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SYMPTOM MANAGEMENT AND SUBSTANCE MISUSE

Opioid Analgesics and Nicotine: More Than Blowing Smoke

Jin H. Yoon, Scott D. Lane, and Michael F. Weaver

ABSTRACT

Practitioners are highly likely to encounter patients with concurrent use of nicotine products and opioid analgesics. Smokers present with more severe and extended chronic pain outcomes and have a higher frequency of prescription opioid use. Current tobacco smoking is a strong predictor of risk for nonmedical use of prescription opioids. Opioid and nicotinic-cholinergic neurotransmitter systems interact in important ways to modulate opioid and nicotine effects: dopamine release induced by nicotine is dependent on facilitation by the opioid system, and the nicotinic-acetylcholine system modulates self-administration of several classes of abused drugs—including opioids. Nicotine can serve as a prime for the use of other drugs, which in the case of the opioid system may be bidirectional. Opioids and compounds in tobacco, including nicotine, are metabolized by the cytochrome P450 enzyme system, but the metabolism of opioids and tobacco products can be complicated. Accordingly, drug interactions are possible but not always clear. Because of these issues, asking about nicotine use in patients taking opioids for pain is recommended. When assessing patient tobacco use, practitioners should also obtain information on products other than cigarettes, such as cigars, pipes, smokeless tobacco, and electronic nicotine delivery systems (ENDS, or e-cigarettes). There are multiple forms of behavioral therapy and pharmacotherapy available to assist patients with smoking cessation, and opioid agonist maintenance and pain clinics represent underutilized opportunities for nicotine intervention programs.

KEYWORDS chronic pain, drug interactions, nicotine, opioids

CONCURRENT USE OF NICOTINE AND OPIOIDS

Practitioners are highly likely to encounter patients who use both nicotine products and opioid analgesics. A significant proportion of the US population smokes or uses other nicotine products, such as chewing tobacco or electronic cigarettes, around 20% of adults.[1] At least 3% of adults receive long-term opioid therapy (LTOT) for chronic pain.[2] There is a high likelihood of overlap among these groups, especially in clinical settings. Recent epidemiological studies have demonstrated that smokers are more likely to be on LTOT.[3,4] In fact, smokers may need higher opioid analgesic doses, as shown in several recent clinical studies.[5–7]

Smokers may have an increased risk of developing chronic pain.[8–10] Smokers with chronic pain complain of pain of greater severity and at more body sites.[11] Of particular interest is the often-reported relationship between smoking and back pain.[10] In relatively recent prospective cohort studies, some have noted a dose-dependent relationship between adolescent smoking and the development of back pain among adolescents[12] and twins.[13] One study including over 50,000 adolescents observed daily smoking to be one of the strongest risk factors for low back pain hospitalization, and this association persisted into adulthood.[14] Overall, smokers experience a greater impact of pain on occupational and social functioning than nonsmokers.[15,16] Smokers also

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tend to have worse chronic pain outcomes with more disability.[17,18]

High rates of nicotine use are well documented in the drug-abusing population. A review of nicotine smoking rates among drug abusers summarizing the literature between 1987 and 2009 reported aggregated (cross-drug class) smoking rates ranging between 65% and 75% annually.[19] Notably, the highest odds ratio (OR) for any drug class was among individuals in methadone maintenance programs (OR = 2.25). Other reviews of methadone maintenance patient populations estimate nicotine smoking rates between 74% and 94%.[20] A study of 305 heroin users on agonist (i.e., substitution) therapy with methadone or buprenorphine found that 97% were cigarette smokers, using an average of approximately 20 cigarettes per day.[21] In addition to the unequivocal data in methadone-maintained individuals, the majority of heroin users are nicotine smokers (heroin is a morphine prodrug), and nicotine smoking may actually extend the duration of heroin reinforcement.[22]

Tobacco-related mortality and morbidity is accordingly high in prescription opioid users. Methadone and other opioid treatment programs represent opportunities for the development of smoking intervention programs in the opiate-using population.[23] A recent review noted that current smoking intervention efforts in methadone maintenance programs generally precipitate short-term reductions in smoking but have been largely unsuccessful in promoting sustained abstinence.[24] One review cites long-term abstinence rates <10%.[20]

Although nicotine use rates in methadone-maintained individuals are well documented, there is a troubling scarcity of population-level data regarding nicotine use among both licit and illicit users of prescription opiates. Although it may be reasonable to conclude—based on smoking rates in methadone users and in the general drug-abusing population—that nicotine use rates are also much higher in prescription opiate users than in the general population, public health/epidemiological data from US samples are currently needed. One population-based study using health surveys in Norway found that frequency of prescription opiate use was greater in both men and women with a history of smoking.[25] Importantly, this study found that odds ratios for prescription opioid use increased as a function of severity of nicotine use (dependent daily smokers: OR = 3.1), suggesting a dose-response relationship between frequency of nicotine use and amount of prescription opiate use.[25] A study based on a sample from Alberta, Canada, focused on past-year prescription drug misuse found that opiates were the most common class of misused prescription drugs. Prescription drug misuse was associated with problem gambling and illicit drug use, but was not associated with nicotine smoking.

