaction as it relates to the patient's response to opioids. In the susceptible patient, a positive, negative, or no response to the drug may well rest with the clinician's style. Identifying features of the office-based clinician-patient interaction/relationship, which enhances the positive effects of opioids, has received some attention. Bingel et al (55), for example, demonstrated the impact of patient expectations on the effectiveness of the opioid remifentanil. Mondaini et al (56) illustrated how side effects can potentially be manipulated by informed consent. Sexual dysfunction was reported by 43% of patients informed of its possibility, but only 15% who were not informed but selected any drug-related side effect from a checklist given post administration.

The observation that the side effect profile of a drug can influence the manner in which the informed consent is framed becomes meaningful when realizing that, by definition, the nocebo-based side effect is not a direct result of the specific pharmacological action of the drug in use but the context in which it is introduced. However, the side effect will be attributed to the drug itself. Land et al (22) and Varelmann et al (23) also demonstrated that the choice of words used to describe a given stimulus or procedure could significantly increase the reported pain intensity (see above). Swannell et al (57) discovered that certain words were associated with higher levels of reported pain intensity and increased physiological reactivity even when present subliminally. They hypothesized that words which were strongly associated with pain provoked pain-related concepts in memory. Some cases of suspected opioid-induced hyperalgesia may in fact be a nocebo response influenced and perpetuated by the context of the clinician-patient interaction (58,59).

LA vs. SA Opioids

The use of LA formulations has been promoted as a means of reducing the likelihood of the patient becoming addicted to opioid medications. The rationale put forth is that the repeated dosing of a SA formulation, e.g., every 4 – 6 hours, the dose-related fluctuation in pain relief, and the physiological/psychological sensation associated with the relatively abrupt onset of the drug's action would foster the development of addiction. When proposed, and even now, there is little evidence to support this contention.

The American Society of Addiction Medicine (ASAM) defines addiction as "...a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads

to characteristic biological, psychological, social, and spiritual manifestations (60)." ASAM emphasizes that addiction resides in the person, as it were, and not in the substance or the method of administration. Addicted persons may well prefer the rapid and profound onset of SA opioids, but this is not necessarily the cause of their addiction. It is noteworthy that the most recent guidelines from the Centers of Disease Control and Prevention (61), regarding the use of opioids by primary care physicians, recommends SA over LA formulations. Furthermore, there is some evidence that the risk of developing opioid-induced hypogonadism is less likely with SA opioids (62). These observations suggest the need for a more careful analysis of the psychology behind prescribing of LA versus SA preparations.

Increased dosing and frequency of dosing was also thought to be a consequence of the use of SA opioids. However, Doleys et al (63) reported on a cohort of 47 patients followed for an average of 31 months. The average number of pills per day remained at 4.1 despite over 70% of patients reporting the average duration of relief to be 4 hours or less; 49% reported 3 hours or less. When asked, the patients noted an increased ability to cope with their pain if they knew they had something to take when they needed it (controllability) and that it would work when they took it (predictability). Therefore, even though the patients acknowledged opioid-related pain relief of 12 – 16 hours/day, their sense of controllability and predictability allowed them to continue to function without additional dosing. Robinson et al (64) also found a sense of controllability to be an important factor in long-term opioid therapy.

Breakthrough Medications

Many patients have come to expect 24 hours/day relief prompting them to request additional medication for what they believe to be 'breakthrough' pain (BTP). The concept of BTP was described by Portenoy and Hagan (65) as a transitory increase in pain intensity that occurs in patients with stable, baseline persistent pain. This concept was originally applied in the treatment of cancer-related pain and supported the use of SA opioids to address unpredictable and spontaneous bursts of severe pain secondary to fluctuations in the disease process. This notion, however, has been generalized to chronic pain. The result has been the prescribing of one or more SA pills a day in addition to a LA drug. There are, however, a number of factors which can account for this BTP including: (a) end of dose, (b) disease progression, (c) incident pain (volitional, e.g., walking, bending, coughing, sitting, etc. or non-volitional, e.g., bowel/bladder distension, diurnal pattern, etc.), (d) weather sensitivity, and/or (e) psychosocial (e.g., depression, anxiety, conflict, etc.).

