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Original Reports

Nonopioid Substance Use Disorders and Opioid Dose Predict Therapeutic Opioid Addiction

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Abstract: **Limited research examines the risk of therapeutic opioid addiction (TOA) in patients with chronic noncancer pain. This study examined TOA among 199 patients undergoing long-term opioid therapy at the time of admission to a pain rehabilitation program. It was hypothesized that nonopioid substance use disorders and opioid dosage would predict TOA. Daily mean opioid dose was 132.85 mg ± 175.39. Patients with nonopioid substance use disorders had 28 times the odds (odds ratio [OR] = 28.58; 95% confidence interval [CI] = 10.86, 75.27) of having TOA. Each 50-mg increase in opioid dose nearly doubled the odds of TOA (OR = 1.73; 95% CI = 1.29, 2.32). A 100-mg increase was associated with a 3-fold increase in odds (OR = 3.00; 95% CI = 1.67, 5.41). Receiver operating characteristic analysis revealed that opioid dose was a moderately accurate predictor (area under the curve = .75; 95% CI = .68, .82) of TOA. The sensitivity (.70) and specificity (.68) of opioid dose in predicting TOA was maximized at 76.10 mg; in addition, 46.00 mg yielded 80% sensitivity in identifying TOA. These results underscore the importance of obtaining a substance use history prior to prescribing and suggest a low screening threshold for TOA in patients who use opioids in the absence of improvement in pain or functional impairment.**

Perspective: ***This article examines TOA in patients with chronic noncancer pain undergoing long-term opioid therapy. Results suggest that patients should be screened for nonopioid substance use disorders prior to prescribing. In the absence of improvement in pain or function, there is a low threshold (∼50 mg daily opioid dose) for addiction screening.***

Key words: *Long-term opioid therapy, chronic pain, therapeutic opioid addiction, opioid dosage, substance abuse.*

Since the late 1980s, the prescribing of opioid analgesics to patients with chronic noncancer pain has risen dramatically.[7,32,33,57] There is now a widely held belief that this practice has contributed to an epidemic of prescription opioid abuse and addiction.[23,34,43] Prescription opioids are now the leading cause of unintentional drug overdose deaths.[44] Thus, clinicians find themselves faced with the dilemma of balancing the potential benefits of long-term opioid therapy with the risk of misuse or addiction. The interplay of chronic pain and addiction is a significant challenge faced by primary care physicians, pain specialists, and addictionologists alike.

The decision on whether to initiate long-term opioid therapy is complicated by a dearth of reliable information on the prevalence of misuse in those who receive it. Recent estimates of the prevalence of misuse and addiction in patients with chronic pain vary widely, ranging anywhere from 0% to 50%.[5,12] Our own data from the Cleveland Clinic Chronic Pain Rehabilitation Program, an interdisciplinary approach that incorporates opioid weaning, suggests that approximately one-third of patients present with a co-occurring therapeutic opioid addiction (TOA).[27] This is a highly select group, given

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that many patients were referred precisely because they were experiencing difficulties with medication use. Therefore, these data may not be reflective of the prevalence of TOA in other settings.

The factors that increase the likelihood that a patient will develop TOA are not completely understood. It is generally believed that past misuse of other substances increases the likelihood that long-term opioid therapy will result in aberrant behavior[12,42,50]; however, there is little empirical data to support this.[12,42] The majority of studies (~66%) in a Cochrane review of randomized clinical trials of long-term opioid therapy not only excluded participants with substance use disorders but also did not assess whether addiction occurred.[42] There is some evidence, mostly from small clinical studies, that other substance use disorders increase the risk of prescription opioid misuse or abuse.[36,50,53] In a large study, Edlund et al reviewed the medical records of ≥15,000 veterans and found that a personal substance abuse history was the single strongest predictor of therapeutic opioid abuse or addiction.[17] Further, as the authors note, this relationship was likely underestimated because substance use disorders often go undetected.[13,37]

