Special Article

Informed Consent in Opioid Therapy: A Potential Obligation and Opportunity

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Abstract
Most patients receiving opioids for the spectrum of pain disorders tolerate opioids well without major complications. However, a subset of this population encounters significant difficulties with opioid therapy (OT). These problems include protracted adverse effects, as well as misuse, abuse, and addiction, which can result in significant morbidity and mortality and make informed consent an important consideration. Opioid treatment agreements (OTAs), which may include documentation of informed consent, have been used to promote the safe use of opioids for pain. There is a debate regarding the effectiveness of OTAs in reducing the risk of opioid misuse; however, most practitioners recognize that OTAs provide an opportunity to discuss the potential risks and benefits of OT and establish mutually agreed-on treatment goals, a clear plan of treatment, and circumstances for continuation and discontinuation of opioids. Informed consent is an important component of an OTA but not often the focus of consideration in discussions of OTAs. This article examines the principles, process, and content of informed consent for OT of pain in the context of OTAs.   J Pain Symptom Manage 2012;44:105−116. Published by Elsevier Inc. on behalf of U.S. Cancer Pain Relief Committee. All rights reserved.

Introduction

Pain is a widespread heterogeneous clinical condition that may manifest in both acute and chronic forms. Chronic pain remains a serious health care problem, with an estimated prevalence as great as 25% of the general population.[1,2] The prevalence of pain in the cancer population is noteworthy. A recent systematic review[3] revealed that 64% of patients with metastatic or advanced diseases, 59% of patients receiving cancer treatments, and 33% of cancer survivors experienced pain. More than one-third of these patients rated their pain as moderate or severe.

Acute pain may occur as a result of trauma, surgery, or illness. Acute pain usually resolves naturally as the acute pathology causing it resolves. Poorly controlled acute pain can cause

physical (e.g., delayed healing, pulmonary complications, increased risk of thrombosis, and so on) and psychological (e.g., increased fear/anxiety and suffering) complications and additional economic burden from increased length of hospital stay or lost productivity from unnecessary disability. Of patients with acute postoperative pain, 10%−50% may develop persistent pain and 2%−10% of these cases may experience severe chronic pain.[4] Effective postoperative pain management may obviate or reduce the incidence of patients developing chronic pain.

One of the barriers to effective pain management across the spectrum of pain conditions (acute, chronic noncancer, and cancer pain) is the clinician's fear of prescribing opioids beyond that merited by the actual risks.[5,6] This has led to the undertreatment of pain, including cancer-related pain.[7] Trepidation regarding the prescription of opioids has been reinforced recently by the rise in the nonmedical use of prescription opioids, resulting in increasing opioid-related harm[8] and deaths,[9,10] as well as an increased demand for treatment of prescription opioid addiction.[11] It is important to appreciate the actual risks associated with opioids and accommodate these when prescribing, but it is not appropriate to abandon the use of opioids because of misperceptions, as many pain experts agree that opioids remain the most effective analgesics available. Opioid risk assessment and management models have been developed in an effort to mitigate risks related to OT and ensure that patients with pain have access to appropriate treatment, including opioids, to alleviate suffering.

There is growing consensus that opioid treatment agreements (OTAs) or contracts are an important component of clinical management of OT for pain.[12−16] For example, recent expert guidelines for the use of chronic opioid therapy (COT) in chronic noncancer pain (CNCP) included a recommendation for the consideration of obtaining informed consent and developing a written management plan.[13] There is less consensus whether OTAs should be used in all types of pain, especially acute pain and pain at the end of life, and whether they should be applied universally with all patients regardless of identified risks or only for selected patients. The effectiveness

of OTAs in reducing opioid misuse requires further research.[17,18]

