Psychiatry and Primary Care
Recent epidemiologic studies have found that most patients with mental illness are seen exclusively in primary care medicine. These patients often present with medically unexplained somatic symptoms and utilize at least twice as many health care visits as controls. There has been an exponential growth in studies in this interface between primary care and psychiatry in the last 10 years. This special section, edited by Jürgen Unutzer, M.D., will publish informative research articles that address primary care-psychiatric issues.

The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care

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A B S T R A C T

Objective: The prevalence of opioid therapy for chronic noncancer pain has increased dramatically in recent years, with a parallel increase in opioid abuse, misuse and deaths from accidental overdose. We review epidemiological and clinical data that point to the important roles psychiatric disorders have in the use and abuse of opioids in patients with chronic pain.

Method: We conducted literature searches on the PubMed with the key phrases “chronic pain” and “opiod therapy” and selected those articles on the epidemiology of comorbidity between chronic pain and psychiatric disorders, the trends in long-term opioid therapy and the clinical trials that involved using opioid therapy for chronic pain or for mental health disorders. We then thoroughly reviewed the bibliography of all relevant articles to identify additional papers to be included in the present review.

Results: Chronic pain is highly comorbid with common psychiatric disorders. Patients with mental health and substance abuse disorders are more likely to receive long-term opioid therapy for chronic pain and more likely to have adverse outcomes from this therapy. Although opioids may exert brief antidepressant and anxiolytic effects in some patients with depression or anxiety, there is scant evidence for long-term benefit from opioid treatment of psychiatric disorders.

Conclusions: Opioids may be used in current clinical practice as the de facto and only psychiatric treatment for patients with chronic pain, despite little evidence for sustained benefit. The opioid epidemic thus reflects a serious unmet need for better recognition and treatment of common mental health problems in patients with chronic pain. Psychiatry is the missing P in chronic pain care.

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1. Introduction

The Institute of Medicine recently estimated that 100 million Americans suffer from chronic pain at a cost of $600 billion [1]. As clinicians have sought to address this challenge, the use of long-term opioid therapy for chronic noncancer pain (CNCP) has quadrupled in the last 15 years [2–4]. This has been accompanied by increased opioid adverse events. The Centers for Disease Control (CDC) has published data showing parallel increases among opioid sales, overdose deaths and abuse from 1999 to 2010, with opioid deaths more than tripling between 1999 and 2008 [5]. More recent statistics indicate that this trend has continued [6]. We will argue in this paper that psychiatric disorders play an important role in linking these trends, because of a pervasive process of “adverse selection.” Adverse selection refers to the fact that patients with mental health and substance use disorders are more likely to receive opioid therapy at higher doses and for longer periods, and are more likely to suffer adverse outcomes. We will review evidence demonstrating that the opioid epidemic points toward a serious unmet need for psychiatric care for patients with CNCP.

Clinical decision making concerning opioid therapy for CNCP is complicated by the fact that randomized controlled trials of opioid efficacy for chronic pain conditions have excluded patients with psychiatric comorbidities, even though these are highly prevalent in patients with chronic pain [7,8]. Common mental disorders, such as depression and anxiety, are known to be associated with higher pain intensity, more pain complaints as well as higher pain interference with daily activities [9–11]. The close association between both the prevalence and severity of chronic pain and psychiatric and substance use disorders makes the safety and efficacy data from randomized
controlled trials of opioid therapy not directly applicable to the patient with chronic pain who are most likely to receive opioid therapy in actual clinical practice.

Below, we review recent research addressing the following clinically important questions: Does the presence of psychiatric disorders influence the likelihood of a patient receiving opioids for CNCP? Do mental disorders affect the outcome of opioid therapy? Are opioids effective treatment for mental health disorders? What are the effects of long-term opioid therapy on mental health outcomes?

