Pain Physician 2007; 10:479-491• ISSN 1533-3159

Invited Review

Opioid Analgesia: Perspectives on Right Use and Utility

Jane C. Ballantyne, MD

From: Massachusetts General Hospital Pain Center, Boston, MA.

Dr. Ballantyne is Associate Professor from Harvard Medical School and Chief, Division of Pain Medicine Massachusetts General Hospital Pain Center, Boston, MA

Address Correspondence:
Jane C. Ballantyne, MD
Massachusetts General Hospital
Pain Center
15 Parkman Street, WACC 333
Boston, MA 02114
E-mail: jballantyne@partners.org

Funding: none.
Conflict of Interest: None.
Manuscript received on: 04/16/2007
Revisions accepted: 04/20/2007
Accepted for publication on: 04/24/2007

Free Full manuscript:
www.painphysicianjournal.com

The ability of opioids to effectively and safely control acute and cancer pain has been one of several arguments used to support extending opioid treatment to patients with chronic pain, against a backdrop of considerable caution that has been based upon fears of addiction. Of course, opioids may cause addiction, but the "principle of balance" may justify that "…efforts to address abuse should not interfere with legitimate medical practice and patient care." Yet, situations are increasingly encountered in which opioid-maintained patients are refractory to analgesia during periods of pain, or even during the course of chronic treatment. The real question is whether analgesic efficacy of opioids can be maintained over time. Overall, the evidence supporting long-term analgesic efficacy is weak.

The putative mechanisms for failed opioid analgesia may be related to tolerance or opioid-induced hyperalgesia. Advances in basic sciences may help in understanding these phenomena, but the question of whether long-term opioid treatment can improve patients' function or quality of life remains a broader issue.

Opioid side effects are well known, but with chronic use, most (except constipation) subside. Still, side effects can negatively affect the outcomes and continuity of therapy. This paper addresses 1) what evidence supports the long-term utility of opioids for chronic pain; 2) how side effects may alter quality of life; 3) the nature of addiction and why it is different in pain patients, and 4) on what grounds could pain medication be denied? These questions are discussed in light of patients' rights, and warrant balancing particular responsibilities with risks. These are framed within the Hippocratic tradition of "producing good for the patient and protecting from harm," so as to enable 1) more informed clinical decision making, and 2) progress towards right use and utility of opioid treatment for chronic pain.

Key Words: Opioids, chronic pain, addiction, side effects, utility, ethics

Pain Physician 2007; 10:479-491

Opioid treatment of chronic pain – must we do it?

Kathleen Foley, one of the first of a generation of opioid advocates who responded to the iniquities of pain under-treatment brought about by twentieth century drug regulations quotes one of her patients:

"I would rather be in pain than be considered an addict".

As Dr Foley herself says: "This clinical anecdote captures the reality of the under-treatment of pain, which is one of the serious, unintended consequences of the war on drugs."

When it became necessary, at the beginning of the twentieth century, to regulate addictive drugs (including opioids) because of rampant street use, opioid treatment of pain declined, especially in the

U.S. The U.S. differs from other Western countries because, unlike the other countries, it made it illegal for physicians to prescribe opioids for addiction. Physicians in the U.S. could face loss of license, loss of practice and possible imprisonment, and in fact, still do. The chilling effects these regulations have had on opioid treatment of pain have been countered by pain (opiate) advocacy, which successfully restored opioid treatment of acute and cancer pain. The ability of opioids to effectively treat severe and short-lived pain is now firmly established. The experience has taught that during short-term treatment, addiction virtually never arises de novo (1).

The ability of opioids to effectively and safely treat acute and cancer pain is one of several arguments that is used to support extending opioid treatment to patients with chronic pain, where there had previously been considerable caution based on fears of addiction. It is argued that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering (2), because uncontrolled pain may have deleterious physical effects (3-5), and because persistent pain destroys people's autonomy, dignity, and decision-making capacity. Of course, it is also recognized that opioids may cause addiction, but the "principle of balance" states that "efforts to address abuse should not interfere with legitimate medical practice and patient care" (6,7). At the start of the movement towards liberalization of opioids to treat chronic pain there seemed a strong ethical basis for compelling opioid treatment of pain, and no ethical basis for withholding treatment since addiction arose only rarely during legitimate treatment of pain.

What have we learned?

One of the foundations of the argument for use is the unquestioned and unique analgesic efficacy of opioids. There is no other medical intervention capable of providing relief from severe pain. It was known from the clinical experience of opioid maintenance treatment for addicts that patients on stable regimes can be fully functional in society and in the workplace despite their chronic use of substances known to affect cognitive function (8,9), so it did not seem at all unreasonable to extend opioid treatment to those suffering chronic pain. Reports from treatment programs pioneering structured opioid regimes for the treatment of chronic pain suggested that most patients in these programs can attain good analgesia and function without developing craving (10-12). Early experience also suggested that while tolerance to the analgesic effects of opioids could be expected, this could always be overcome by dose escalation. However, the ongoing experience suggests a less rosy state of affairs. When formal trials of opioids for chronic pain began to be conducted, it was found that 50% of patients abandon the treatment because of either lack of efficacy or intolerable side effects (13). Increasingly, situations are encountered where patients whose pain is treated chronically with opioids become refractory to the treatment when there is a pain exacerbation or new pain complaint, or even during the course of chronic treatment. It has also become apparent that the neuroendocrine effects of opioids may have significant clinical effects during long-term treatment, and that behavioral problems, if not addiction, interfere with treatment success in a substantial proportion of patients treated long-term.

What is the evidence?

Efficacy

Short-term analgesic efficacy

Randomized trials (RCTs) have been conducted to test the analgesic efficacy of opioids for various chronic pain conditions, including the arthritides and various neuropathic pain conditions. Table 1 lists these trials and summarizes their results (14-31). Measured pain scales from the RCTs show a statistically significant improvement across all the studies, both in case of painful arthritides and neuropathic pain. The question underlying the trials was whether chronic pain conditions, particularly neuropathic pain conditions, are opioid responsive (There had been a traditionally held view that neuropathic pain is not opioid responsive). The randomized studies make it clear that contrary to this traditional belief, neuropathic pain is indeed opioid responsive, although larger doses are required than those needed to treat nociceptive pain (20,24,27-32). It must be noted that these trials are conducted only over the short term (usually weeks, although one trial reached 32 weeks) (18,33), and that doses used in these trials are generally moderate (up to 180 mg morphine or morphine equivalent per day).