The substantial evidence linking nicotine smoking and opiate use argues for a neurobiological interaction between the neurotransmitter systems that underlie the actions of opiates (opioid system) and nicotine (nicotinic-cholinergic system). Indeed, as reviewed in the next section, these two transmitter systems interact in important ways to modulate opiate and nicotine effects on drug reward, drug tolerance, drug withdrawal, and nociception. Knowledge of these interactions has led clinicians to utilize opioid antagonists to promote cessation from nicotine smoking. However, reviews and meta-analyses indicate that the use of opioid antagonists (particularly naltrexone) provide no benefit over placebo, either as a stand-alone pharmacotherapy or as an adjunct to nicotine replacement.[26]

Nicotine produces antinociception in preclincial models,[27,28] and cigarette smoking rates are elevated in patients with chronic pain.[29] Accordingly, nicotine has been examined as an analgesic for postoperative pain; the most common modalities have been nicotine patch and nasal spray. However, a recent review and meta-analysis found that the use of nicotine as an analgesic increased postoperative nausea and did not reduce pain in a statistically significant fashion.[30] However, this review did find that postoperative use of nicotine did significantly reduce the need for opioids 24 hours post operation. Perhaps counterintuitively, nicotine smoking increases risk for chronic pain symptoms.[10,25] In summary, nicotine has not been demonstrated as a clinically effective analgesic in humans.

INTERACTIONS BETWEEN ENDOGENOUS OPIOID AND CHOLINERGIC SYSTEMS

The endogenous opioid system is a diffuse and complex component of the central nervous system (CNS). It interacts with many of the major neurotransmitter systems and plays a direct or modulating role in facilitating the action of many drugs of abuse.[31] In addition to abused opiates, there is both preclinical and clinical evidence to suggest that the endogenous opioid system interacts with drugs that act on dopaminergic, cannabinoid, and (most relevant to the present report) nicotine-acetylcholine neurons.[28,32,33]

The endogenous opioid system involves at least three major peptide classes that facilitate neurochemical transmission: beta-endorphins; met-, and

leu-enkephalins; and dynorphins; and three classes of G-protein-coupled opioid receptors: mu, delta, and kappa. A fourth peptide and the corresponding receptor, nociceptin/orphanin FQ, have more recently been identified, but are less well characterized than the extensively studied mu, delta, and kappa systems[27,28]. The three receptor peptide classes appear to have unique properties and different affinities for the three major receptor units. Of relevance to this review, the delta receptor is known to regulate analgesia and physical dependence; the kappa receptor facilitates dissociative and dysphoric effects and modulates stress reactions; and the mu receptor (for which morphine/heroin has the greatest affinity) facilitates euphoria and physical dependence.[34]

Similar to the opiate system, the nicotinic-cholinergic system interacts with and modulates the action of several other neurotransmitter systems, including dopamine, norepinephrine, glutamate, and most notably the opioid system.[28,35] The nicotinic-acetylcholine system has two major receptor classes: alpha (α) and beta (β), with a range of identified subunits ($\alpha2$–$\alpha10$ and $\beta2$–$\beta4$), which are ligand-gated ion channels. The most abundant, widely distributed, and arguably most well-studied subtypes with regard to nicotine and other drugs of abuse are the $\alpha7$ and the $\alpha4\beta2$ complex. The $\alpha4\beta2$ complex is believed to mediate nicotine reinforcement by activating dopamine transmission, as well as stimulating the release of the opioid peptides (i.e., beta-endorphins, enkephalins, and dynorphins) in the ventral tegmental area and nucleus accumbens, particularly via action at the mu opioid receptor.[32] Thus, CNS dopamine release induced by nicotine administration is dependent on facilitation by the opioid system. In particular, the following relationships have been identified: (i) the endogenous opioid enkephalins and beta-endorphins act on mu receptors in facilitating the reinforcing effects of nicotine; (ii) the aversive effects of nicotine (e.g., nausea, negative emotional states) appear to be facilitated by dynorphins and delta and kappa receptor systems; and (iii) the enkephalin peptides and mu receptors largely facilitate the somatic components of nicotine withdrawal.[33] Further, it is suggested that the $\alpha7$ nicotinic subunit interacts with the endogenous opioid system to facilitate physical dependence, whereas the $\alpha4\beta2$ nicotinic subunit complex interacts with mu opioid receptors in the ventral tegmental area, nucleus accumbens, and extended amygdala (key components of the well-established mesocorticolimbic reinforcement pathway) to modulate nicotine reinforcement and facilitate psychological dependence.[27]