2. Chronic pain and psychiatric disorders

The high rates of comorbidity among chronic pain and psychiatric disorders have been well documented [11,12]. Studies of prevalence of pain in depression showed that various forms of chronic pain complaints (back/neck, arthritis and migraine/chronic headaches) were more common in depressed patients across different demographic groups [13–20]. Patients with both pain and depression tend to have more pain complaints [21], higher pain intensity [22] and more pain chronicity [23] compared to patients without depression. Studies of depression prevalence in patients with chronic pain showed a reciprocal trend. In the general population, 12-month prevalence rates for major depression and dysthymia are 6.7 and 1.5%, respectively [24]; having one or more chronic pain conditions increases the rates of depression to 10–30% [25–28]. Overall, chronic pain increases depression risk by two- to fivefold [29–32]. In a recent interventional cohort study, Kroenke et al. [33] showed that changes in pain severity predicted subsequent depression severity, and vice versa. This study confirmed previous epidemiological data suggesting a bidirectional relationship between pain and depression [34].

A close association has also been observed between pain and anxiety disorders. For example, 12-month prevalence rates of panic disorder are estimated to be 1–2.7% in the US general population [24], in comparison to 28% in patients with irritable bowel syndrome [35] and 13–15% in patients with chronic headaches [36]. The prevalence of posttraumatic stress disorder (PTSD) has also been shown to be elevated in various pain populations [28,37–39]. The 12-month prevalence rate of PTSD is 3.5% in the general population [24], in comparison to 30%–50% in patients who developed pain as a result of motor vehicle accidents [40], 15% in patients seeking treatment for idiopathic facial pain [41], and 21% in patients with fibromyalgia [42].

The 12-month and lifetime prevalence of substance use disorders in the US general population are 3.8% [24] and 14.6% [43]. Estimates for the rates of substance abuse and dependence in patients with chronic pain tend to vary depending on the study population and the definition of addiction [44]. Nonetheless, persistent pain appears to increase the risk of problem substance use by two- to fivefold [45,46].

The causal relationship between chronic pain and various psychiatric disorders has been a matter of interest and research. Prospective studies have suggested that chronic pain can cause depression [47,48], and that depression can also cause chronic pain [23,49]. There may also be common susceptibility traits and environmental factors such as childhood abuse and neglect that predispose individuals to pain, substance use and mental health disorders [35,50–53]. A bidirectional relationship likely underlies the strong association between pain and common mental disorders. This means that psychiatric disorders are not solely a reaction to chronic pain. They also predispose individuals to the development of chronic pain. Since chronic pain is often accompanied by severe emotional distress, this raises the question whether clinicians who prescribe opioid therapy to treat CNCP are not also using opioids as the de facto treatment for the patient’s emotional distress. Epidemiological studies on the association between psychiatric diagnoses and the use of chronic opioid therapy as described below seem to support this hypothesis.

3. Psychiatric disorders and the likelihood of receiving chronic opioid therapy

Studies using data from pain clinics, general population surveys and health insurance administrative data concerning general medical patients have suggested that patients with common psychiatric problems such as depression, anxiety and substance use disorders are more likely to receive opioids for CNCP than patients without mental disorders [3,34–56]. Sullivan et al. [55,56] published two reports involving epidemiological data from Health Care for Communities (HCC) survey. The HCC was a large nationwide community-based telephone survey that collected information on a number of self-reported chronic medical conditions including chronic back pain, chronic headaches and other chronic pain. Common mental health disorders in the past 12 months, including major depression, dysthymia, generalized anxiety disorder and panic disorder, as well as problem drug and alcohol use, were assessed using common assessment tools. The first wave of the survey (HCC1) was completed in 1998, and the second wave (HCC2) was in 2001. In their 2005 article [55], the authors examined cross-sectional data from HCC1 and identified 282 (3% of the respondents) regular opioid users. Regular opioid use was defined by using opioids at least several times a week for a month or more in the past 12 months. The presence of a common mental disorder or problem substance use was found to increase the likelihood of prescription opioid use. In a subsequent study [56], the authors looked at the longitudinal data from HCC1 and HCC2 and found that respondents with a common mental health disorder and those with a substance abuse disorder in HCC1 (1998) were twice as likely to report regular opioid use in HCC2 (2001) than those without any of these disorders, after adjustment for demographic and clinical variables. The study provided the first prospective, population-based data about the association of psychiatric disorders with opioid therapy. The authors postulated that opioids may be used to “treat a poorly differentiated state of mental and physical pain.”