The end-of-dose phenomenon refers to the duration of relief which may or may not correlate with the pharmacological properties of the drug. As already noted, the duration of relief of an opioid may vary considerably compared to that found during the controlled, short-term clinical trials. Furthermore, the expectation of stable relief for 24 hours/day seems unrealistic and inconsistent with the general clinical narrative. Patients with chronic pain need to be educated about the disease concept of chronic pain and that there are likely to be diurnal fluctuations which can be effectively managed without increased dosing (66).

Frequent requests for additional opioids to address BTP are often interpreted as aberrant drug behavior or 'medication-seeking.' In some, perhaps many, instances it may well be iatrogenic in nature, i.e., the patient's request for more opioid is reinforced by the clinician acquiescing. The addition of a SA breakthrough opioid could inadvertently serve to reinforce the patient's verbal complaints, increase the opioid load, and encourage a psychological dependence on medications. In addition, the salience of the DOC (see above) of the SA opioid may well contribute to a more rapid development of tolerance and drug-seeking behavior.

Alternatively, a detailed assessment of the complaint of BTP could be carried out by having the patient self-monitor their pain levels and activity. A musculoskeletal/mechanical examination may reveal abnormalities which could be addressed by self-administered modality therapy/exercise. Taking time to interview the patient may uncover psychological factors such as stress, depression, anxiety, etc. secondary to a change in life circumstances. Brief psychological intervention could be very effective. If an analgesic is required, the use of an over-the-counter agent should be considered. Psychologically, this approach involves the patient in their own problem-solving and imparts an element of responsibility onto them rather than encouraging further dependence on medications and the medical system. This tactic is not unlike that used when instructing patients with diabetes on how to manage fluctuations in glucose blood sugars.

The Dosing Pattern

In much the same way that CR/LA/SR preparations were assumed to be superior to SA preparations, 'time-contingent' dosing was believed to be preferable to 'pain-contingent' dosing. Pain-contingent dosing was thought to maintain the patient's attention on their pain and to reinforce the experience of pain by self-administration of a pain pill. Presumably, watching-the-clock disconnected the pill from the pain. However, Von Korff et al (67) surveyed 1,781 patients undergoing long-term opioid therapy for chronic noncancer pain; 967 patients used time-scheduled opioid dosing, and 325 patients used pain-contingent opioid dosing only. The results showed that patients using time-contingent dosing reported being (a) more preoccupied with opioid use, (b) less able to control their opioid use, and (c) more worried about opioid dependence. Also, they were more likely to report that family or friends thought they may be dependent on opioids. Similarly, Doleys et al (63) found predictability and controllability to be important psychological factors relating to pain control in patients using pain-continent dosing. Therefore, it may not be the dosing pattern itself as much as the patients overall psychological approach to the role of opioids in their pain management and the use of other self-administered coping strategies.

Impact of the Environment

The impact of the environment can be considered from at least 2 different perspectives, individual and societal. Regarding the individual's environment, Raza and Bergerd (68) explored the effect of short-term (21 days) social isolation on morphine consumption in rats. They compared total isolation versus partial isolation (60 minutes per day of social-physical interaction) versus paired animals. The rats housed in short-term isolation consumed significantly more morphine than rats living in pairs. There were no gender differences and the total water consumption was the same. It appeared that even a limited amount of daily interaction with a conspecific was sufficient to abolish the effects of total isolation. Whether this is a result of distraction or social contact is not clear.

Distraction is known to have an effect on pain severity and intensity (69). Two studies examined the effect of distraction on the use of opioids in a hospital setting. Dolce et al (70) compared the use of opioids postoperatively in patients assigned a private room verus semi-private room in the hospital. The patients in semi-private rooms used less injectable request-contingent (i.e., as needed) opioids than the patients in the private rooms. This appeared to be related to the amount of distraction from having a roommate to interact with and the overall increased socialization and activity.