Because treatment of acute pain is generally time limited and provides less opportunity for individual patients to develop adverse consequences of opioid use, OTAs have not been widely used in this context. Nonetheless, adverse consequences may occur, and, therefore, some level of informed consent is appropriate and a plan of treatment may be beneficial, particularly in an outpatient treatment setting. OTAs have been less widely used in the treatment of chronic cancer-related pain than in the treatment of CNCP, likely for multiple reasons that include the presence of clearly defined and often progressive pathology as a basis of pain and the close supervision of clinical personnel in longitudinal care, among others. However, cancer is becoming, in many cases, a chronic, at times relapsing, disease and at some point in time, pain is not acute or related to active treatment, and the same chronic pain model may be beneficial. Certain persons with chronic cancer-related pain clearly are at risk for adverse opioid-related consequences, including self-medication, addiction, or other misuse.[19] Informed consent is equally important in this patient population, and the use of often higher doses of opioids and presence of diverse caretakers may, in fact, engender special risks for diversion.[20] It is reasonable to consider that patients with cancer may benefit from the same clear documentation of informed consent and the plan of care afforded patients with CNCP.

It is clear that increased prescribing of opioids for pain has resulted in increased opioids available for misuse, and available evidence suggests that clinical prescribing is a major source of nonmedically used opioids.[21] However, it is not clear what portion of opioids is diverted from prescription for acute pain, cancer-related pain, or CNCP. Therefore, all prescribers need to use care in prescribing and educating patients about safe use, storage, and disposal of medication.

Informed consent is often mentioned as one part of an OTA, but the elements of informed consent have not been as widely discussed or characterized in the literature as other elements of the OTA. There is little consensus on the universality of OTAs or whether informed consent and OTAs should be distinct separate processes.

It has been strongly argued that informed consent is an ethical and medical obligation to discuss the risks and benefits of COT and an opportunity to facilitate ongoing communication regarding the goals of treatment.[22,23] This article briefly reviews the general purpose and components of OTAs in COT for pain and then focuses on key elements of the informed consent component of OTAs. General medical standards related to informed consent for treatment are reviewed, and the clinical and ethical implications in the context of COT for pain are explored.

Opioid Agreements

The exact elements of OTAs vary between practices, but OTAs generally serve two important functions: to document understanding between patient and clinician of the goals and plan of care and to provide informed. consent for treatment. These functions will be considered separately. Written OTAs ideally should provide documentation of mutual understanding between patient and provider of the goals of treatment, the roles and responsibilities of each with respect to the treatment plan, and the grounds for continuation or discontinuation of therapy.[16] Active utilization of such structured agreements, including both a thoughtful process of implementation and later referencing them to shape treatment decisions, may have value in simplifying clinical care, reducing risk, improving patient outcomes, and identifying patients for whom COT is not helpful and may be harmful.[17−19] This process may be facilitated by comparing treatment response with mutually established written goals. It also provides a clear pathway for discontinuing COT when the risk/benefit ratio of therapy does not appear favorable either because of personal risk to the patient related, for example, to misuse or addiction, or risk to the public as a result of diversion or both.[14]

Common goals outlined in OTAs include reduction in reported pain; improved function in valued areas, such as physical activity, relationships, work, or avocational activities; and generally improved quality of life. General improvement in quality of life may be suggested by stable or improved mood and outlook; a tendency toward self-control rather than chaos; greater engagement in valued activity; less focus on self and greater interest in others; and normalized daily routine, including wake-sleep cycles in addition to improved functions suggested above. When such goals are not approached or met, the rationale for continuing OT must be reconsidered.

Continuation of therapy is appropriate if movement toward established goals is apparent, sustained adverse effects (AEs) do not occur, and the patient is able to adhere to the terms of the therapy agreement. The agreement may provide a basis for discontinuation of therapy if goals are not being met, sustained important AEs do not improve or resolve with opioid rotation or dose adjustment, significant nonadherence to the agreement is identified, or other risks are strongly suspected or documented.