Edlund et al. [3] examined the linkage between psychiatric disorders and use of opioids for CNCP in the Trends and Risks of Opioid Use for Pain (TROUP) study. The study analyzed claims data from 2000 through 2005 on two disparate populations: a national, commercially insured population (HealthCore) and Arkansas Medicaid enrollees. The use of administrative data, which provided diagnoses and prescription records, had the advantage of offering much larger samples than studies from pain clinics or community-based surveys. However, these studies used chart diagnoses rather than structured psychiatric interviews to assess psychiatric disorders. These chart diagnoses tend to be specific (with few false positives) but not sensitive (with many false negatives). Chronic opioid therapy was defined as receiving greater than 90-day supply of opioids during the calendar year. In both populations, chronic opioid use in 2000 for CNCP was more common among those with at least one mental or substance use disorder diagnosis than among those without. Between 2000 and 2005, opioid use in these samples started higher and grew faster in patients with mental health or substance use diagnoses than in those without these diagnoses.

Also using claims data from HealthCore, Richardson et al. [57] reported a similar association between a preexisting mental health diagnosis and increased risk for receiving long-term opioids among adolescents and young adults with chronic pain complaints (back pain, neck pain, headache and arthritis/joint pain).

Braden et al. [58] reported a linkage between depression and long-term (>90 days) opioid use episodes as a part of the CONsortium to Study Opioid Risks and Trends (CONSORT) study. The report looked at claims data from Group Health in Washington State and Kaiser Permanente of Northern California between 1997 and 2005, and found that, compared to nondepressed, a chart diagnosis of depression over the previous 2 years was associated with three times higher likelihood of receiving long-term opioids, a higher
average daily dose, greater days supplied, and more use of Drug Enforcement Administration Schedule II opioids. Also reporting from the CONSORT study, Weisner et al. [59] found that chronic opioid users with a prior substance abuse diagnosis received higher opioid dosages and were more likely to receive Schedule II opioids.

PTSD is strongly associated with opioid use in veteran and civilian populations. Among Iraq and Afghanistan veterans with pain, 6% of veterans without mental health disorders, 12% with non-PTSD mental health disorders and 18% with PTSD were prescribed opioids within a year of their pain diagnosis. Among those prescribed opioids, those with PTSD were more likely than those without mental health disorders to receive higher dose opioids, receive two or more opioids concurrently, receive sedative hypnotics concurrently or obtain early opioid refills [60]. Among civilian primary care patients, those with a current PTSD diagnosis had significantly higher pain and pain-related impairment ratings than those with no PTSD. They were also more likely to have used opioid analogics for pain control. All PTSD symptom subclusters (reexperiencing, avoidance and hyperarousal) were significantly related to pain and pain-related impairment ratings, but only the avoidance cluster was significantly related to opioid pain medication use [61].

These studies of various sample size and methodology have consistently pointed to common psychiatric disorders being an important risk factor in increasing the likelihood of patients receiving long-term opioid therapy for chronic pain.

4. Psychiatric disorders and the outcome of opioid therapy

The evaluation of the outcomes of opioid treatment for chronic pain is a complex issue and cannot be limited to reductions in pain intensity alone. Although clinical trials of long-term opioid therapy have included functional measures, these generally measured the intensity alone. Although clinical trials of long-term opioid therapy will be received, there is evidence that psychopathology impacted by opioid adverse effects and the risk of opioid misuse and abuse. For example, opioid adverse effects go beyond classical medication side effects and include a broad range of psychosocial difficulties and opioid control concerns [63].

Although psychiatric disorders increase the likelihood that opioid therapy will be received, there is evidence that psychopathology reduces opioid analgesia [64,65]. Wasan et al. [66] tested this hypothesis in patients with discogenic low back pain in a double blind, placebo controlled, randomized crossover trial. Patients were stratified into three groups of 20 subjects based on composite scores that measure the severity of their psychological symptoms, including depression, anxiety and neuroticism. The subjects received an intravenous bolus injection of either morphine or saline placebo, and their level of pain was rated over the subsequent 3 h. The same procedure was repeated 1 week later with the subjects crossed over to either morphine or placebo. High levels of psychopathology were found to be associated with diminished opioid analgesia and, also interestingly, with higher placebo analgesia. This study remains the only direct test of the effect of mental health problems on opioid analgesia in patients with chronic pain. However, because the duration of the opioid trial was very brief and involved a single iv dose only, it is difficult to translate its findings into real-world practice of long-term opioid therapy of chronic pain.