Long-term analgesic efficacy

The real question, however, when embarking on a course of opioid treatment for chronic pain, is whether analgesic efficacy is maintained over time. Here it is necessary to turn to less rigorous forms of evidence,

Table 1. *Controlled Studies: Summary of results*

Reference	Study type	Type of pain	n/N	Drug	Daily dose (mg)	Follow-up	Pain Relief	Level of Function
Kjaersgaard-Andersen (14)	RCT	Osteoarthritis of the hip, in elderly patients	83/75	Codeine with acetaminophen vs. acetaminophen	180	4 weeks	+	
Moran (15)	RCT, crossover	Rheumatoid arthritis	20	CR morphine vs. placebo	up to 120	10 weeks	+	0
Arkinstall (16)	RCT	Musculoskeletal in most patients	46	CR codeine vs. placebo	200-400	1 week	+	+
Moulin (17)	RCT, crossover	Musculoskeletal or soft tissue	46	CR morphine vs. active placebo (benztropine)	up to 120	11 weeks	+	0
Jamison (18)	RCT	Back pain	24/12	Oxycodone or CR morphine plus oxycodone vs. naproxen	Up to 130 (morphine equivalent)	16-32 weeks	+	+
Sheather-Reid (19)	RCT, crossover	Cervicobrachial syndrome, fibromylagia	6	Codeine vs. ibuprofen or placebo	120	12 weeks	0	0
Watson (20)	RCT, crossover	Postherpetic neuralgia	38	CR oxycodone vs. placebo	28-62	8 weeks	+	+
Caldwell (21)	RCT	Osteoarthritis	71/36	CR oxycodone or oxycodone with acetaminophen vs. placebo	up to 60	8 weeks	+	+
Peloso (22)	RCT	Osteoarthritis hip and knee	31/35	CR codeine vs. placebo	up to 400	4 weeks	+	+
Roth (23)	RCT	Osteoarthritis	44/(44) /45	CR oxycodone, high dose (or low dose) vs. placebo	up to 40	14 weeks	+ (0)	+ (0)
Huse (24)	RCT, crossover	Phantom limb pain	12/12	CR morphine vs. placebo	70-160 (300 in one patient)	4 weeks	+	0
Caldwell (25)	RCT	Osteoarthritis	73/73/ 76/73	CR morphine (24 hr) or CR morphine (12 hr) vs. placebo	30	4 weeks	+	0
Maier (26)	RCT, crossover	Mixed	49	CR morphine vs. placebo	up to 180	2 weeks	+	+
Raja (27)	RCT, crossover	Postherpetic neuralgia	76/44	CR morphine or methadone vs. placebo (or tricyclic antidepressant)	15-225 morphine, 40-140 methadone	8-24 weeks	+ (0)	0
Gimbel (28)	RCT	Diabetic neuropathy	63/52	CR oxycodone vs. placebo	20-120	6 weeks	+	+
Morley (29)	RCT, crossover	Mixed neuropathic	11/(18)	Methadone high dose (or low dose) vs. placebo	20 (10)	20 days	+ (0)	
Rowbotham (30)	RCT	Peripheral and central neuropathic pain	43/38	High-dose levorphanol vs. low-dose levorphanol	up to 11.8 (approximately 60 morphine equivalent)	8 weeks	+	0
Watson (31)	RCT, crossover	Diabetic neuropathy	35/36	CR oxycodone vs. active placebo (benztropine)	10-40	4 weeks	+	+

since it is not feasible to conduct RCTs over prolonged periods. The only knowledge of long-term analgesic efficacy comes from surveys, case series, open-label follow-up studies in association with some RCTs and epidemiological studies (13,33-36). Many of the case and case series reports cite satisfactory analgesia for all patients who stay on the treatment. A review of the open-label follow-up studies, however, has shown that 56% of patients abandon the treatment because of lack of efficacy or side-effects (13). Moreover, many

opioid trials utilize enrichment in their protocols (patients who do not respond are selected out during a pre-trial phase), and there is an unusually high drop-out rate across opioid trials during enrichment, likely reducing the internal validity of the trials (37). A recent epidemiological study from Denmark, where opioids are prescribed liberally for chronic pain, demonstrated worse pain, higher healthcare utilization and lower activity levels in opioid treated patients compared to a matched cohort of chronic pain patients not using opioids (35), suggesting that even if some patients benefit, the overall population does not when opioids are prescribed liberally. Overall, the evidence supporting long-term analgesic efficacy is weak.

Treatment in the long-term studies has been based on the traditional premise that dosage should be titrated upwards to overcome pharmacological tolerance, this being an inevitable consequence of long-term opioid treatment. In fact, the majority of patients are able to reach a stable, non-escalating effective dose, and analgesic tolerance seems to stabilize over time. Some patients, however, fail dose escalation, reporting no change or a worsening of their pain, despite high doses of opioids (38,39). Some report actual improvement in pain once opioid treatment is discontinued (40,41). The putative mechanisms for failed opioid analgesia may be related to rampant tolerance or opioid-induced hyperalgesia (38). Advances in basic science help understand these phenomena and their clinical relevance, but it remains unclear exactly what aspects of treatment – drug choice, dose or timing – cause these phenomena to compromise opioid efficacy. The premise that tolerance can always be overcome by dose escalation is now questioned (33).

Function and quality of life

Whether long-term opioid treatment can improve patients' function or quality of life (QOL) is clearly a broader issue than whether opioids can reduce a pain score. Surprisingly, only a few of the existing opioid studies have focused on this issue, and there are few available data. Several case series report on function, and these consistently report improvement, although the quality of this type of evidence must be questioned (42). Epidemiological studies are less positive, and report failure of opioids to improve QOL in chronic pain patients (43). The RCTs provide mixed results on function (Table 1); some find improvement, others do not. The focus of the functional testing in studies varies with the primary interest of the investigators – for example, physical function, joint tenderness, activity levels and grip strength for arthritis patients, sleep, anxiety, psychomotor function and disability scores for back pain patients. This variability precludes an overall assessment. Moreover, RCTs are only able to assess short-term functional achievements. Studies specifically assessing cognitive function, including the ability to drive and operate machinery, find that cognitive function, manual dexterity and reaction times are maintained provided a stable dose of opioid is used (44-48). This is not true when the dosing is irregular or escalates (44,49,50). This becomes an important issue if the goal of treatment is to return to work and to full functioning.