Whether such arrangements should be called agreements or contracts has been a subject of discussion. The term contract implies a legally binding agreement between the treating physician and the patient. Collen[24] argues that such contracts would most likely be unenforceable because they constitute an "unconscionable adhesion contract," defined as the patient having no meaningful alternative or choice when in need of treatment as a result of the scarcity of pain physicians. There is also evidence that most contracts are worded in a fashion that is not fully comprehensible by the average pain patient.[25] It has been suggested that potential negative consequences of OTAs or contracts include the undertreatment of pain, as outlining and emphasizing the potential risks of opioids and negative consequences of nonadherence may prejudice both physician and patient against the use of opioids,[26] increased risk of physician liability, further stigmatization of OT because this level of scrutiny is not typically associated with other high-risk medications (benzodiazepines and stimulants), and compromised integrity of the physician-patient relationship.[23,26] Despite these potential limitations, it has been argued that a patient-centered agreement that is fully vested in the best interests of the patient does provide an opportunity to clarify patient and physician expectations of treatment and responsibilities, enhances adherence, promotes a therapeutic alliance, and obtains informed consent, thereby serving the ethical obligations inherent in patient care.[27]

Informed Consent

The American Medical Association[28] considers informed consent as a communication process between the patient and the physician and suggests that elements of informed consent include:

- the patient's diagnosis
- the nature and purpose of the proposed treatment
- risks and benefits of the proposed treatment
- alternative treatments
- risks and benefits of alternative treatments
- risks and benefits of not receiving a treatment

The purpose of informed consent, whether as a separate process or as a component of the OTA, is to outline the major potential benefits and risks of COT weighed against the risks and benefits of other options. Informed consent theoretically permits the patient to make an informed decision whether to elect entry into treatment (or continuation of treatment if, for example, acute pain treatment extends into chronic pain treatment or if opioid prescribing is transitioned to a new prescriber). Given the imprecise predictability both of individual patient vulnerability to opioid misuse and addiction and of the occurrence of opioid-related effects, such as tolerance, dependence, and hyperalgesia, informed consent may become particularly important retrospectively if a patient develops such adverse outcomes so as to diminish any patient-physician conflict and reduce liability potential.

Informed consent traditionally includes those elements of risk and benefit perceived by the provider to be of potential significance for the individual patient. The potential benefits of COT have been considered in the discussion of goals of therapy. Providers may elect to include all or some of the following potential risks (Table 1) in informed consent for COT depending on the context of care (acute, postoperative pain, cancer-related pain, CNCP, hospice care, and so on) and the individual being treated.

Common AEs/Complications

COT may be associated with a number of AEs and complications that vary with regard to severity and incidence. Common AEs

Table 1
Potential Risk Inclusions in Informed Consent for OT in Chronic Pain

1. Physical side effects/complications
2. Cognitive effects
3. Addiction
4. Physical dependence
5. Psychological dependence
6. Tolerance
7. Hyperalgesia
8. Patient victimization
9. Overdose

include gastrointestinal effects, bladder dysfunction, pruritus, cardiac side effects, hormonal changes, immunologic effects, sleep disorders, and sedation.

A more detailed description and incidence rate of each of these AEs is provided in Appendix 1. Practitioners prescribing opioids should be familiar with these common AEs, how frequently they occur, and methods to mitigate or control bothersome AEs (e.g., hormone supplements for hypogonadism, dose reduction, or opioid rotation for sedation).

Cognitive Effects

Patients receiving opioids often complain of cognitive problems, such as forgetfulness or inattention.[29] A recent review of the literature on the effects of opioids on cognition[30] revealed mixed findings. Some high-quality studies using a randomized controlled trial design demonstrated no change and, in some cases, cognitive improvement in pain patients receiving OT. Several studies suggested that improved cognitive abilities may be mediated by reducing the stress of pain. Other studies provided evidence that opioids had no effect or worsened cognitive function, but these studies tended to have methodological limitations. Many factors influence the cognitive effects of opioids, including whether the patient is opioid naive at the initiation of therapy, dose titration, age, and the extent of medical and psychological comorbidities. Because cognitive complaints are common in patients receiving opioids, patients should be informed of this risk and advised to report any concerns to the prescribing physician.

