Opioid effectiveness and side effects in chronic pain

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In the United States, approximately 50 million people have become disabled by chronic pain [1]. Because of fears of addiction, the effective pain treatment offered by opioids was, for many years, reserved for patients with cancer and a short life expectancy. During the past two decades, however, a lot has been learned about the mechanism of action of opioids and we now know that chronic, non-cancer pain conditions can be appropriately treated with these pharmaceuticals [2,3].

Opioid effectiveness

One of the most important lessons learned about pain therapy in general and opioid therapy in particular is that therapeutic regimens for pain require individualization [4]. Thus, one cannot necessarily expect universal therapeutic success when the same opioid regimen is prescribed, or even the same opioid, to two patients with the same pain condition. In fact, the titration ceiling of an opioid dose is set only by the achievement of analgesia or the occurrence of adverse effects, and these events cannot be predicted for individual patients.

To provide a framework for maximizing the efficacy of opioid use in patients with chronic pain, Portenoy et al [5] proposed that clinicians seek to achieve maximum analgesia while limiting toxicity using a strategy that involves gradually increasing the opioid dose until the most favorable balance (as defined by the clinician and patient working together) is reached. It is also useful to categorize the various factors that influence opioid efficacy in chronic pain patients as mainly patient-centered and drug-centered.

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Patient-centered characteristics

Patient-centered characteristics are factors peculiar to an individual patient (beyond those created by the pain syndrome) that affect opioid responsiveness [5]. An example of a common patient-centered characteristic is a predisposition to opioid side effects that is manifest when a patient has exceptionally high plasma levels of opioid from a single dose (a pharmacokinetic response) or has an exaggerated response to modest plasma levels of opioid (a pharmacodynamic response). Such a predisposition to side effects may make it impossible or difficult to achieve adequate analgesia with opioids.

Another patient-centered characteristic is psychologic distress (including depression and anxiety) which, if untreated, reduces the efficacy of many pain therapies [6]. Fortunately, treatment in the form of psychologic interventions or administration of a psychotropic medication can restore the patient's ability to benefit from opioid therapy.

A situation affecting opioid efficacy that is signaled by a patient's history but is actually a combination of pain- and drug-characteristics is the fact that patients who are accustomed to high doses of opioids may require larger than normal incremental increases to achieve analgesia. Note that escalating opioid requirements may signal the onset of disease progression in the case of cancer related pain or of tolerance if tumor expansion has been excluded.

Another obvious area in which patient characteristics will have an impact is genetics. Now that we are receiving a flood of genetic information, it may soon be possible to discover which, if any, genetic determinants alter the density or proportion of opioid receptors or change the expression of opioid isoforms in an individual patient. This will give us new tools to predict a patient's response to opioid therapy or tailor a particular opioid to a specific individual.

Pain-centered characteristics

Pain-centered characteristics are those factors peculiar to a pain condition that generally affect responsiveness to opioids. An example of a pain-centered characteristic is the temporal pattern of the pain [7]. Opioids tend to be less effective in dealing with pain of rapid onset, perhaps because the rapidity of the pain response outstrips our ability to deliver the drug fast enough to bind to the receptors. Two more pain-centered characteristics are intermittency and severity, both of which will respond less favorably to opioids unless large or quickly escalating doses that often cause intolerable side effects are administered (which, of course, renders the opioids of dubious value) [8].

The type of pain, that is, the manner in which it is generated, is also a pain-centered characteristic. Neuropathic pain arises in response to an injury of the central or peripheral nervous system and produces a burning sensation. Postherapeutic neuralgia, complex regional pain syndrome, nerve injury, diabetic neuropathy, and chemical neuropathy are examples of neuropathic associated pain. A different sort of pain, somatic or nociceptive pain, arises when peripheral

receptors and somatic sensory afferent nerves are activated but peripheral nerves remain undamaged. Poorly localized somatic pain is termed, "visceral pain," and is frequently deep, aching, and cramping. For years, clinicians reserved opioids for treatment of nociceptive pain, believing that they were ineffective against neuropathic pain [9,10]. There is evidence now to support the use of opioids to treat neuropathic pain [11–15], but, even though neuropathic pain responds to standard doses of opioids [16–19], less analgesia is often achieved than for nociceptive pain.