In vitro studies demonstrate that morphine binds to and functionally interacts with $\alpha4\beta2$ receptors in the CNS, providing one mechanism through which morphine exerts its reinforcing/euphoric effects.[35] Like morphine, prescription opiates such as oxycodone and hydrocodone bind to the mu receptor, but also exert action on delta receptors.[36] They are thus likely to interact with the nicotinic-acetylcholine system in a fashion similar to morphine.

Notably, increasing evidence implicates the nicotinic-acetylcholine system in modulating the intake (including self-administration) of several classes of abused drugs, including (clearly) nicotine, and also opioids, cocaine, alcohol, and marijuana. This observation may be linked to the established finding that nicotine can serve as a prime for the use of other drugs.[37] In the case of the opioid system, this priming effect may be bidirectional; a postulate supported both by the biochemical interactions of the nicotinic-acetylcholine and opioid systems, and the alarmingly high rates of smoking among opiate users.

CHRONIC PAIN, NICOTINE USE, AND OPIOID ANALGESICS

Pain can be the result of injury or disease such as in the case of postoperative pain or cancer-related pain. Pain can also be the disease itself, such as in the case of neuropathic pain. Neuropathic pain refers to pain resulting from damaged nerves, contrasting with nociceptive pain caused by damage to body tissue. Chronic pain is widely experienced by the general population, causing significant loss of quality of life and morbidity[38,39] and has substantial public health costs. Approximately 1 out of every 3 (100 million) Americans experiences chronic pain, but as described earlier, only 3% of adults receive LTOT for chronic pain.[2]

The first step in pain relief medication typically involves administration of nonprescription, oral medications such as aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs). If these medications are not effective in controlling pain, opioids may be administered either in conjunction with the above medications or as a replacement. Relatively weaker opiates are administered orally. Some opioids can be administered orally, but others are also administered transdermally via patches (e.g., fentanyl), through suppositories, or through injections or with an external infusion system. The existence of endogenous opioids (endorphins, enkephalins, and dynorphins) was discovered in 1975. The majority of

opioids are agonists, with common examples including morphine, hydromorphone, fentanyl, methadone, and oxycodone. Among opioid analgesics, there also exist partial agonists such as buprenorphine as well as mixed agonists, including butorphanol, nalbuphine, and pentazocine. The latter should be used with caution, as analgesic effects plateau with increasing dose and may actually reverse the effects of agonist opioids.[40]

There has been increasing awareness and interest in the relationship across opioid use, cigarette smoking, and chronic pain.[10] A commonly observed trend is higher rates of cigarette smoking among individuals using a variety of drugs.[41,42] This effect has not been as widely reported for individuals receiving LTOT for pain, but this may reflect the relatively recent increase in individuals receiving LTOT rather than the absence of a specific relationship between opioids received for chronic pain and smoking. Nicotine itself is known to have analgesic effects, but generally induces nausea among individuals who do not receive nicotine chronically.

DRUG INTERACTIONS BETWEEN OPIOIDS AND NICOTINE

Drugs are metabolized by chemical reactions that fall into two categories. Phase I reactions include hydrolysis and oxidation, whereas Phase II reactions involve making substances more hydrophilic.[43] For opioids, the most important Phase II reaction is glucuronidation, which is catalyzed by uridine diphosphate glucuronosyltransferase (UGT). In regards to Phase I reactions, approximately half of all medications, including many opioids, are metabolized by the cytochrome P450 enzyme system.[44–46] The cytochrome P450 (CYP450) enzyme system is involved in the pharmacokinetics of multiple drugs, including nicotine and opiates. The CYP450 system comprises a number of enzymes. Over 30 enzymes have been identified as part of the CYP450 system, with more likely to be discovered, but 90% of human drug oxidation can be attribute primarily to six enzymes (i.e., CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4/5).[47] Opioids that undergo Phase I metabolism are catalyzed predominately by CYP3A4 and CYP2D6 (e.g., codeine, hydrocodone, oxycodone, methadone, tramadol, fentanyl, hydromorphone) and are therefore prone to possible drug-drug interactions.[43,46] In the case of the CYP450 system, drug-drug interactions can result when one drug induces or inhibits one of the CYP450 enzymes. In contrast, opioids that are primarily metabolized by UGT via Phase II reactions (e.g., morphine, oxymorphone, tapentadol, hydromorphone) are less likely to have drug-drug interactions.[43]