Side effects

Common side effects

Opioid side effects are well known and include respiratory depression, nausea, sedation, euphoria or dysphoria, constipation and itching. With chronic use, most side effects subside, since tolerance seems greater to side effects than to analgesic effects. Constipation is an exception, and there appears to be no tolerance to the direct slowing effects of opioids on the bowel, so that constipation remains a high risk and usually requires treatment. Although common side effects (except constipation), usually subside during chronic treatment, they can sometimes interfere to the extent that patients abandon the therapy (13). Respiratory depression is rarely seen during chronic opioid therapy, but since this is a potentially lethal side effect, one should remain vigilent. The situation in which it most likely arises during chronic opioid pain treatment is when dose is rapidly escalated, dosing errors occur, or when drugs with unpredictable pharmacokinetics such as methadone are used (51).

Hormonal and immune effects

Long-term opioid therapy results in clinically relevant suppression of both hypothalamopituitary -adrenal and -gonadal axes with suppression in testosterone, estrogen, and cortisol, resulting in male and female infertility, decreased libido, aggression and drive and galactorrhea. These effects have been demonstrated in past addicts treated with methadone maintenance (52), as well as in opioid-treated chronic pain patients (53). Clinically, testosterone deficiency is the most frequently manifest of the deficiencies, and male patients can benefit from testosterone replacement (54,55). The effects are exaggerated when opioids are delivered intrathecally (55-57).

Preclinical research convincingly demonstrates that opioids alter the development, differentiation

and function of immune cells (58, 59). Immune modulation is complex, and pain as well as opioids can suppress immune function (60). Whether or not opioids have a deleterious effect on immune function, and in what circumstances is unclear, although prolonged exposure and abrupt withdrawal have both been implicated in animal studies (61).

Addiction

Perhaps it is not surprising that we currently have no satisfactory definition or criteria for addiction arising in patients receiving therapeutic opioids, considering that the currently accepted definition of *substance dependence (or drug addiction)* was arrived at only after decades of debate (62). This lack of a widely accepted definition makes it hard to determine rates of iatrogenic addiction.

The criteria for substance abuse listed in the DSM-IV manual include tolerance, physical dependence and 5 further criteria that are behaviors associated with illicit drug use, and not relevant in the case of therapeutic opioid use (Table 2). Behaviors that are considered typical of "problematic opioid use" are nuisance behaviors that annoy the prescribing physician and clinic staff (eg repeated lost prescriptions), but because they are not associated with illicit drug use, do not appear similar to DSM-IV criteria (Table 3). These "nuisance" behaviors could be the result of a chaotic lifestyle, uncontrolled pain or fear of withdrawal, and have never formally been accepted as signs of addiction. To make matters worse, tolerance (a pharmacological phenomenon resulting in the need for dose escalation to achieve the same effect) and physical dependence (a state of adaptation that results in a withdrawal when drug is stopped) are inevitable consequences of chronic opioid use, and therefore not considered criteria for abuse or addiction during opioid therapy. A consensus document from American pain and addiction societies lists the following addiction criteria: impaired control over drug use, compulsive use, continued use despite harm, and craving (63). Yet in the clinical setting, these are likely to be manifest as the "nuisance" behaviors described above, and hard to distinguish from other factors driving such behaviors. All in all, we are faced with real difficulties both defining and recognizing addiction in opioid treated patients, and in assessing risk.

Table 2. *DSM-IV Substance Dependence Criteria*

Addiction (termed substance dependence by the American Psychiatric Association) is defined as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. **Tolerance, as defined by either of the following:**
   (a) A need for markedly increased amount of the substance to achieve intoxication or the desired effect
   or
   (b) Markedly diminished effect with continued use of the same amount of the substance.
2. **Withdrawal, as manifested by either of the following:**
   (a) The characteristic withdrawal syndrome for the substance
   or
   (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. **The substance is often taken in larger amounts or over a longer period than intended.**
4. **There is a persistent desire or unsuccessful efforts to cut down or control substance use.**
5. **A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.**
6. **Important social, occupational, or recreational activities are given up or reduced because of substance use.**
7. **The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).**

DSM-IV criteria for substance dependence include several specifiers, one of which outlines whether substance dependence is with physiologic dependence (evidence of tolerance or withdrawal) or without physiologic dependence (no evidence of tolerance or withdrawal). In addition, remission categories are classified into four subtypes: (1) full, (2) early partial, (3) sustained, and (4) sustained partial; on the basis of whether any of the criteria for abuse or dependence have been met and over what time frame. The remission category can also be used for patients receiving agonist therapy (such as methadone maintenance) or for those living in a controlled, drug-free environment.

Source: Ref (62).

Table 3. *Criteria for Problematic Opioid Use*

1. The patient displays an overwhelming focus on opiate issues during pain clinic visits that occupy a significant proportion of the pain clinic visit and impedes progress with other issues regarding the patient's pain. This behavior must persist beyond the third clinic treatment session.
2. The patient has a pattern of early refills (3 or more) or escalating drug use in the absence of an acute change in his or her medical condition.
3. The patient generates multiple telephone calls or visits to the administrative office to request more opiates, early refills, or problems associated with the opiate prescription. A patient may qualify with less visits if he or she creates a disturbance with the office staff.
4. There is a pattern of prescription problems for a variety of reasons that may include lost medications, spilled medications, or stolen medications.
5. The patient has supplemental sources of opiates obtained from multiple providers, emergency rooms, or illegal sources.

Source: Ref (81).