Past and current substance use orders are generally accepted as risk factors for prescription opioid abuse and dependence [67–72]. Several studies have also identified the association between mental health disorders and opioid abuse or misuse in patients receiving chronic opioid therapy [73–79]. Schieffer et al. [76] assessed for opioid misuse with a modified version of Prescription Drug Use Questionnaire (PDUQ) in 288 patients referred to a Veterans Affairs pain clinic. Patients with any history of substance abuse by chart review scored higher on the PDUQ than those without. In addition, patients with a history of substance abuse as well as mental health disorders scored higher on the PDUQ than patients with substance abuse diagnoses only, suggesting that mental health diagnoses confer added risk for opioid misuse. In a regression analysis, state anxiety, but not depression, was significantly correlated with the level of misuse behaviors on the PDUQ.

Wasan et al. [79] studied 228 patients receiving opioids for chronic pain and identified medication misuse/abuse according to a combination of self-reported questionnaires, physician-reported measures and urine toxicology results. The patients were classified into high-psychiatric and low-psychiatric morbidity groups based on the psychiatric subscale scores of the PDUQ. The high-psychiatric morbidity group had significantly more opioid misuse and abuse than the low-psychiatric morbidity group.

Analyzing data from the TROUP study, Edlund et al. [73] estimated the prevalence of and risk factors for opioid abuse and dependence in patients receiving long-term opioids for chronic pain and found that 3% of both the commercially insured and Medicaid samples had a claims-based opioid abuse/dependence diagnosis. Preexisting mental health and substance use disorder diagnoses were found to be associated with an increased risk of opioid abuse/dependence. Preexisting mental health disorders were also associated with nonopioid substance abuse/dependence and emergency department visits [80].

Boscarino et al. [78] conducted structured diagnostic interviews to identify substance use disorders, mental health disorders and trauma exposure among a random sample of 705 outpatients who had received long-term opioid therapy for noncancer pain in the preceding 12 months. Major depression and psychotropic medication use were found to be linked to current opioid dependence.

Park and Lavin [75] surveyed a sample of 163 community-dwelling older adults (age 65 years or older) from outpatient clinics to identify risk factors for opioid misuse. The participants were receiving opioids for at least 1 month for chronic pain. High levels of depressive symptoms, as well as high pain severity and low physical disability, were found to be associated with opioid misuse in the survey respondents.

Grattan et al. [74] also found an association between depression and opioid misuse by analyzing data from the CONSORT study [81]. The study involved a one-time telephone interview of 1334 Group Health Cooperative and Kaiser Permanente of Northern California members prescribed with long-term opioids for CNCP who had no known substance abuse problem. Three types of opioid misuse were defined a priori: medicating nonpain symptoms like anxiety or sleep, self-increasing dose and getting opioids from family or friends or giving opioids to them. Depression was found to be associated with the first two types of misuse but not the third type. The authors concluded that patients with current depressive symptoms are more likely to use opioids for the nonpain symptoms of stress and insomnia and to thus use more medication than prescribed. On the other hand, more clearly aberrant behaviors, such as sharing or obtaining medications from others, were not more common in depressed patients and may be limited to those with substance use disorders.

5. Opioid treatment of mental health disorders

Because of its euphoric, sedating and anxiolytic effect, opium was widely used in the late 19th century and early 20th century to treat melancholia, mania and other forms of psychological distress [82]. However, the use of opioids to treat psychiatric disorders gradually became obsolete when nonaddictive antidepressants became available in the 1950s [83]. Opioids primarily act through binding to the opioid receptors, which produce both analgesic and hedonic effects. Recently, opioid medications have also been found to exert complex influence on other neural signaling systems implicated in the
regulation of mood and stress response, including the serotonin, catecholamine, dopamine, corticosteroid and N-methyl-D-aspartate-glutamate systems [82]. In the last two decades, there have been several small clinical trials, case reports and case series looking at the effect of opioids on treatment-refractory mood and anxiety disorders. The results of these studies are mixed.