Addiction

More study is needed to precisely determine the risk of addiction in OT for pain. Aberrant

drug-related behaviors are more commonly observed than addiction per se and may reflect a variety of issues, including misunderstanding of instructions; self medication of mood, sleep or other symptoms; elective use for reward; or diversion for profit, as well as addiction. A recent structured review of available studies suggested that clinically significant abuse or addiction occurs in about one in 500 persons with no prior substance use disorder (SUD) and in about 3–4% of all persons using opioids long term for pain treatment.[31] However, the risk of addiction to opioids appears to be significantly higher in individuals with a prior history of SUD, although the actual level of risk is not clearly defined. Available epidemiologic data suggest a lifetime prevalence of at least 7.5% for drug dependence and 14.1% for alcohol dependence, so this higher risk for the development of opioid addiction is relevant to many patients.[32]

Addiction in the context of COT for pain has been defined by the American Society of Addition Medicine, the American Pain Society, and the American Academy of Pain Medicine[33] as a "primary, chronic, and neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations." It is characterized by continued use despite harm (adverse consequences, e.g., loss of work and family roles and legal actions); impaired control over use (compulsive use: unable to suspend the use of an illicit drug even with the knowledge of scheduled urine drug test); and preoccupation with the use for nonpain relief purposes (craving: anticipation of next dose to achieve state of euphoria) (Table 2). These characteristics

may aid in the identification of addiction in clinical practice.

Using the influential *Diagnostic and Statistical Manual, Fourth Edition, Text Revision* (DSM-IV-TR) of the American Psychiatric Association,[34] clinicians must take care not to overdiagnose addiction. The DSM-IV-TR establishes seven criteria for substance dependence (addiction) of which an individual must manifest three to make the diagnosis (Table 3). Of the seven criteria, however, five are common in nonaddicted pain patients (tolerance, physical dependence-withdrawal, used in greater amounts or longer than intended, unsuccessful attempts to cut down or discontinue, and much time spent pursuing or recovering from use).[35]

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 drug, and/or administration of an agonist."[33] Physical dependence is common in many drugs that are used chronically, such as beta-blockers, antidepressants, and corticosteroids, as well as opioids. Physical dependence on opioids is sometimes mistaken as suggesting addiction, for example, when a patient presents with signs of withdrawal if medications are not available or expresses concern about renewing opioids on time to prevent withdrawal. Patients may not always take their opioids (or other medications) exactly as prescribed and can develop withdrawal symptoms, which may be viewed by an untrained clinician as a sign of addiction in the

Table 2
Consensus Statement of the AAPM, APS, and ASAM on the Definition of Addiction

- A primary, chronic, and neurologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations
- Characterized by behaviors that include one or more of the following:
    - Continued use despite harm (adverse consequences)
    - Impaired control over use (compulsive use)
    - Preoccupation with the use for non–pain relief purposes (craving)
    Physical dependence and tolerance not necessary

AAPM = American Academy of Pain Medicine; APS = American Pain Society; ASAM = American Society of Addiction Medicine.

Table 3
DSM-IV-TR Criteria for Dependence (Addiction)

- Tolerance
- Physical dependence/withdrawal
- Used in greater amounts or longer than intended
- Unsuccessful attempts to cut down or discontinue
- Much time spent pursuing or recovering from use
- Important activities reduced or given up
- Continued use despite knowledge of persistent physical or psychological harm
    Three of the seven criteria are required for diagnosis. Five of seven are common in non–addicted pain patients[35]

DSM-IV-TR = Diagnostic and Statistical Manual, Fourth Edition, Text Revision.

absence of critical behaviors suggestive of addiction. End-of-dose failure may occur if opioid doses are widely spaced, which also can lead to withdrawal symptoms. Patients should be made aware that altering the dosing schedule may result in withdrawal symptoms; clinicians should foster a relationship with the patient that encourages open discussion so that such problems can be identified and medications can be adjusted accordingly.