At the start of the movement towards broadening opioid therapy to reach those with chronic non-cancer and non-terminal pain, addiction rates were considered to be very low. A key paper reporting hospital rates of addiction was taken out of context and widely used to support an extremely low rate of addiction (0.03%) (1). More realistically, Portenoy and Foley, in a sentinel paper describing opioid therapy for non-cancer pain, reported rates of addiction of 5% (10). Rates of this order were widely accepted, despite the weak level of evidence. Controlled studies made no attempt to evaluate addiction. After a decade or more of acceptance that therapeutic opioid use was unlikely to result in addiction, the medical community began to question the supposed low rates of addiction because of a perceived increase in the number of problematic patients, and because of the documented increase in prescription drug abuse (64). A systematic review published in 1992 reporting addiction rates of up to 18.9% (65), failed to penetrate the vast number of educational materials that were used during the 1990s to persuade the medical community that addiction was extremely rare during the treatment of pain. Yet today, when we are justifiably more concerned, this higher rate has become widely accepted. Whatever we believe or accept, the true incidence of addiction in opioid-treated chronic pain patients is unknown.

What is addiction and why is it different in pain patients?

Risk factors for addiction can be considered in three categories (Fig. 1):

i) psychosocial factors,

ii) drug-related factors and

iii) genetic factors (66,67).

The highest risk for addiction arises when risk factors in each category arise together. Pain patients with no genetic predisposition, no psycho-social comorbidity, and taking stable doses of opioid for the treatment of severe pain in a controlled setting are unlikely to develop addiction. On the other hand, patients with a personal or family history of substance abuse, displaying one or several psychosocial comorbidities, are at risk of developing addiction, especially if the treatment is not carefully structured and monitored.

The so-called "reward circuitry" is central to addiction processes. The "reward center" is located within mesocorticolimbic dopamine systems in the brain, where opioids play a critical role (68). Both dopamine and opioids have a central role in addiction processes (69,70). While the predominant role of the positive reinforcing (rewarding) effects of addictive drugs mediated through the mesocorticolimbic reward systems is firmly established, withdrawal phenomena, acting both on this reward circuitry, as well as on other systems, also contribute to craving and compulsive drug seeking, at least during active use and early abstinence (68,71,72). Withdrawal phenomena are both psychological (withdrawal anhedonia) and physical, and unpleasant feelings and symptoms during withdrawal induce craving. Upregulation of cAMP pathways in the brain (locus coeruleus) and spinal cord leads to acute physical withdrawal symptoms when the administered opioid is reduced or stopped, resulting in excessive central norepinephrine release, and its manifestations (73-75). While withdrawal phenomena are important in early drug seeking behaviors, it is important to distinguish these from the more enduring effects of addiction, which are learned, reinforced behaviors. As drug addiction develops, drug use combined with behaviors, circumstances, and stressors associated with obtaining and using the drug form a powerful memory imprint through involvement of secondary areas of the brain normally involved in memory, conditioning, and learning (69,70). As with all conditioned responses, this memory is hard to eradicate, and is often irreversible, unlike the craving associated with early with-