Drug-centered characteristics

Drug-centered characteristics are, as the name implies, drug-specific effects, and different opioids may have different effects in the same patient, with one drug offering adequate analgesia and few side effects and another failing to provide adequate analgesia or yet another causing intolerable side effects [5,20]. These differences may be caused by the varying binding properties of different opioids on variously sensitive or density-related receptor subtypes (κ, μ, δ) or isoforms [21]. (Drug-centered characteristics obviously include aspects of patient-centered characteristics.)

Another drug-centered characteristic is the fact that the efficacy of an opioid pain regimen can often be enhanced by the adjuvant use of agents such as N-methyl-D-aspartate (NMDA) antagonists, calcium channel blockers, clonidine, or low-dose opioid antagonists. NMDA antagonists may directly reduce pain that is less responsive to opioids or may reverse opioid tolerance. The non-competitive NMDA antagonist, ketamine, for example, blocks the dorsal horn ion channel from releases of glutamate and exhibits a synergism with opioids [22]. In one study, for example, cancer patients in whom high-dose morphine no longer provided analgesia were able to regain analgesia with half the morphine dose plus 110 mg per day of ketamine [23]. Ketamine plus morphine also provided analgesia to cancer patients with uncontrolled neuropathic pain who were evaluated in a double-blind, crossover study [24]. Ketamine use requires careful monitoring to avoid associated psychotomimetic side effects (illusions, disturbing dreams, delirium). Such adverse effects can be preempted, however, with the addition of benzodiazepines or haloperidol at doses of 2 to 4 mg per day [25].

Investigation into the adjuvant use of calcium channel blockers revealed that adjuvant nimodipine provided analgesia with a decreased morphine dose in 16 of 23 patients but failed in 2 patients and was discontinued in 5 patients (another example of the intersection of patient- and drug-centered characteristics) [26]. Another study, however, found no benefit with nimodipine 30 mg by mouth every 8 hours in cancer patients on sustained-release morphine [27]. It is possible that the hemodynamic properties of calcium channel blockers will reduce their usefulness in an opioid analgesic regimen.

The alpha-2 adrenergic agonist, clonidine, however, may prove to be a beneficial addition to an opioid regimen. Clonidine inhibits primary afferent transmission and substance P release [28] and, when used intraspinally, can reduce

intractable, neuropathic cancer pain [29]. Clonidine likely operates independently of opioid pathways [30], and, instead of augmenting morphine-induced suppression of dorsal horn neurons may exert a direct effect [31].

The opioid antagonist, methadone, which activates μ-opioid receptors and is an NMDA receptor antagonist, may be the most effective opioid against neuropathic pain or pain related to tolerance [32]. The NMDA antagonist, dextromethorphan, also potentiates analgesia [33], and it may be especially useful because it has a good antitussive safety profile [34] and lacks psychomimetic effects. Randomized, controlled trials, however, have failed to show beneficial effects on pain of dextromethorphan or of another NMDA antagonist, amantadine [35,36].

On the other hand, low-dose opioid antagonists enhance the analgesic potency of opioids. In one double-blind study, low-dose naloxone plus pentazocine provided greater analgesia than could be achieved with high-dose morphine in 100 tooth extraction patients [37]. Another double-blind study showed that a 24-hour infusion of low-dose naloxone (narcan) decreased patient-controlled morphine use by 60 hysterectomy patients from 60 to 40 mg and concomitantly reduced the incidence of morphine side effects [38]. In 120 lower abdominal surgery patients participating in a randomized, double-blind, placebo-controlled trial, ultra-low-dose intravenous nalmefene (a pure μ receptor antagonist) enhanced postoperative patient-controlled analgesia while also reducing the incidence of nausea and pruritus [39].

Opioid side effects

General principles

Although any given opioid is associated with a constellation of potential side effects, each patient will exhibit a unique response to that pharmaceutical. These varying responses mirror the varying abilities of patients to tolerate side effects or, indeed, to respond to efforts to treat side effects. For example, similar doses of an opioid may produce different side effects and patients suffering the same pain condition may experience different side effects from the same treatment. The best way to predict how any given patient will respond to an opioid, therefore, is to base that prediction on any experience the patient may have had with that drug.