Ulrich (71) examined the effect of patients assigned to hospital rooms with a view of a small stand of 'deciduous' trees or a 'brown brick wall.' The same nurses were assigned to the rooms on a given floor. Those patients with 'a view' recovered faster, had shorter lengths of stay, and required less opioid medications. It is not hard to imagine a patient with chronic pain altering their dose to compensate for the social isolation experienced as a result of reduced activity and interaction. Again, reinforcing increased functioning as an equally or even more important outcome than reduction in NRS scores.

A study by Hoffman et al (72) examined distraction in the form of virtual reality (VR) alone and in combination with opioids on experimentally-induced thermal pain. Combined opioid + VR reduced pain reports more effectively than did opioid alone on all subjective pain measures. Patterns of pain-related brain activity support the significant subjective analgesic effects of VR distraction when used as an adjunct to opioid analgesia. They concluded that VR distraction enhanced the analgesic effects of the opioids and suggested the potential benefit of combining pharmacologic and psychological analgesic techniques in the clinical setting.

On a societal scale, accessibility and social influences can play a role. Canada and the United States rank first and second, respectively, in per capita use of opioids. Together the 2 countries consume the majority of the world's hydrocodone (99.9%), oxycodone (87.3%), morphine (60.1%), and methadone (51.8%) (73-75); many of which are unavailable in more than 150 countries (74). The element of accessibility reinforces the notion of acceptability, desirability, and effectiveness.

Media coverage is another societal element. Studies related to the use of alcohol among children and adolescents found them to be influenced by their perception of alcohol advertisement and alcohol use as portrayed in movies and on television. Those holding a positive impression also held more favorable beliefs about alcohol and indicated a plan to drink more frequently as adults and also consumed alcohol more frequently and in larger amounts. It was concluded that alcohol advertising, much the same as cigarette-related advertising in the past, influenced beliefs, desirability, and behaviors (76). There seems to be little reason to doubt that the same would not hold true of opioids.

The glamorization of high-profile entertainers' and athletes' drug-use could easily affect one's perception of the substance used and encourage imitation.

Blendon and Young (77) found that the way in which the public views drugs and drug policy is significantly impacted by the amount and type of media coverage. An ecological study examining unintentional poisoning deaths involving SA prescription opioid substances from 1999 to 2005 noted a strong correlation between media reports and death rates (78). The frequency of the reports mentioning prescription opioids began escalating in 2001 and seemed to coincide with reports of nonmedical use of OxyContin (R). It was as though media coverage, although emphasizing the dangers of opioid use, may have inadvertently reinforced the desirability of the drug to a vulnerable population.

McGinty et al (79) reviewed the manner in which opioid use had been portrayed in the media from 1998–2012. More than 75% of the news stories mentioned a growing opioid crisis involving illicit drug dealing by physicians, patients, and others (57%). Most of the news stories depicted individual abusers of opioids as being involved in criminal activity rather than emphasizing the risk to the individual, such as opioid-related cortical changes (80,81), endocrinopathies (82), osteoporosis (83), and unintentional/accidental overdose (84,85), and the public health concerns. The differences in the media's approach to opioids may explain some of the vast regional differences in opioid prescribing and use (86-88). The manner in which the consequences of opioid use are reported in the media may lead to biases, beliefs, and expectations which alter the outcomes of their use.

Patient Characteristics

Certain patient characteristics have been associated with increased opioid use in the absence of any change in nociceptive input or opioid effectiveness. McHugh et al (89) studied a group of chronic back pain patients involved in long-term opioid therapy. They examined the role of distress intolerance, defined as the perceived or actual inability to handle aversive somatic or emotional states, in opioid-taking patterns. Those with higher levels of intolerance were more likely to misuse opioids in an apparent attempt to obtain relief from these states and/or the associated increase pain.

Patients with chronic pain often have a strong disease conviction or somatic preoccupation (90) and an externalized locus of control (48), each of which may lead to opioid-seeking behaviors and altered responsiveness.

It is unclear if patients seeking additional opioids are seeking relief or if the opioids fulfill some other function. For example, opioid-seeking behavior may be stimulated by the non-analgesic operant reinforcing effects of taking opioids (e.g., euphoria, anxiety reduction, sense of well-being (91-93)). Likewise, opioid use/abuse has been more commonly associated with lower education, unemployment, disability payments, unstable psychiatric disorder, a history of substance abuse, and previous suicide attempts (94). This further suggests that factors other than the analgesic properties of the opioid may be motiving this opioid-seeking behavior. The possibility of diverting as means of supplementing one's income or helping another that is in pain and unable to secure medications cannot be over looked.