Psychological Dependence

Psychological dependence can be conceptualized as a nonphysiological attachment to the availability of the prescribed opioid. Such dependency may be related to fear of increased pain or other concomitant symptoms (sleep disturbance, anxiety, and depression) that the drug is, or is perceived to be, controlling, if the medication is no longer available to control the symptoms. This is often simply a natural response to effective relief of distressing symptoms. Patients with persistent and poorly controlled pain, however, tend to engage in catastrophizing, which is a negative cognitive-affective response to anticipated or actual pain and can contribute to increased pain and emotional stress.[36] Catastrophizing and a general state of anticipatory fear of the potential of increased pain can lead to a heightened attachment or psychological dependence on the medication. Psychological dependence does not equate with addiction, although it often occurs in the context of addiction.

Tolerance

Like physical dependence, tolerance is "a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time."[33] In the case of opioids, with prolonged use, the patient may require an increasing dose of the opioid to maintain analgesia and improve functionality. Patients should be counseled that, when initiating OT, they may require an increase in dosage or rotation to a different opioid over time if they continue on opioids. Many patients are fearful of becoming addicted and should be reassured on a regular basis that this increased need for higher doses of opioids is not necessarily suggestive of becoming addicted.

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) is a paradoxical phenomenon that may occur in long-term opioid users and is related to a drug-induced pronociceptive process resulting in an increase in pain. Hyperalgesia is commonly seen during opioid withdrawal, but increased pain also can occur during COT in the absence of withdrawal. OIH is more often seen in patients receiving high doses of opioids over a prolonged period of treatment.[37,38] Rotation to an alternative opioid at a lower equianalgesic dose or a trial of opioid tapering and addition of adjunctive medications may be helpful in managing OIH.

Patient Victimization by Others

Physicians are often concerned about diversion when prescribing opioids to their patients, and there is compelling evidence supporting these concerns. Friends and relatives who have received opioids from one prescribing clinician appear to be the most frequent source of opioids for persons who use opioids nonmedically.[21] Sometimes the source willingly provides the opioids, but sometimes theft is involved. This means that the legitimate pain patient can be subject to victimization by those seeking opioids for nonmedical purposes. Victimization can occur through theft, violation of property, assault, and other acts. In addition, a treating physician may reduce access or discontinue OT when the act of diversion is reported or because of concerns that the patient may be diverting medication (early request for refills and patient complaining of withdrawal symptoms). In either case, the patient will be without needed medication and endure increased pain, possible withdrawal symptoms, and a reduction in quality of life.

Overdose

Opioids are usually safe when prescribed appropriately and taken as prescribed. However, among persons who abuse prescription opioids, research suggests that an alarming 40% to 70% have at least one nonfatal overdose.[39–42] In a study of drug overdose rates in West Virginia, it was discovered that the majority of these deaths were associated with opioids.[43] Unintentional overdose in

patients prescribed opioids is significantly lower but does occur.[44−46] Methadone is particularly risky when misused because of its highly variable pharmacokinetics and pharmacodynamics, as well as possible cardiac arrhythmias. Patients should be clearly cautioned to take methadone only as prescribed and to hold back on the medication should they feel sedated.

Ethical Considerations in Informed Consent

The traditionally recognized pillars of medical ethics include respect for the principles of *autonomy, beneficence, nonmaleficence* (do no harm), and *justice.*[47] Jacobson and Mann[48] suggest that the valid opioid informed consent enhances the doctor-patient relationship and encourages ongoing dialogue regarding treatment. A valid informed consent also supports, to some degree, the ethical obligations of providers. Informed consent ensures that patient *autonomy* is protected when the patient is able to elect treatment based on a full understanding of the potential risks and benefits of a therapy and on a full delineation of their responsibilities, contained in the OTA's plan of care.

Three key elements are traditionally recognized as requisite to a patient providing autonomous and valid informed consent;[48,49] the patient (or his guardian) must be 1) capable of understanding the information provided and communicating his or her wishes, 2) fully informed about the potential benefits and risks of the treatment and those of other treatments, and 3) free to make a decision (without internal or external coercion). In a discussion of informed consent for methadone maintenance therapy of addiction, Carter and Hall[49] suggested a fourth requirement, which also may be relevant for pain treatment: "Patients have equal access to all effective forms of treatment where treatment is appropriately operated and resourced." Lack of availability of alternative forms of effective treatment (such as cognitive behavioral therapy or physical therapy) should not necessitate adoption of OT when other therapies might be equally as effective with lower risk. This may be viewed as a subset of the third requirement, a form of health system coercion. Each of these

elements bears careful consideration in the context of OT for pain.