Varga et al. [84] in 1982 reported an open-label study of the effect of codeine for up to 3 weeks on 12 patients with severe depression with no current substance use disorders that failed to respond to tricyclic antidepressants. None of these patients developed euphoria or dependence, but all complained of constipation and sedation. Eight patients received codeine in combination with other tricyclic antidepressants, and only one of them had improvement in depression. Four received codeine alone, and none of them improved.

Also in 1982, Emrich et al. [85] reported a double-blind trial of 10 patients with treatment-refractory depression, who received 4 days of buprenorphine in a A1/B2, A2/B1-design (A1 = placebo; B = buprenorphine). Approximately half of the patients had a significant reduction in depressive symptoms when they were taking buprenorphine compared to when they were taking placebo. Slight nausea and sedation were the common side effects reported.

Bodkin et al. [86] did a 4-week, open-label study of buprenorphine in 10 patients with refractory depression. Five subjects dropped out of treatment at various points due to nausea, malaise, dysphoria and sedation. Of seven who completed at least 4 weeks of treatment, six had improvement in depressive symptoms, but one deteriorated.

Some authors have studied the effect of opioid maintenance treatment on depressive symptoms in individuals with existing opioid addiction. For example, Kosten et al. [87] assessed depression severity in 40 opioid-addicted patients who were entered into a 1-month open trial of outpatient buprenorphine treatment. Those patients who had clinically significant depression at study entry showed reduction of depressive symptoms over the course of the treatment, but it was not clear whether this improvement in depression was due to buprenorphine itself or to increased psychosocial stability in patients who stopped illicit substance use.

Dean et al. [88] compared the effect of buprenorphine and methadone on depressive symptoms in 54 patients with heroin dependence. Depression improved in both buprenorphine and methadone groups by the end of the 3-month treatment period. Subjects with lower heroin use during the treatment period had less baseline depression and less depression at study completion, while subjects with higher heroin use during treatment had greater reduction in depressive symptoms over the treatment period. One may interpret these findings as buprenorphine and methadone having antidepressant benefit independent of their effect on heroin use [82]. However, it is also possible that the subjects who had reduction in depressive symptoms did so at least in part due to a relative reduction in their heroin use and psychosocial chaos.

Other researchers have looked at the effect of opioids on mania. Judd et al. [89] reported that methadone produced a subtle reduction in manic behavior in nine nonopioid-dependent inpatients. Clear-headedness was also decreased with methadone administration, suggesting that the observed decrease in mania could well be due to sedation. Pacini and Maremmani [90] noted that methadone use during hospitalization decreased the need for antimanic and antipsychotic medications in 114 heroin-dependent patients admitted for acute manic and/or psychotic episodes. In these patients, sedation and the prevention of opiate withdrawal, rather than any specific antimanic or antipsychotic properties, were probably the basis for the beneficial effects of methadone use.

The endogenous opioid system has also been postulated to play a role in the pathogenesis of obsessive-compulsive disorder (OCD) [91]. Shapiro et al. [92] did an open-label trial of tramadol for 6 weeks in seven patients with treatment-refractory OCD and no substance abuse history. Six patients reported reduction in their OCD symptoms, while one subject dropped out in Week 1 because of nausea and exacerbation of trichotillomania. Koran et al. [93] conducted a double-blind trial of once-weekly oral morphine in 23 patients with serotonin reuptake inhibitor-resistant OCD. The subjects were given, in random order, 2-week blocks of once-weekly oral morphine, lorazepam and placebo. Seven subjects responded to oral morphine and four to lorazepam, and no subjects responded to placebo. Median OCD symptoms were reduced more with morphine than with placebo but similar to lorazepam.

These studies of opioid treatment for mental health disorders were generally small open-label trials often with no control groups. Duration of opioid administration tended to be short, ranging from days up to 6 weeks, with the exception of one opioid maintenance trial for opiate addiction that lasted 3 months [88]. Long-term follow-up data were not provided, so it is not possible to know if benefit from opioid therapy would be maintained over time or if problems with dependence and abuse developed. In the two double-blind trials summarized above [85,93], the effects of opioids appeared to be rapid but transient. Thus, although opioids may exert brief antidepressant and anxiolytic effects in a subset of patients with depression or anxiety, there is limited evidence for long-term benefit from opioid treatment of mental health disorders.