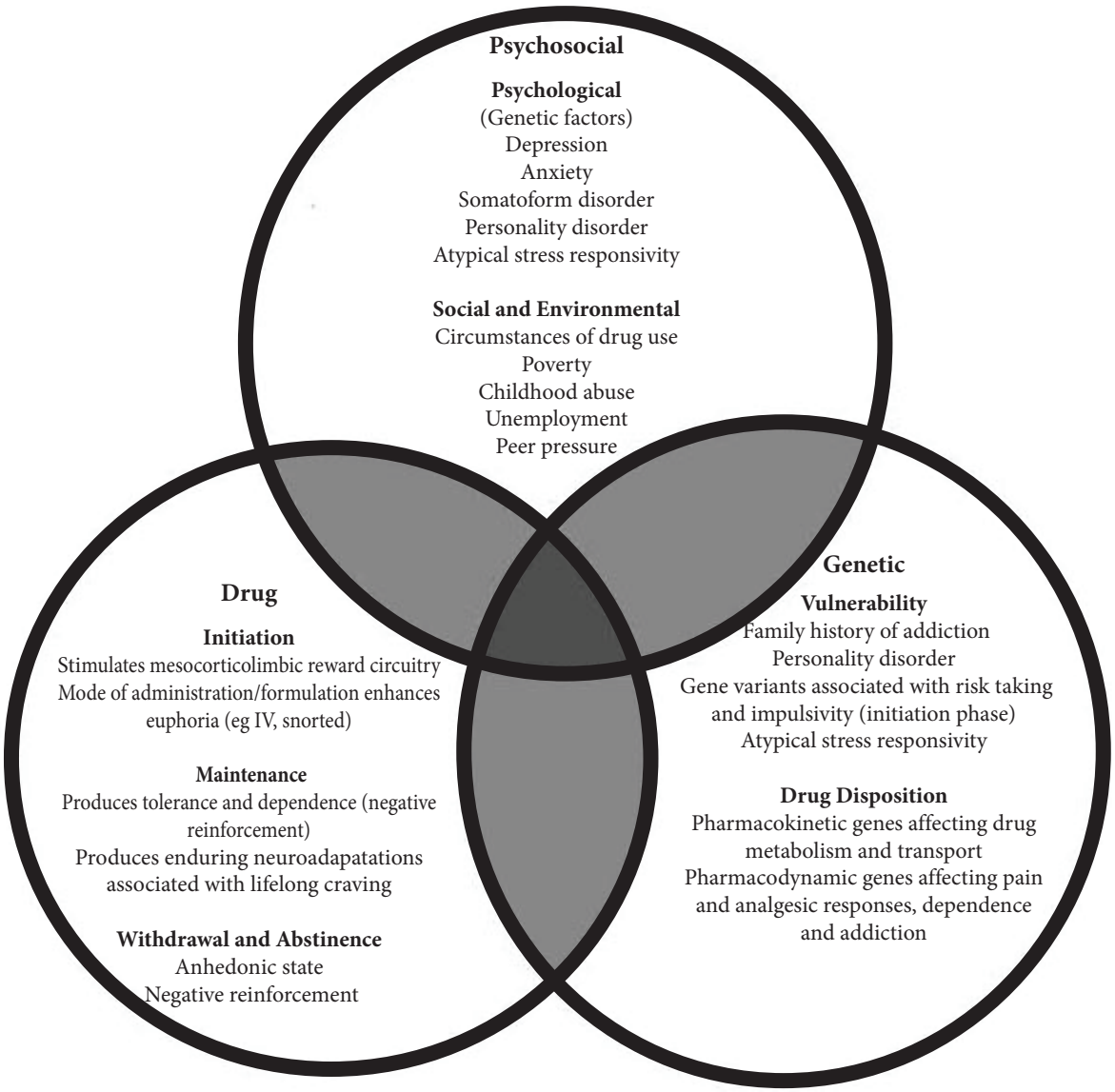

Fig. 1. *The 3 domains contributing to addiction.*

drawal. Continued and uncontrolled drug seeking behavior is, therefore, probably the most important factor producing the enduring state of addiction (a learned state), whereas craving associated with withdrawal (psychological and physical) may reverse once opioid treatment has been weaned. Opioid-treated pain patients may be less likely to develop addiction as long as they are maintained on a stable regime, since the steady state is protective (76). On the other hand, chronic pain patients as a cohort tend to present with high rates of addiction comorbidity (Fig. 1) (77-80). Logically, then, these opposing factors may explain why addiction rates in opioid treated chronic pain patients seem similar to those in the general population (i.e. the general population exposed to an addictive substance).

Who do you deprive of pain medication?

The devastating effect of regulations on the medical treatment of pain with opioids seemed largely overcome by successful advocacy that reestablished opioids as safe (most notably, addiction-free) and effective treatment for acute and cancer pain. But when opioids were extended to patients with chronic pain, which was done largely because of the success of short-term treatment, a quite different picture arose: reports in the medical literature began to suggest that problematic behavior, if not true addiction, was arising in enough patients to be of significant concern (81-83), there were sharp increases in prescription drug abuse (64), and reports such as that of the proliferation on the streets of Oxycontin – "hillbilly heroin" — and the addiction to pain medication of celebrities such as Rush Limbaugh, were appearing in the press. Moreover, epidemiological reports began to suggest that the treatment is not as successful as early enthusiasts once believed (36). In the context of uncertainty about sustained efficacy, an addiction risk that seems greater than was once predicted, and the knowledge that established addiction cannot be reversed so that the *try-it-and-see* approach is not advisable, it would seem that one should be highly selective about applying opioids for the treatment of chronic pain. The core ethical dilemma becomes: what is an acceptable basis for selecting patients for opioid treatment of pain, or who do you deprive of pain medication?

Patients' rights

Traditionally, physicians have taken a paternalistic role based on their superior knowledge and status, the patients being vulnerable and passive partners in physician-patient relationships. Contemporary medical ethics, however, have had to adapt to the political liberalisation. The philosophy of liberalism is described as "*a political philosophy based in belief in progress, the essential goodness of man, and autonomy of the individual and standing for the protection of political and civil liberties*" (84). The physician is no longer seen as all-powerful or the chief decision maker in an active-passive relationship, but instead enters a guidance-cooperation relationship whereby the patient is the chief decision maker, guided by the physician (85). The patient assumes the right to self-determination. The need to reformulate medical ethics became urgent in the twentieth century because of threats posed to life itself by rapidly evolving biomedical sciences. This culminated in the writing of a patients' charter adopted by the U.S. Advisory Commission on Consumer Protection and Quality in the Health Care Industry in 1998 (86). Many health plans now incorporate the charter's principles. Participation in treatment decisions is considered a right: "*You have the right to know your treatment options and to participate in decisions about your care. Parents, guardians, family members, or other individuals that you designate can represent you if you cannot make your own decisions.*" Patients' right to pain treatment, including opioid treatment, has now been established, albeit after years of lobbying and political activism on the part of pain advocates, culminating in the enactment of so-called "intractable pain" statutes (87). *Controlled substances and, in particular, narcotic analgesics may be used in the treatment of pain experienced by a patient with a terminal illness or* **chronic disorder***. These drugs have a legitimate clinical use and the physician should not hesitate to prescribe, dispense, or administer them when they are indicated for a legitimate medical purpose* (88).

Is there a validated screening instrument?

While the need for careful, structured treatment is amply supported, the methods by which patients should be selected for treatment or for termination of treatment are not well defined. Probably the most difficult question is whether certain patients should be excluded from opioid pain treatment. Exclusion produces a range of difficult ethical dilemmas. It is generally assumed that known substance abusers carry the greatest risk of addiction during opioid treatment of pain. Yet evidence to date suggests that even these high-risk patients do not necessarily present an increased risk during pain treatment (89-93). This may be because the drug itself constitutes only one component of complex circumstances involving the psychosocial situation of both the individual patients and their community. Thus, provided the treatment is "medicalized," and the circumstances associated with abuse are avoided, it is possible that the drug itself will not reinstate addiction.

Several research groups are now developing screening instruments that could be used to stratify risk, identify deterioration in life measures and record important outcomes in a standardized manner (81,94-100). This effort aims to screen for risk so that patients can be identified who are not suitable for therapy, or who warrant special vigilance and monitoring. There is also a recognized need to produce standardized entry and outcomes data to be used in multicenter studies to validate the screening instruments as pre-

dictors of risk. Screening tools that have been developed for use in addicts are used to identify craving (e.g. the CAGE questionnaire for alcoholics), but have not been found good predictors of aberrant behavior in opioid-treated pain patients (98, 99). The screening tools in development for use during opioid pain treatment are based on the knowledge, derived through genetic and epidemiological studies, that psychological comorbidities and a personal or family history of drug abuse are strong associates of addiction. The latest, developed by Belgrade et al (100) takes a new, intriguing and conceptually attractive approach in that it incorporates a measure of the likelihood of success (improved pain) as well as of risk. A validated screening instrument could have enormous benefit in that it could provide physicians with an effective means of selecting patients for treatment, and allow patients to be selected on a more rational basis. It remains to be determined whether screening instruments will be more useful for predicting risk or for identifying problems once they arise, or indeed, what their exact role will be in minimizing iatrogenic addiction risk. A validated screening instrument may also be useful for persuading patients not at risk, as well as those involved in their care, that the risk for them of addiction is negligible.

How bad or intrusive does the pain have to be to warrant taking risk?