The distribution of enzymes can be varied across individuals, with polymorphisms that can affect drug metabolism. For example, CYP3A activity can vary 5-fold, but this variability can increase to 400-fold as a result of drug-drug interactions.[44] These genetic variations are categorized into four groups: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers.[48] For example, CYP2D6 metabolizes codeine to morphine and tramadol to *O*-desmethyltramadol. Individuals with the ultrarapid metabolizing phenotype are susceptible to toxicity from the metabolized forms.[49] Conversely, individuals who are slow metabolizers of CYP2B6 are also susceptible to methadone toxicity due to slower methadone metabolism.[50] CYP3A4 and CYP2D6 are the most relevant P450 enzymes in relation to opioid metabolism. The majority of CYP3A4 polymorphisms result in decreased enzyme function. The proportion of patients without a genetic polymorphism is relatively low, except for specific polymorphisms in Hispanics and Indo-Pakistanis. In regards to CYP2D6, the wild-type consists of extensive metabolizers.[51] The majority of polymorphisms results in decreases or absent enzyme activity, although one polymorphism has been identified to increase enzyme activity. African Americans and Asians are at the greatest risk for being poor metabolizers.[52] An exhaustive review on the topic is available in a series of articles by Zhou and colleagues.[53–55]

Cigarette smoking also affects both Phase I and II reactions. In regards to Phase I reactions, smoking primarily induces CYP1A1 and CYP1A2 and less consistently CYP2E1.[56–58] Cigarette smoking enhances CYP1A2 via polycyclic aromatic hydrocarbons binding to aryl hydrocarbon receptors, which consequently transcriptionally activates the CYP1A2 gene.[57] As noted above, individuals on methadone maintenance engage in high rates of cigarette smoking in a dose-dependent manner. Methadone is primarily metabolized by CYP3A4, but also by CYP1A2 to a lesser degree. In a recent case study, methadone toxicity was observed in an individual on a methadone maintenance program who had stopped smoking.[59] CYP1A2 induces a number of drugs, including duloxetine, a serotonin-norepinephrine reuptake inhibitor, which can be prescribed for neuropathic pain. The effects of smoking on CYP2E1 appears to be relatively moderate and not present in all individuals.[56] However, CYP2E1 is of interest, as it is involved in the metabolism of acetaminophen as well as ethanol and may activate smoking-related carcinogens.[60,61] Therefore, induction of CYP2E1 may lead to acetaminophen hepa-

totoxicity and explain individual variation in the development of smoking-related cancer. Interestingly, smoking appears to inhibit CYP2A6, which is primarily responsible for the metabolism of nicotine.[58,62] In regards to Phase II reactions, polycyclic aryl hydrocarbons in cigarette smoking induces UGT-related metabolism,[63,64] including codeine.[65] Although it has been consistently observed that smokers have increased requirements for opioids postoperatively, the metabolism of various opiates can be complicated, so the relationship between smoking and UGT is not clear.[66]

Other issues should be considered when faced with cigarette smoking. In vitro studies have observed carbon monoxide (CO) to inhibit the CYP450 system.[56] For example, CO inhibited CYP2D6 enzymes in human liver microsomes,[67] but this effect has not been observed clinically in humans.[62] In addition to CO, the presence of trace amounts of heavy metals such as cadmium, nickel, chromium, lead, and arsenic may potentially have effects on the CYP450 system in humans.[68] Additionally, psychodynamic effects of smoking decreasing the analgesic efficacy of the opioids propoxyphene (discontinued) and pentazocine have been noted, although the mechanism is unknown.[58]

GUIDELINES FOR PRESCRIBERS

It is good for practitioners who prescribe opioid analgesics to be aware of the connections between opioid use and nicotine use. This can help improve prescribing practices in terms of patient safety and treatment outcomes.