Despite the known risks, patients with histories of substance abuse are more likely to be prescribed opioids, more likely to be prescribed Schedule II drugs, and more likely to be prescribed higher dosages.[57] For example, a large-scale study of adult health plan enrollees demonstrated that 51.5% of patients with a prior history of an opioid use disorder were on long-term opioid therapy. In addition, 17.0% of patients with substance use disorder histories were on long-term opioid therapy versus only 3.9% of those without.[57] Similarly, Morasco et al examined the prevalence of high-dose opioid use among veterans with chronic pain in a Veterans Affairs regional health network and found that patients receiving high doses had the highest rates of comorbid substance use disorders.[38]

There is a clear need for physicians to balance the benefits of long-term opioid therapy with the risk of addiction. The aim of the present study was to examine the associations of nonopioid substance use disorders, opioid dosage, and TOA in a population of patients thought to be representative of those at highest risk. It was hypothesized that nonopioid substance use disorders and increasing opioid dosages would be associated with increased odds of TOA. An additional aim was to examine whether opioid dosage can be used as a diagnostic indicator of opioid addiction and to determine dosage thresholds for prompting screening for TOA. It was hypothesized that opioid dosage is predictive of TOA.

Methods

Participants

This retrospective study examined clinical outcomes, tracked in an institutional review board–approved data registry, among adult outpatients with chronic noncancer pain treated in an interdisciplinary chronic pain rehabilitation program. The majority of patients were admitted after having failed to respond favorably to extensive treatment, such as interventional procedures, surgery, long-term opioid therapy, other medication management, and physical therapy. Many participants had additional concerns such as multiple medical conditions, TOA, a personal history of a substance use disorder, or psychological comorbidities. Thus, participants in this study were representative of those believed to be at the highest risk of developing TOA.

Data were available for 352 patients admitted between January 2010 and March 2011. Cases were included in the study if patients 1) were undergoing long-term opioid therapy at the time of admission or 2) had been weaned from opioids as part of chemical dependency treatment (or by virtue of running out of opioids) directly before admission. Patients were excluded if 1) they had a history of nonmedicinal opioid use that preceded the introduction of therapeutic opioids; 2) they had abused therapeutic opioids but did not meet full criteria for TOA; or 3) the diagnosis of TOA could not be excluded or made conclusively (however, in most such cases, there were clear indications of misuse or abuse). Patients were not excluded on the basis of gender, race/ethnicity, disability status, or comorbid conditions such as chronic disease, psychiatric illness, and

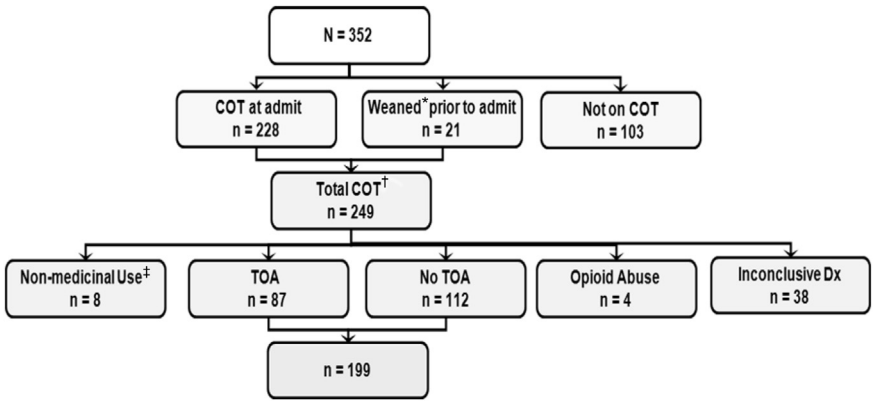

Figure 1. Inclusion flow sheet. *Includes 13 participants weaned in chemical dependency treatment prior to admission, 5 participants with TOA in remission, and 3 participants who ran out of opioids prior to admission. †Includes 12 participants on tramadol and no other opioids and 8 participants on buprenorphine. ‡Includes 2 participants with known and 6 with probable nonmedicinal use of opioids preceding the introduction of therapeutic opioids. Abbreviation: COT, chronic opioid therapy.