If there existed a screening instrument capable of reliably identifying patients who may not be suitable for chronic opioid therapy, or patients who have begun to deteriorate once on the therapy, would this instrument be able to predict future success? The decision to use or not to use opioids, like all medical decisions, is based on a balance between risk and benefit. Screening instruments may help predict risk, but the benefit side of the question is even more difficult. How debilitating or intrusive does the pain have to be to warrant taking the risk of dependence, problematic opioid seeking, functional deterioration or possibly addiction? Who is in the best position to make this judgment; can the physician possibly judge? Should the knowledge that analgesic efficacy is not always maintained, and that chronic opioid use can compromise opioid efficacy when acute pain intervenes, make a difference to the decision to embark on a commitment to chronic therapy? The screening instrument developed by Belgrade et al goes some way towards providing an instrument that considers likely benefit as well as likely risk, but since it assesses prior opioid analgesic efficacy, not the degree of disruption caused by pain, it goes only part of the way (100). Inevitably, it is physicians, not patients, who decide on risk, and on whether the degree of pain and disruption warrants the risk.

How does one avoid interference from prejudices against race, culture, employment status, and social status, as well as against opioid use and drugs in general?

Physicians, like all humans, are fallible, and come with prejudices built on their own experience. When one sees the social devastation caused by addiction, it is not surprising that those who have been close to it, fear it. When one considers that under some creeds, the use of addictive drugs (including alcohol) is forbidden, it is not surprising that those from certain cultures or religions have difficulty condoning the use of opioids, even for the treatment of pain. When a physician knows that his patient is a drug offender, it is probably inevitable that the physician will find it difficult to separate that patient's need for analgesia from that patient's clear risk for abuse and diversion. When one knows that unemployed patients are less likely to rehabilitate effectively and more likely to become permanently pain disabled, this may weigh against initiating opioid treatment. The use of reliable screening instruments is likely the best hope of minimizing the influence of such prejudices on medical decision-making, since physicians will then be less reliant on a judgment that currently tends to be based solely on personal knowledge and experience. Several such screening instruments are in development, and are listed in Table 4 (101).

How does one protect the community from diversion, trade, and criminal activity?

In liberal states such as the U.S., the law respects individual freedom, and anti-drug laws target the production, importation, and dissemination of drugs, not individual users. The aim of anti-drug laws is to control illicit drug availability, thereby protecting the population, particularly its vulnerable sectors. Thus the laws aim to protect communal values. Communitarianism, so-called, has tended to be the province of political rather than traditional biomedical ethics, where the physician's primary duty is to the patient (102). But as medicine moves away from the model of highly individualist relationships between patients and their physicians, where moral issues are decided within its partnerships, and patients are

Table 4. *Screening for Risk*

1997	Chabal et al (81)	Prescription abuse checklist to be used by physicians.
1998	Compton et al (94)	Pilot assessment tool – Prescription Drug Use Questionnaire 42 items for structured interview completed by physicians.
2003	Friedman et al (95)	Screening tool for addiction risk (STAR). 14 true or false questions to be completed by patients.
2004	Passik et al (96)	Pain Assessment and Documentation Tool (PADT). Assesses 4 domains. Completed by physicians.
2004	Adams et al (97)	Pain Medication Questionnaire (PMQ) 26-item instrument. Self-report, completed by patients and scored by physicians.
2004	Butler et al (98)	Screener and Opioid Assessment for Patients with Pain (SOAPP). 24-item questionnaire. Completed by patients.
2005	Webster et al (99)	Opioid risk tool (ORT). 10 yes/no questions to be completed by patients.
2006	Belgrade et al (100)	Scoring system to predict outcome (DIRE) Assesses 4 domains (diagnosis, intractability, risk, efficacy). Completed by physicians.

protected by the tenets of the Hippocratic tradition *producing good for the patient and protecting that patient from harm* (103), it becomes necessary that public morality constrains and modifies medical ethics (84). Increasingly, physicians' practices are directed by protocols, guidelines, and standards of care determined by outside bodies of experts rather than by the individual physician's knowledge, expertise, and judgment.

Conclusion

Drug regulations certainly do not make it easy to provide opioid therapy for pain in a manner unfettered by prejudice and fear. Patients fear addiction — a fear that has been compounded by the criminalization of addiction brought about by drug laws. Physicians fear both causing addiction in their patients, and being punished for prescribing. Yet it is important to keep the risks of addiction and prosecution in proportion, to understand that both carry extremely small risk, and that they must be weighed against the devastating effect of chronic uncontrolled pain. There is a way to provide opioid therapy in a careful, selective and rational manner, and in so doing, of helping certain patients bear chronic pain and improve their lives. Much has been learned from the experience of the past few decades about how to optimize analgesia and minimize behavioral problems. Perhaps most difficult is the lesson that not all patients benefit, and that therefore we must be selective. Deciding which patients are suitable for treatment will never be easy, but if we can get that right, we will have made much progress towards right use and utility of opioid treatment for chronic pain.

References

1. Porter J, Jick H. Addiction rare in patients treated with narcotics (letter). *N Engl J Med* 1980; 302:123
2. AAPM Council on Ethics. American Academy of Pain Medicine. Ethics Charter Available at: www.painmed.org/productpub/pdfs/EthicsCharter.pdf. 2005;
3. Carr DB, Goudas LC. Acute pain. *Lancet* 1999; 353:2051-8.
4. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; 362:1921-8.
5. Brennan TJ, Kehlet H. Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain. Not an easy path. *Anesthesiol* 2005; 103:681-683.
6. Dubois MY. The birth of an ethics charter for pain medicine. *Pain Med* 2005; 6:201-2.
7. Joranson DE, Gilson AM, Dahl JL, Haddox JD. Pain medicine, controlled substances, and state medical board policy: a decade of change. *J Pain Symptom Manage* 2002; 23:138-47.
8. Dole V. What we have learned from three decades of methadone maintenance treatment. *Drug & Alcohol Review 1994;* 13:3-4.
9. Brecher E, Editors of Consumer Reports Magazine. How well does methadone mainenance work? In: The Consumers Union Report on Licit and Illicit Drugs. Schaffer Library of Drug Policy. Available at: http://www.druglibrary.org/schaffer/Library/studies/cu/cument/htm Accessed 10/12/2006. 2006;
10. Portenoy RK, Foley KM. Chronic use of

opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986; 25:171-186.