6. Discussion

Evidence reviewed in this paper underscores the phenomenon of adverse selection in chronic pain management where high-risk patients are more likely to end up on high-risk opioid regimens, and shows the important ways in which psychiatric comorbidities contribute to these high-risk levels. Psychiatric disorders, especially substance abuse, depression and PTSD, are highly prevalent in patients with CNCP. Patients with these substance use and mental health diagnoses are more likely to receive long-term opioid therapy for their pain, at higher doses, and with concurrent sedatives. These patients are also more likely to have adverse outcomes such as overdose, opioid misuse and abuse and emergency department visits. There is experimental evidence that common mental health conditions, such as depression and anxiety, may decrease opioid analgesia. Transient improvements in pain and psychological distress might be promising because increases in patients with chronic pain and psychiatric disorders, thereby increasing the risk of opioid abuse and other adverse outcomes.

The endogenous opioid system and a relative endorphin deficiency have been implicated in the pathophysiology of depression [94–96] and anxiety disorders [91]. The neuroanatomical and pathophysiological links between pain and psychiatric conditions were nicely summarized in a recent review by Elman et al. [97]. The epidemiological observations summarized above are consistent with this neurobiological connection.

Emerging evidence suggests that emotional distress associated with social disconnection in primates (i.e., rejection, humiliation, isolation) may arise from some of the same neurobiological structures that underlie experiences of physical pain such as the dorsal anterior cingulate cortex and the anterior insula [98]. These areas have some of the highest densities of mu-opioid receptors in the central nervous system [99]. Opioids have long been known to reduce separation distress behaviors in nonhuman mammals. Indeed, an intact endogenous opioid system appears essential for normal maternal–infant bonding. Mice lacking the mu-opioid receptor gene (OPRM1) do not show normal attachment behaviors with little evidence of distress with separation from their mothers [100]. On the other hand, early postnatal maternal separation increases the rewarding value of morphine in genetically normal rat pups [101]. Later in life, opioid agonists reduce efforts at social affiliation [102,103] while opioid antagonists increase efforts at social affiliation [104]. These findings
are consistent with the idea that opioids substitute for the rewards of social connection. Observational and experimental studies have shown that social support decreases the intensity of physical pain as well as that of social pain [105]. Acetaminophen has been shown in a double-blind, placebo-controlled study to reduce hurt feelings in response to experimental social exclusion [106]. It appears that opioids may be used in current clinical practice as the only psychiatric treatment for patients with chronic pain. This has been associated with high rates of opioid adverse events including misuse, abuse and overdose. Moreover, there is little evidence of sustained benefit from opioid treatment of psychiatric disorders.

It has been debated as to whether chronic opioid therapy can cause iatrogenic addiction in patients with no prior substance abuse problems [44]. However, research on prescription opioid abuse and dependence among physicians suggests that easy access to potentially addictive drugs is a risk factor for abuse of the drugs [107]. This is consistent with the CDC statistics on the parallel increase of opioid sales and opioid abuse. Furthermore, there has been data showing that craving, a risk factor for opioid misuse and abuse, is linked to high levels of negative affect [108]. Thus, the high prevalence of depression and anxiety among chronic pain patients likely means increased craving for opioids, thereby leading to problematic opioid use.

The central role of psychiatric disorders in the epidemiology of CNCP and the pharmaco-epidemiology of chronic opioid therapy, clinicians must be vigilant about identifying and treating these problems in patients receiving, or being considered for, long-term opioid therapy. The current opioid epidemic has revealed the dire need for psychiatric services — the presently missing “p” — in chronic pain care. Psychosocial screening to identify possible depression and anxiety disorders as well as substance abuse problems should be part of the initial assessment for every patient who presents with chronic pain. The evaluation should also include assessment of a patient’s functional status in the areas of physical activities, social and occupational status. Timely treatment of the identified psychiatric comorbidities including the use of appropriate pharmacotherapy and behavioral interventions, which when conducted in conjunction with physical rehabilitation, can often lead to improvements in a patient’s physical and social functioning and help avoid the problems associated with long-term opioid use.

References