With respect to the first requirement, it may be difficult for a patient to thoughtfully weigh the long-term risks and benefits of a treatment when he or she is distressed by severe pain and has a compelling immediate goal to reduce pain, which will likely be the initial result of using opioids. Unlike many drugs that have a primary therapeutic action and may have secondary, usually unwanted, side effects, opioids have a number of side effects in some patients that may attract their use for reasons other than pain—reward (euphoria), mood modulation, sedation, and sleep induction among others. In addition, some individuals may become addicted to them and feel a compulsive desire to use to satisfy craving. The denial of, or failure by, the user to recognize the addicted condition is a cardinal element of the addiction. A person, therefore, with co-occurring pain and addiction, may be unable to thoughtfully consider the risks and benefits of opioids because of the influences of pain, addiction, and/or a compelling desire to manipulate affective states when providing consent for OT. This raises the question of whether patients under these circumstances can provide valid consent for OT free from internal coercion. Are they truly autonomous, acting of their own free will?

In this context, it is important for clinicians to seek a balance between the obligations to support patient autonomy and provide pain relief (*beneficence*) while limiting the risk of harm (*nonmaleficence*) in a person he or she identifies as being at higher risk for misuse or addiction. At the same time, it is important to respect the principle of *justice*, which does not permit discrimination against a patient based on diagnosis or condition or other factors, in this case addiction. This is a difficult balancing act. Resolving the tension between these principles may be facilitated by appreciating a shift in the risk:benefit balance for persons at risk for opioid misuse and providing special supports to avert negative sequelae in those with addiction when opioids are used, or making aggressive efforts to provide effective alternative treatments.

In fact, persons with addiction are often subject to injustice or discriminated against, not necessarily in the decisions made by clinicians,

who often reflexively err on the side of avoiding harm in persons with SUDs, but in attitude. In fully informing patients of the potential risks and benefits of COT (Requirement 2) and aiding the patient in decision making, clinicians must be cognizant of their own prejudices and take care that decisions regarding COT are based on the perceived risk:benefit balance for the individual patient rather than prejudicial attitudes toward persons with addiction. Risks and benefits should be understood and explained to patients in medical terms. When SUDs are framed and addressed as the personal and public health problems that they are, rather than as willful misbehavior, decision making and communications can be accomplished in a manner that meets the ethical requirement of justice. Persons with addictive disorders have the same right to pain relief as persons without these disorders; however, the choice and structure of treatment must be adapted to serve both beneficence and nonmaleficence while respecting internal and external sources of comprised autonomy. OTAs and informed consent must be worded medically and respectfully.

Such a respectful medical approach emphatically does not mean that important nonadherence to OTAs should not be addressed seriously. The medical consequences of opioid misuse and addiction can be tragic for both patients and the public. But they should be addressed medically, rather than punitively, as matters of health and not as matters of willful misbehavior. This necessity does not extend to persons without pain who feign pain and attempt to divert opioids for profit, clearly criminal behavior that does not require a medical approach to treatment unless identifiable and treatable psychopathology is identified to be driving the behavior.