11. Tennant FS, Uelman GF. Narcotic maintenance for chronic pain: medical and legal guidelines. *Postgrad Med* 1983; 73:81-94.
12. Bouckoms A, Masand P, Murray G, Cassem E, Stern T, Tesar G. Chronic nonmalignant pain treatment with long term analgesics. *Ann Clin Psychiatry* 1992; 4:185-192.
13. Kalso E, Edwards J, Moore R, McQuay H. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004; 112:372-380.
14. Kjaersgaard-Andersen P, Nafei A, Skov O, Madsen F, Andersen HM, Kroner K, Hvass I, Gjoderum O, Pedersen L, Branebjerg PE. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip: a randomised, double-blind, multicentre study. *Pain* 1990; 43:309-318.
15. Moran C. MST continus tablets and pain control in severe rheumatoid arthritis. *Br J Clin Res* 1991; 2:1-12.
16. Arkinstall W, Sandler A, Groghnour B, Babul N, Harsanyi Z, Darke AC. Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized placebo-controlled clinical trial. *Pain* 1995; 62:168-178.
17. Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Merskey H. Randomized trial of oral morphine for chronic noncancer pain. *Lancet* 1996; 347:143-147.
18. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain: a randomized prospective study. *Spine* 1998; 23:2591-2600.
19. Sheather-Reid RB, Cohen ML. Efficacy of analgesics in chronic pain: a series of n-of-1 studies. *J Pain Symptom Manage* 1998; 15:244-252.
20. Watson CPN, Babul N . Efficacy of oxycodone in neuropathic pain. A randomized trial in postherpetic neuralgia. *Neurology* 1998; 50:1837-1841.
21. Caldwell JR, Hale ME, Boyd RE, Hague JM, Iwan T, Shi M, Lacouture PG. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatology* 1999; 26:862-869.
22. Peloso PM, Bellamy N, Bensen W, Thomson GTD, Harsanyi Z, Bubul N, Darke AC. Double blind randomized placebo-control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol* 2000; 27:764-771.
23. Roth SH, Fleischmann RM, Burch RX, Dietz F, Bochow B, Rapaport RJ, Rutstein J, Lacouture PG. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. *Arch Intern Med* 2000; 160:853-860.
24. Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001; 90:47-55.
25. Caldwell JR, Rapoport RJ, Davis JC, Offenberg HL, Marker HW, Roth SH, Yuan W, Eliot L, Babul N, Lynch PM.Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage* 2002; 23:278-291.
26. Maier C, Hildebrandt J, Klinger R, Henrich-Eberl C, Lindena G. Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS). *Pain* 2002 ; 97:223-233.
27. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. A placebo-controlled trial comparing the analgesic and cognitive effects of opioids and tricyclic antidepressants in postherpetic neuralgia. *Neurology* 2002; 59:1015-1021.
28. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial.[see comment]. *Neurology* 2003; 60:927-934.
29. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliative Medicine 2003; 17:576-587.
30. Rowbotham MD, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003; 348:1223-32.
31. Watson CPN, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003; 105:71-78.
32. Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. *Anesth Analg* 2001; 92:488-495.
33. Ballantyne J, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003; 349:1943-1953.
34. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005; 7:R1046-1051.
35. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain. An epidemiological study. *Pain* 2006; 125:172-179.
36. Ballantyne JC. Opioids for chronic pain: taking stock. *Pain* 2006; 125:3-4.
37. Katz N. Methodological issues in clinical trials of opioids for chronic pain. *Neurology* 2005; 65:S32-49.
38. Mao J. Opioid induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain* 2002; 100:213-217.
39. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer* 1999; 86:1856-1866.
40. Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. *J Pain Symptom Manage* 1993; 8:279-288.
41. Harden RN. Chronic opioid therapy: another reappraisal. *APS Bulletin* 2002; 12:
42. Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Curr Med Res Opin* 2005; 21:1555-1568.
43. Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain* 2000; 84:203-211.
44. Bruera E, Macmillan K, Hanson J, MacDonald N. The cognitive effects of the administration of narcotic analgesic in patients with cancer pain. *Pain* 1989 ; 39:13-16.
45. Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer

patients receiving long-term morphine analgesia. *Lancet* 1995; 346:667-70.