Cognitive Function

Opioid responsiveness can be affected by the patient's neurocognitive status. Patients with Alzheimer's disease (AD) appear to have a fairly normal response to sensory stimuli (95,96). However, they demonstrate an altered pain response as indicated by lower pain intensity and pain affect, as well as a diminished analgesic response when compared to individuals of similar age without dementia (97-99). Benedetti et al (99) studied a group of patients with AD and noted what appeared to be the loss of placebo-related and expectation-related mechanisms. In general, the altered response to pain and opioids in the cognitively impaired may result from: (a) altered central processing, (b) altered functional connectivity, (c) impaired contextual appraisal, (d) altered expression, (e) altered fear or affective response, and (f) altered response to opioids secondary to disruption of the expectancy due to cognitive impairment.

Karp et al (100) suggested the presence of a diminished response to the stress associated with aging and cognitive dysfunction suppresses the otherwise strong homeostatic drive associated with pain. This reduced homeostatic drive leads to a state of homeostenosis (constriction of an ageing organism's ability to effectively respond to stress because of diminished biological, psychological, and social reserves). Patients suffering traumatic brain injury can also experience a variety of cortical network dysfunctions (101), which influence how they interpret nociceptive input and can be associated with a variety of cognitive, behavioral, and emotional alterations impacting the manner in which they use opioids and the effect they derive.

There is increasing evidence of altered brain structure, especially gray matter volume, in patients with chronic pain (102-105). There is some suggestion that this is more profound in those with chronic neuropathic pain. Although not to the extent of patients with dementia, patients with long-standing pain may exhibit subtle neurocognitive deficits secondary to these cortical changes (106) that could impact the effects of opioids. In addition, any neurocognitive side-effects of opioids may be accentuated further, compromising any potential benefit.

Impact of Mood and Psychopathology

Not surprisingly, the effect of opioids appears to be influenced by mood states. Jamison et al (107) evaluated the effects of ER hydromorphone in a group of chronic low back pain patients. The patients were designated as low, moderate, or high negative affect based on the Hospital Anxiety and Depression Scale (HADS). The patients in the moderate and high negative affect groups had: (a) a higher drop-out rate because of the adverse effects or lack of efficacy, (b) significantly higher pain intensity scores, (c) a greater disability on the Roland-Morris Scale, and (d) more withdrawal symptoms. The authors concluded that negative affect was associated with diminished benefit during a trial of opioid therapy and was predictive of drop-outs in a controlled clinical trial. Interestingly, they also observed that the high group had the most improvement in pain in the placebo condition. Howe et al (108) reported that despite reported benefit, depressed patients were more likely to be ambivalent about the use of opioids and request a reduction or discontinuation of therapy.

Wasan et al (109) segregated patients into low, medium, or high levels of psychopathology based on scores of depression, pain anxiety, and neuroticism. Those in the high group reported less pain relief compared to the low group, 41% and 65% respectively, indicating high levels of psychopathology to be associated with diminished opioid analgesia. Taylor et al (110) have suggested that molecular and cellular changes can occur in the mesolimbic dopamine system in the presence of chronic pain and may be a significant factor in the emergence of negative affects and could alter the effectiveness of opioid medications.

Dysfunction/Dysregulation of Endogenous Opioid System

The incidence of psychiatric/psychological disorders among patients with chronic pain ranges from 50–80% (111,112). Psychological factors such as anxiety and depression are among the most common and are known to play a significant role in the experience of pain. Indeed, Basbaum (113), consistent with the IASP definition of pain as a sensory and emotional experience, indicated that one cannot have chronic pain absent of an emotional (psychological) component. Controlled, research-based studies often attempt to exclude such patients in an effort to create a homogeneous sample.

The severity of the psychological disorder is likely to vary across patients and within a given patient across time. The multitude of changes a patient may be exposed to, i.e., job, family, personal loses, medical/health, etc., over their lifetime, will, by definition, affect their experience of pain. These events can neither be anticipated nor controlled. Such psychological factors would necessarily impact the patient's mood and psychological status and, therefore, the effectiveness of opioids.