Source of opioid side effects

Various opioid receptors are implicated for various side effects. The μ 2 receptor is associated with sedation and respiratory depression; the κ receptor with dysphoria; and the σ receptor with dysphoria, depersonalization, and hypnogogic imagery. In addition, toxic opioid metabolites can lead to side effects, hypoproteinemia can lead to increased availability of "free drug," renal impairment may decrease clearance, and hepatic dysfunction may alter drug metabolism.

Strategies

Because side effects may limit a patient's acceptance of opioids and a clinician's willingness to prescribe this effective pain therapy, various strategies have been developed to counter side effects. First, patients are encouraged to report side effects and routinely assess their impact. Once what the patient is experiencing is known, specific agents can be used to counter the effects. Fortunately, with opioids, patients develop tolerance to most side effects within 3 to 7 days, which is faster than they develop tolerance to the ability of a particular dosing regimen to provide pain relief. Thus, intermittent use of opioids is avoided, because this prevents the development of tolerance to side effects. The side effects that may be mitigated by tolerance include sedation, nausea, cognitive impairment, pruritus, dysphoria, hypnogogic imagery, and respiratory depression. Unfortunately, no tolerance develops for constipation or myoclonus. During the first week of opioid use, therefore, any nausea is treated, for example, with an anti-emetic to give tolerance a chance to develop. Should side effects become intolerable or persist, we try using a different opioid, changing the opioid dosing regimen, or adding supplemental medications.

Nausea or vomiting

The side effect of nausea or vomiting may be unpredictable, especially in ambulatory patients. Thus, it is commonly encountered in the outpatient population. Nausea and/or vomiting occurs because opioids directly stimulate the chemoreceptor trigger zone, increase antral gastric tone, and decrease gastrointestinal motility. As noted earlier, tolerance usually develops, but the persistence of symptoms may decrease opioid compliance. To treat nausea and/or vomiting, one may consider metoclopramide, cisapride, haloperidol, prochlorperazine, dimenhydrinate, transdermal scopolamine, ondansetron, or dexamethasone. Should these agents be ineffective, then changing the route of opioid administration (for example, to oral from intravenous) or rotating opioids is indicated.

Constipation

Constipation is arbitrarily defined as experiencing fewer than three bowel movements per week and is almost always a side effect of opioid use. The symptoms of constipation include experiencing hard, dry stools, straining, incomplete evacuation, bloating, abdominal distension, and increased gastric reflux. Opioid-induced constipation is also known as "opioid bowel dysfunction."

Opioids lead to constipation through μ receptor stimulation of the enteric nervous system, which influences gastrointestinal motility, secretion, absorption, and blood flow. Opioids, thus, exert a direct, local effect on the bowel. Opioids may also change the autonomic nervous system outflow to the gut. Thus, a decreased tendency is seen for constipation with the use of transdermal fentanyl as opposed to oral or parenteral opioids. As mentioned earlier, tolerance to constipation rarely develops.

Not only is constipation the most common side effect of opioid use, it may be most debilitating and often leads to patient noncompliance. Constipation is exacerbated by diabetes, hypercalcemia, hyperkalemia, uremia, hypothyroidism, dehydration, increased age, decreased physical activity, low-fluid or fiber intake, mechanical obstruction, neurologic disorders, autonomic nervous system failure, and ondansetron.

The goal of treatment is to restore gastrointestinal tone and increase fluid content. Nonpharmacologic treatment options, thus, include increasing dietary fiber, fluid intake, and mobility or ambulation. Pharmacologic options include administration of stool softeners and stimulant laxatives, such as docusate sodium (Colace) and senna (Senokot); of osmotic agents, such as a 70% sorbitol solution or milk of magnesia; of mineral oil (softens and lubricates stool); of bulk-forming laxatives, such as psyllium (Metamucil) or bran (these therapies require a high fluid intake of 1200 cc per day or the patient risks developing hard stools that can lead to intestinal obstruction); and of prokinetic agents (if nausea/vomiting/ bloating/early satiety is related to delayed gastric emptying), such as metoclopramide (Reglan).