Conclusion

OT can be a safe and effective component of pain treatment in patients with pain from varying etiologies. In some cases, it is the mainstay of alleviating suffering, such as in end-of-life care. However, the rising prevalence of opioid misuse, addiction and diversion,[50,51] as well as the inherent AEs of opioids, necessitates the use of risk mitigation strategies. Opioid treatment

agreements, which include a thoughtful process of informed consent combined with clear goals and a well-documented plan of care, may serve an important role in improving pain management and reducing risk. Whereas the efficacy and legal status of OTAs per se are not well established and it has been argued that OTAs may increase disparities and further stigmatize the pain patient,[23] the informed consent portion of an OTA clearly provides an important foundation for care. The process of informed consent allows the practitioner to establish an ongoing open dialogue with the patient regarding the risks and benefits of treatment. This promotes a collaborative relationship and prompts exploration of alternative and/or adjunctive treatments if opioid treatment is not achieving its objective or if AEs are problematic. Informed consent is a fluid ongoing process emphasizing a patient-centered approach, with the inherent goal of maximizing benefit and enhancing quality of life while reducing the risk of AEs, addiction, abuse, diversion, and, most importantly, the undertreatment of pain. The ethical tenets of informed consent also should be applied to other medications with high risk for misuse or abuse (benzodiazepines, muscle relaxants, and stimulants).

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Appendix 1

Common AEs/Complications of OT

Gastrointestinal

Constipation as well as nausea and vomiting are very common with OT, with prevalence of greater than 80%,[52] 20%,[53] and 15%,[54] respectively. Typically, constipation as a result of opioids can be managed with adjunctive therapy; however, chronic constipation can result in more significant complications, from hemorrhoids to bowel obstruction, as well as, in rare cases, bowel rupture and death. Nausea and vomiting usually is transient on initiation of an opioid and, in most cases, resolves with time;[55] or, it may be drug specific so may resolve with rotation to an alternative opioid. If it persists, it can be treated with a number of agents (antipsychotics, metoclopramide, hydroxyzine, serotonin, antagonists, and so on), which have their own set of AEs.

Bladder Dysfunction

Urinary retention and voiding difficulties are common in postoperative patients receiving opioids. In the use of opioids long term, the prevalence of urinary retention and dysfunction is uncertain but relatively low.[56]

Pruritus

Pruritus or an itching sensation can occur in 10% of patients on opioids[57] and is treatable with antihistamines. It should be distinguished from urticarial reactions or rashes, which may indicate allergic responses.

Cardiac Side Effects

Cardiac side effects are not common with the use of oral opioids at therapeutic doses in chronic pain. However, QT prolongation leading to torsade des pointes syndrome may occur in association with methadone use, which can, on rare occasion, lead to death.[58−60] The circumstances of its occurrence are currently the subject of intense study and debate.

Hormonal Changes

Opioids have an effect on a number of hormones, including testosterone, gonadotropin, estrogen, progesterone, luteinizing hormone, and possibly follicle-stimulating hormone.[61] Men on COT may develop difficulties with sexual dysfunction, including erectile dysfunction, suppressed libido, depression, anergia, or lowered energy, typically related to hypogonadism. Women, likewise, can experience hormonal side effects to COT, including depression, sexual dysfunction, menstrual irregularities, and galactorrhea.

Immunologic Effects

Acute and chronic opioid use can lead to an inhibition of antibody and cellular immune responses and cytokine expression. The mechanism of this immunologic suppression involves the hypothalamic-pituitary-adrenal axis in the autonomic nervous system.[62,63] The clinical and/or long-term effects of demonstrated immune changes are not known. It should be noted, however, that the presence of untreated pain also may compromise immune function.[64]

Sleep Disorders

Patients suffering from acute and chronic pain often report difficulties sleeping. There are conflicting reports of the effect of opioids on sleep. Studies have reported improved sleep quality and efficiency,[65] but other studies report that opioids may cause inhibition of rapid eye movement and non−rapid eye movement phases of sleep,[66,67] possibly contributing to exacerbation of pain.[68,69] There is a high prevalence of sleep apnea[70−72] and hypoxemia[73] in patients receiving COT. Sleep apnea may interfere with restorative sleep and exacerbate other medical disorders.[74]

Sedation

Many patients experience sedation and drowsiness when they first initiate opioids or increase the opioid dose, possibly related to the anticholinergic effect of opioids. Patients on stable doses of opioids often experience a reduction in sedation and drowsiness through the process of tolerance but, when doses are titrated, can have recurrent sedation. Dose reduction or opioid rotation may be helpful if sedation persists.