Opioids have a long history of use in patients with psychiatric/psychological disorders (114). Opioids have been reported to be beneficial in the treatment of bipolar disorder (115), depression/mood disorder (116-118), anxiety (119,120), PTSD (121), OCD (122), panic (123), and agitation (124,125). Dysfunction/dysregulation in the endogenous opioid system has been associated with borderline personality disorder (126), pain from social rejection (127), impulsiveness (128), and fibromyalgia (129). The endogenous opioid system dysfunction appears to include an altered opioid receptor concentration and/or altered opioid receptor system response to negative emotion (126).

The implication is that opioids may be influencing or stabilizing any number of psychological conditions. This effect could account for patients claiming significant benefit in the absence of improved function and pain relief. Their expressed need for the opioid could easily be interpreted as a maladaptive 'drug dependence.' The unanticipated effect of opioids on underlying psychological disorders may be more evident in the return of these psychological symptoms upon a significant reduction of the opioid.

Summary

The effectiveness of opioid therapy will be determined by a number of factors, including one's philosophical approach to chronic pain. As a complex disease process, chronic pain has many component parts, the most important of which may vary with time. Outcomes are likely to differ based on which aspect is assessed,

e.g., NRS score, mood, function, global improvement, etc. The sole use of the NRS may not accurately reflect the complexity of chronic pain (130) and reliance on it may impact patient satisfaction with treatment. Furthermore, its pervasive use has been linked to an increase in opioid prescribing (14,131). The NRS may be most applicable in the experimental and acute setting.

Opioid effectiveness can vary as a function of treatment expectations. Becoming skillful at maneuvering the psychological context of the consultation to take advantage of the placebo effect/response can easily impact the potential benefit and/or side effect(s) of opioid therapy (132,133). The manner in which medical agreements and informed consent are written and executed may be more influential than previously thought.

The influence of opioid-specific variables, such as the formulation (LA vs. SA), dosing pattern (time-contingent vs. pain-contingent), and magnitude of the drug, can be altered by a variety of patient and contextual variables. The most beneficial results may relate as much to the skillfulness of the clinician as to the kinetics of the drug. The addition of BTP medications may facilitate the short-term outcome but compromise the long-term therapy. The role of CCR, predictability, and controllability may be relevant and help to minimize unwarranted and potentially detrimental dose escalations.

The presence, onset, duration, and intensity of moods such as depression and anxiety will fluctuate. Changes in life circumstances can be unpredictable and cause a generalized stress response. Pain enhanced by negative emotions may feel the same to the patient but may not respond to changes in the opioid therapy. A one-time positive analgesic response to an opioid can be compromised by a change in the patient's psychosocial status. The combined use of other therapies to address these problems may well enhance the perceived effectiveness of the opioid.

Unfortunately, there is little incentive for the industry to conduct studies relating to manner in which psychological factors and processes can modulate the effectiveness of opioids. Information gathered in this area will likely come from grant-supported efforts or systematic observations in the clinical setting. The clinician needs to be cautious about generalizing data from well control and short-term experimental studies to the clinical setting. Effective use of opioids will require consideration of the psychological context including the clinician, setting, and patient.

This manuscript has provided illustrations of how philosophical issues and psychological variables (processes) can impact the clinical effectiveness of opioids. Some of psychological variables, such as catastrophizing, have yet to be exposed to systematic study. However, their potential influence seems logical based upon clinical observation and reports. It appears plausible that the psychological predilections of the patient, the overall context in which opioids are used, and the conditioning processes associated with opioid use may impact their long-term effectiveness beyond what was predicted based on the pharmacodynamics, pharmacokinetics, and pharmacogenetics of the drug. The principles and guidelines developed in the experimental, acute, and peri-operative setting may not translate easily to the chronic setting. Understanding the psychological nuances (complexity and dynamics) of the clinical setting and the manner in which they influence the degree of contextual sensitivity can help to inform the decision making process regarding the use of opioids and maximize the clinical benefit.

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