Additional pharmacologic strategies include administration of one of the tertiary opioid antagonists, naloxone, naltrexone, and nalmefene, which are centrally and peripherally active at the μ, δ, and κ receptors. The tertiary antagonists can reverse opioid-induced bowel dysfunction, but the drugs penetrate the central nervous system and can lead to opioid withdrawal and analgesia antagonism. A possible choice among this class of agents could be 2 amps naloxone given three times a day in applesauce.

The quaternary opioid antagonist, methylnaltrexone, is associated with fewer delays in gastric motility and induces laxation without causing withdrawal or decreased analgesia.

Available laxatives and their mechanism of action include:

Bisacodyl (Dulcolax), a direct colonic stimulant, delivered by way of tablet, liquid, or enema;

Castor oil or mineral oil, a liquid, softens and lubricates stool;

Docusate sodium (Colace), softens stool and is delivered orally or by way of enema;

Docusate plus casanthranol (Peri-Colace), softens stool and is a stimulant laxative available in tablet or liquid formulations;

Glycerin, softens and lubricates stool, delivered per rectum or by way of enema;

Lactulose, converts NH_3 to NH_4, delivered by way of syrup, powder, or enema;

Magnesium citrate, a liquid with an osmotic effect in the lumen;

Magnesium hydroxide (Milk of Magnesia), osmotic effect in the lumen, available as a liquid or tablet;

Methylcellulose (Citrucel), osmotic effect in the lumen, available as powder;

Sorbitol, a liquid with an osmotic and cathartic effect;

Senna (Senokot), a stimulant laxative, available in tablet, granule, syrup, or liquid formulations;

Polyethyleneglycol (Miralax), a powder with osmotic and cathartic effects in the lumen;

Psyllium (Metamucil), absorbs water to bulk-up stool, available in powder, granule, or wafer formulations.

Sedation

Sedation affects 20% to 60% of patients receiving continuous opioid therapy, but tolerance usually develops. Consider discontinuing concurrent central nervous system depressants or rotating to another opioid to reduce the prevalence and severity of sedation. Otherwise, amphetamines (eg, dextroamphetamine) may reduce sedation and cognitive dysfunction associated with opioid use. Agents such as caffeine, methylphenidate, modafinil (Provigil), and sibutramine (Meridia) may be helpful in countering opioid-induced sedation, although they are only FDA approved for the treatment of attention deficit or hyperactivity disorder, narcolepsy, fatigue, and obesity (sibutramine). In one study, administration of methylphenidate not only decreased confusion and drowsiness but also increased analgesia in cancer patients [40].

Psychostimulants are often used to decrease somnolence, augment analgesia, and improve cognitive performance. Use of these drugs, however, is associated with the following adverse effects: hallucinations, delirium, psychosis, decreased appetite, tremor, dependence, and tachycardia. In addition, psychostimulants may be contraindicated in patients with a history of substance abuse or paroxysmal tachyarrhythmias.

Cognitive dysfunction

Mild cognitive impairment is not unusual after a patient initiates opioid therapy or after dose escalation, and this usually improves due to tolerance. The potential of opioids for causing temporary, mild cognitive impairment must be balanced by the fact that intense, untreated pain itself can alter mood, and depressed mood can impair neuropsychologic performance.

Studies of continuous opioid use in patients with chronic, non-cancer pain found that opioids do not have a deleterious effect on attention, vigilance, or memory [15,41]. Another investigator conducted neuropsychologic tests of attention, psychomotor speed, and memory and found patients retain stable cognitive function even after 6 to 12 months of opioid therapy [42]. Administration of neurologic and psychologic function tests designed for professional motor vehicle drives to cancer patients receiving mean 209 mg of oral morphine each day found that morphine had only slight, selective effects on functions pertinent to driving [43].

Haldol is typically used to manage severe cognitive dysfunction manifesting as delirium, and a benzodiazepine is added if agitation is problematic (but this drug may exacerbate sedation or confusion). As with many opioid side effects, cognitive dysfunction may be mitigated by opioid rotation.