46. Galski T, Willimas B, Ehle HT. Effects of opioids on driving ability. *J Pain Symptom Manage* 2000; 19:200-8.
47. Haythornthwaite JA, Menefee LA, Quatrano-Piacentini AL, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. *J Pain Symptom Manage* 1998; 15:185-194.
48. Tassain V, Attal N, Fletcher D, Brasseur L, Degieux P, Chauvin M, Bouhassira D. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. *Pain* 2003; 104:389-400.
49. Kamboj SK, Tookman A, Jones L, Curran HV. The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. *Pain* 2005; 117:388-395.
50. Sjogren P, Christrup LL, Petersen MA, Hojsted J. Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. *Eur J Pain* 2005; 9:453-462.
51. Fishman SM, Wilsey B, Mahajan G, Molina P. Methadone reincarnated: novel clinical applications with related concerns. *Pain Med* 2002; 3:339-348.
52. Mendelson JH, Meyer RE, Ellingboe J, Mirin SM, McDougle M. Effects of heroin and methadone on plasma cortisol and testosterone. *J Pharmacol Exp Ther* 1975; 195:296-302.
53. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain* 2002; 3:377-384.
54. Daniell HW. Narcotic-induced hypogonadism during therapy for heroin addiction. *Journal of Addictive Diseases* 2002; 21:47-53.
55. Finch P M, Roberts L J, Price L, Hadlow N C, Pullan P T. Hypogonadism in patients treated with intrathecal morphine. *Clinical Journal of Pain* 2000; 3:251-254.
56. Paice JA, Penn RD, Shott S. Intraspinal morphine for chronic pain: a retrospective, multicenter study. *J Pain Symptom Manage* 1996; 11: 71-80.
57. Abs R, Verhelst J, Maeyaert J, Van Buyten J P, Opsomer F, Adriaensen H, Verlooy J, Van Havenbergh T, Smet M, Van Acker K. Endocrine consequences of long-term intrathecal administration of opioids. *J Clinic Endocrinology & Metabolism* 2000; 85:2215-2222.
58. Roy S, Loh H H. Effects of opioids on the immune system. *Neurochem Res* 1996; 21:1375-1386.
59. Risdahl J M, Khanno K V, Peterson P K, Molitor T W. Opiates and infection. J *Neuroimmunol* 1998; 83:4-18.
60. Page GG. Immunologic effects of opioids in the presence or absence of pain. *J Pain Symptom Manage* 2005; 29:S25-31.
61. Rahim RT, Adler MW, Meissler JJ Jr, Cowan A, Rogers TJ, Geller EB, Eisenstein TK. Abrupt or precipitated withdrawal from morphine induces immunosuppression. J *Neuroimmunol* 2002; 127: 88-95.
62. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. American Psychiatric Association, Washington, DC 1994;
63. Savage S, Covington E, Ehit H, Hunt J, Joranson D, Schnoll S. Definitions related to the use of opioids for the treatment of pain. A consensus document from the American Academy of *Pain Med*icine, the American *Pain* Society and the American Society of Addiction Medicine 2001;
64. Office of Applied Studies. National Survey on Drug Use and Health. Substance Abuse and Mental Services Administration (SAMHSA) 2004. http://oas.samhsa.gov/NHSDA/2k3NSDUH/2keresults.htm :
65. Fishbain D, Rosomoff H, Rosomoff R. Drug abuse, dependence and addiction in chronic pain patients. *Clin J Pain* 1992; 8:77-85.
66. Hyman S. Dispelling the myths about addiction. Institute of Medicine. National Academy of Sciences Press, Washington 1997; 44-46.
67. Kreek MJ. Drug addictions: molecular and cellular endpoints. *Ann N Y Acad Sci* 2001; 937:27-49.
68. Cami J, Farre M. Drug addiction. *N Engl J Med* 2003; 349:975-986.
69. Hyman S, Malenka R. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci* 2001; 2:695-703.
70. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci* 2006; 29:565-598.
71. Koob G, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropharm* 2001; 24: 97-129.
72. Koob G, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. *Science* 1997; 278:52-58.
73. Koob G, Maldonado R, Stinus L. Neural substrates of opiate withdrawal. *Trends Neurosci* 1992; 15:186-191.
74. Nestler EJ, Aghajanian GK. Molecular and cellular basis of addiction. *Science* 1997; 278:58-63.
75. Nestler EJ. Historical review: Molecular and cellular mechanisms of opiate and cocaine addiction. *Trends Pharmacol* Sci 2004; 25: 210-218.
76. Kreek MJ, Nielsen DA, LaForge KS. Genes associated with addiction: alcoholism, opiate, and cocaine addiction. *Neuromolecular Med* 2004; 5:85-108.
77. Fishbain D, Goldberg M, Meagher B, Steele R, Rosomoff H. Male and Female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. *Pain* 1986; 26:181-197.
78. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. *American Psychologist* 2004; 59: 795-805.
79. Polatin P, Kinney R, Gatchel R, Lillo E, Mayer T. Psychiatric illness and chronic low-back pain. The mind and the spine--which goes first? *Spine* 1993; 18:66-71.
80. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, Fiellin DA. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007; 146:116-1127.
81. Chabal C, Erjavec M, Jacobson L, Mariano A, Chanev E. Prescription opiate abuse in chronic pain patinets: clinical criteria, incidence and predictors. *Clin J Pain* 1997; 13:150-155.
82. Saper J, Lake A, Hamel R, Lutz T, Branca B, Sims D, Kroll MM. Daily scheduled opioids for intractable head pain: long-term observations of a treatment program. *Neurology* 2004; 62:1687-1694.
83. Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: A literature review. *Eur J Pain* 2006;
84. Brennan TA. Just Doctoring. Medical Ethics in the Liberal State. University of California Press, Berkeley and Los Angeles, CA . 1991a; p 3 (Brennan quotes the Webster Dictionary definition of liberalism)
85. Szasz T, Hollender J. The Basic Model of the Doctor-Patients Relationship. *Arch Int Med* 1956; 97: 85-90.
86. Advisory Commission on Consumer Protection and Quality in the Health Care Industry. Patients' Rights and Responsibilities http://www.consumer.gov/qualityhealth/rights/htm 1998;

87. Joranson D, Gilson A. State intractable pain policy: Current status. APS Bulletin 1997; 7:7-9.
88. Drug Enforcement Administration. Physician's Manual. Alexandria, VA. 1990;
89. Weaver M, Schnoll S. Opioid treatment of chronic pain in patients with addiction. *J Pain & Palliat Care Pharmacotherapy* 2002; 16:5-26.
90. Collins E, Streltzer J. Should opioid analgesics be used in the management of chronic pain in opiate addicts? *Am J on Addictions* 2003; 12:93-100.
91. Newman R. Analgesia and opiate addicts. *Am J on Addictions* 2004; 13:494.
92. Dunbar S, Katz N. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: Report of 20 cases. *J Pain Symptom Manage* 1996; 11:163-167.
93. Kennedy J, Crowley T. Chronic pain and substance abuse: a pilot study of opioid maintenance. *J Subst Abuse Treat* 1990; 7:233-238.
94. Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain with "problematic" substance use: Evaluation of a pilot assessment tool. *J Pain Symptom Manage* 1998; 16:355-363.
95. Friedman R, Li V, Mehrotra D. Treating pain patients at risk: evaluation of a screening tool in opioid-treated pain patients with and without addiction. *Pain Med*icine 2003; 4:182-185.
96. Passik SD, Kirsh KL, Whitcomb L, Portenoy RK, Katz NP, Kleinman L, Dodd SL, Schein JR. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clinical Therapeutics* 2004; 26:552-561.
97. Adams L, Gatchel R, Robinson RC, Polatin P, Gajraj N, Deschner M, Noe, C. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. *J Pain Sympt Manage* 2004; 27:440-459.
98. Butler S, Budman S, Fernandez K, Jamison R. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain* 2004; 112:65-75.
99. Webster L, Webster R. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med* 2005; 6:432-442.
100. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: Predicting outcomes of opioid prescribing for chronic pain. *J Pain* 2006; 7:671-681.
101. Passik SD, Kirsh KL. Opioid therapy in patients with a history of substance abuse. CNS Drugs 2004; 18:13-25.
102. Sullivan M. Ethical principles in pain management. *Pain Med* 2001; 2:106-111.
103. Veach RM. The Theory of Medical Ethics. New York: Basic Books pp23. 1981.