Myoclonus

Myoclonus is the occurrence of brief synchronous or asynchronous muscular contractions. This condition is rare and unpredictable and seems to be limited to patients receiving high doses of oral or intrathecal opioids. The suspected cause of this condition is that neuroexcitatory morphine metabolites (morphine-3-glucuronide) may alter the glycine-ergic or GABA-ergic inhibitory control exerted over the low threshold afferents that converge on nociceptive neurons in the spinal cord [44–47]. (Glycine receptors help regulate afferent stimuli and maintain normal sensory processing.).

Treatment includes decreasing the dose; rotating the opioids; or adding clonazepam, diazepam, or midazolam (benzodiazepines that activate GABA in the central nervous system) to the treatment regimen. Opioid antagonists are not generally useful in reversing myoclonus.

Pruritus

Pruritus is a common and distressing side effect of opioid use. It is often localized to the face, neck, and upper thorax. Although the etiology of opioid-induced pruritus is unknown, it may be the result of a central effect or of histamine release (histamine stimulates unmyelinated primary afferent nerves in the epidermis). Others have postulated that serotonin may activate peripheral serotoninergic receptors that induce itching or that a plexus of polymodal nociceptors in the epidermo-dermal junction may transduce the pruritic sensation by way of unmyelinated C-fibers

Changing the route of opioid administration does not seem helpful in treating pruritus, but opioid rotation may be a useful strategy. Other treatment includes cooling the skin, stimulating the area with a TENS unit, and/or applying calamine lotion, EMLA cream, or capsaicin (0.025%), or using morphine hydrochloride instead of morphine sulfate. In addition, switching to oxycodone, oxymorphone, fentanyl, or hydromorphone may reduce the histamine response. Finally, antihistamines, histamine (H2) blockers, low-dose naloxone, 10 mg bolus doses of propofol, tricyclic antidepressants, paroxetine, or serotonin (5HT3) antagonists can be administered.

Organ toxicity

Long-term opioid therapy is not associated with major organ toxicity in cancer patients or in patients on methadone maintenance [48,49].

Hypogonadism

In the 1970s, researchers noted that heroin users and patients receiving methadone maintenance therapy experienced a decreased libido, impotence, and amenorrhea [50–53].

Today, we know that continuous opioid use causes sex organ atrophy and suppresses serum testosterone in humans but that testosterone levels generally recover 1 month after ending opioid use. Several studies report associations between the use of intrathecal opioids and amenorrhea, impotence, and decreased libido.

The hypothesized mechanism of action includes opioid-induced hyperprolactinemia causes exogenous opioids (either intrathecal or perhaps oral) to bind to opioid receptors in the hypothalamus where they inhibit Gonadotrophin releasing hormone (GnRH) release, then inhibit luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release from the pituitary, which, in turn, decreases gonadal release of estradiol, testosterone, and progesterone (Fig. 1).

Hypogonadism is a concern because of the increased interest in and use of opioids (oral, intrathecal, epidural) for the treatment of chronic, non-cancer pain, especially in a younger patient population. Several retrospective studies [54–58] and one prospective study (Roberts et al 2000) report associations between intrathecal opioids and amenorrhea, impotence, and decreased libido. Further, intrathecal opioids may alter quality of life by impairing fertility and sexual pleasure.

The lowered testosterone in men and suppression of FSH and LH in postmenopausal women are indicative of central hypothalamic–pituitary-gonadal axis suppression. Testosterone deficiency in men significantly reduces bone mineral density, which can cause an increase in bone fractures. Treatment with testosterone restitution therapy can restore serum levels to normal and bone mineral density to their age-dependent reference points. In women, estrogen or progesterone deficiency can lead to infertility.

In 1994, investigators conducted a retrospective study of six male patients who had been receiving intrathecal morphine (n = 5) or hydromorphone hydrochloride (Dilaudid) (n = 1) for 47 months [54]. The patients were concurrently supplementing the intrathecal therapy with oral opioids to control pain from failed back surgery syndrome, complex regional pain syndrome type 1, hemangioma, multiple abdominal lipomas, postherpetic neuralgia, and spondylolisthesis with arachnoiditis. All patients reported reduced libido, and four experienced impaired sexual functioning with intrathecal opioids within 1 month of treatment. All but one patient denied sexual dysfunction before intrathecal therapy. Five of the patients had sub-normal serum testosterone levels with a mean for the group of 119.8 mg/dl (350–1500). Treatment with intramuscular testosterone benefited three patients, and reducing the morphine dose led to improved libido in a fourth.

In 2000, Abs et al [57] reported their retrospective analysis of 73 patients (29 women 44 men, average age 49 years) who had been receiving intrathecal morphine or hydromorphone (mean dose 4.8 mg) for a mean of 26 months to treat the pain associated with failed back surgery syndrome, chronic pancreatitis, complex regional pain syndrome type 1, phantom limb pain, or spinal stenosis. The investigators conducted a comparative analysis in 20 patients (11 men and 9 women) with comparable pain syndromes who were candidates for opioid treatment but not yet receiving it. Of the men, 95.8% reported a decrease in libido and potency soon after initiating intrathecal opioids, and 86% had serum
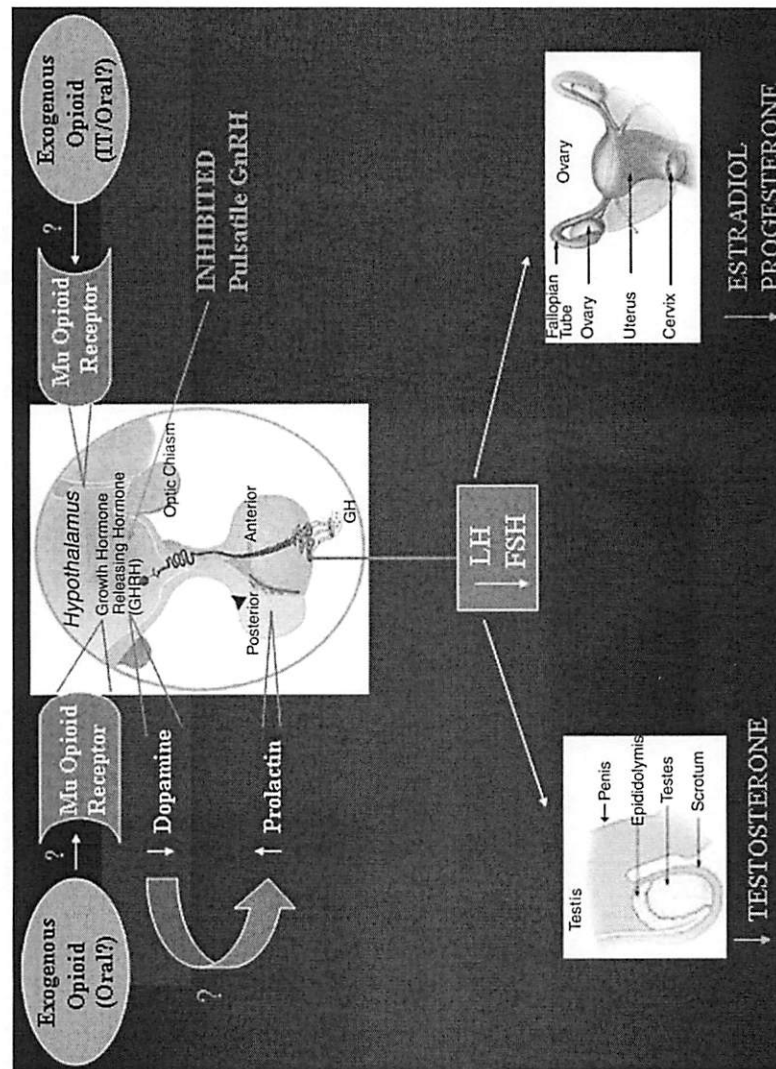
Fig. 1. Hypothesized mechanism of opioid induced hypogonadism.

testosterone of less than 9.0 nmol/L (nl 9–26 nmol/L). Compared with controls, the treatment group showed no difference in sex hormone binding globulin (SHBG) or FSH; but 69% had significantly lower serum LH levels. Of the women, 68% reported decreased libido after starting opioids; of 21 premenopausal women, 14 became amenorrheic, and 7 had irregular menses. Compared with controls, the treatment women had lower serum LH, FSH, estradiol, and progesterone, but no effect was seen on prolactin secretion. Androgen replacement therapy in 14 men improved libido in 10. Estrogen and progesterone supplementation in 12 premenopausal women improved libido in 7. The investigators concluded that long-term intrathecal opioid therapy induces hypogonadotropic hypogonadism in a high percentage of patients, which is clinically important in most men and premenopausal women.

Another retrospective analysis published in 2001 involved 88 patients (58 women, 30 men, mean age 53 years) who had suffered chronic, non-cancer pain for an average of 10 years and had been treated with intrathecal opioids for average of 36 months [58]. Morphine (at widely varying doses) was the initial intrathecal agent in 93% of these patients who then had trials of other agents (hydromorphone, sufentanil or bupivacaine, or clonidine). The most common diagnosis for these patients was lumbar spinal pain or radicular pain after failed back surgery syndrome. In this study, the investigators used a questionnaire to gather data and found 71% of the men reported decreased libido and erectile difficulty; 48% of the women reported decreased libido, and 47% of the women described symptoms of oligomenorrhea or amenorrhea. All of these symptoms appeared after intrathecal opioid administration.

In a prospective, uncontrolled, non-randomized study published in 2002, investigators evaluated 10 men (mean age of 52 years) with an average pain duration of 11 years, who suffered from failed back surgery syndrome or complex regional pain syndrome type 1 [59]. The mean dose of intrathecal morphine was 2.6 mg at 1 week, 3.5 mg at 4 weeks, and 5.3 mg at 12 weeks, and oral opioid supplements were permitted. The patient assessments at these treatment time intervals and at baseline included questions about libido and erectile dysfunction. The investigators also measured serum testosterone, LH, FSH, prolactin, and SHBG. Most of the patients reported poor libido and abnormal erectile function at baseline, but more reported sexual dysfunction toward 12 weeks (poor libido, not sexually active, erectile difficulty). Serum testosterone decreased significantly from baseline as did FSH levels. The investigators concluded that intrathecal opioid treatment suppresses hypothalamic-pituitary-gonadal axis and decreases serum testosterone.

The implications of these findings should lead clinicians to consider discussing hypothalamic-pituitary-gonadal axis suppression as part of the informed consent process that precedes initiation of intrathecal opioid therapy. Patients should understand the possibility that this therapy may lead to sexual dysfunction, infertility, bone mineralization changes, and possible hormone replacement therapy for treatment. Clinicians should consider conducting hypothalamic-pituitary-gonadal axis surveillance at initiation of intrathecal therapy.

Treatment strategies for hypogonadism in men include applying testosterone gel, 5 g per day or injecting testosterone intramuscularly, 200 mg every 2 weeks. It is important to monitor serum testosterone in the first 4 weeks of therapy, then every 6 months during treatment. Monitoring clinical signs of hypogonadism such as decreased libido or altered sexual activity is also recommended. In premenopausal women, oral contraceptive therapy may be beneficial. Postmenopausal women are more difficult to treat now that serious problems have been related to hormone replacement therapy. Lowering the dose may be useful, and withdrawing intrathecal therapy may be necessary.

In short, intrathecal opioids even at small doses can disrupt the hypothalamic-pituitary-gonadal axis and thus cause reproductive and metabolic disturbances. HPG suppression probably occurs at the level of the hypothalamus because opioid receptors have been located in the hypothalamus and not the anterior pituitary [60]. Though intrathecal opioids can improve quality of life through pain reduction, they may limit quality of life by inducing sexual dysfunction. Consequently, physicians should consider monitoring testosterone, estrogen, and progesterone during therapy, then treating hypogonadism with replacement therapy, dose reduction, or intrathecal therapy withdrawal if necessary.

Summary

Opioids can provide effective analgesia by way of different routes of administration without limiting side effects for most patients suffering from chronic pain when clinicians properly manage the pertinent patient-, pain-, and drug-centered characteristics. Randomized, placebo-controlled, prospective studies are needed to establish a causal relationship between opioids and hypogonadism. Many of the current studies are retrospective, which only lead to suggestive associations between opioids and hypogonadism and incorporate bias. Clinicians may incorporate available tools, including urine toxicology tests, to assess any aberrant behavior on the part of patients using opioids and to maximize compliance with an opioid regimen.

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