In terms of risk assessment for patients for whom the practitioner is considering a therapeutic trial of opioid analgesics, asking about nicotine use can be valuable. Since there is no definitive test to predict which patients will do well with a therapeutic trial of opioids for chronic pain, it makes sense to take a "universal precautions" approach to all patients with chronic pain.[69] This reduces stigma, improves patient care, and reduces risks by adopting a minimum level of care applicable to all patients presenting with chronic pain. Universal precautions include asking patients about personal and family history of substance use. A less threatening way to begin gathering information about substance use from patients is to start by asking about use of nicotine products. Because tobacco products are legal and relatively socially acceptable, asking patients about smoking is generally nonthreatening and allows the patient to give a yes-or-no answer to a straightforward question. This is simple and often routine for both the patient and practitioner. An affirmative answer can be followed up with some additional questions about quantity and frequency of tobacco product use in a matter-of-fact manner, which helps set the stage for later questions about substance use with a nonthreatening approach. Obtaining information about smoking can be very important as a predictor for potential patient outcomes.

Smoking has been associated with nonmedical use of prescription opioids. The strongest predictor of higher risk for nonmedical use of prescription opioids is a history of substance abuse, especially polysubstance abuse, although a significant single substance identified in various research studies is current tobacco smoking.[70] However, history alone is usually insufficient to predict risk accurately and should be combined with collateral information from significant others and previous health care providers.[71] A likely reason for the association between higher risk for opioid misuse and nicotine use is because nicotine is a known addictive substance, so tobacco users have already demonstrated establishment of at least one addiction. Nicotine is a potent gateway drug for diverse illegal drugs,[72] especially among adolescents.[73] With the revelation of use of one addictive substance, patients are at higher risk for manifestation of addiction to other substances, including opioid analgesics, due to the presence of shared risk factors.

Cigarettes are the most prevalent form of tobacco consumption in the United States, but not the only popular nicotine delivery method. When asking about nicotine or tobacco products, it is often useful to include an open-ended question, such as, "What types of tobacco or nicotine products have you used?" This provides an opportunity to obtain information on tobacco products other than cigarettes, such as cigars, cigarillos, pipes, hookah pipes, smokeless tobacco (snuff, snus), and electronic nicotine delivery systems (ENDS, or e-cigarettes).[74] It is helpful for clinicians to ask about specific products by name, since patients may not consider ENDS to be a "tobacco product" or may not realize that a hookah pipe contains tobacco.[75] Asking specifically about a variety of nicotine products allows a prescriber to more accurately determine the impact of nicotine consumed on the patient's chronic pain and use of opioid analgesics.

Although ENDS may have the potential for less physical harm compared with tobacco, due to the fact that they do not deliver carbon monoxide and some carcinogens,[76,77] they do deliver nicotine. As with other drugs of abuse, including opioids, users may escalate the dose due to physical tolerance. Users may also tamper with the ENDS to provide larger doses of nicotine, or make changes to the liquid that is

used in these devices ("e-liquid"). One of the ways in which users tamper with ENDS is by "dripping."[78] To engage in "dripping," the user applies the e-liquid directly from the bottle onto the heating element of the ENDS and then inhales the vapor produced. Dripping has gained popularity through dissemination via the Internet, and specialized "drip tips" are available for purchase.[74] This process may provide a larger dose of nicotine when a nicotine-containing solution is used, but also allows for higher exposure to byproducts of heating the other ingredients of the liquid, such as formaldehyde.[79] Another method of tampering with ENDS is by mixing different e-liquids with higher concentrations of nicotine. Variable-voltage ENDS are available, and higher voltage appears to increase the nicotine yield of the vapor.[80] Asking patients about unorthodox use of ENDS is helpful to determine the risk of harm. Intentional misuse of ENDS puts the patient at higher risk for intentional misuse of other substances, including prescribed opioid analgesics.

While asking about nicotine product use, practitioners can take advantage of the opportunity to address smoking cessation with the patient. Patients who use tobacco products perceive the advice from a health care professional to quit as a strong motivator for a cessation attempt.[81–83] Providing appropriate, accurate information about risks of tobacco products, and encouraging healthy choices, can help patients to make the best informed decision about changing behavior with respect to use of nicotine.[74] The responsibility of the practitioner is to motivate the patient to seek recovery from nicotine use instead of blaming the patient for being unmotivated to change.[84] Brief counseling provided by a clinician in a health care setting significantly increases nicotine quit rates versus no counseling.[85] There are multiple forms of behavioral therapy available, including smoking cessation group counseling or individual therapy based on cognitive-behavioral principles. Randomized control trials demonstrate that nicotine replacement therapy, varenicline, and bupropion all increase the long-term success of quit attempts for tobacco smoking.[86] Clinicians can also refer patients to the national toll-free telephone quitline number, 800-QUIT-NOW (800-784-8669), or to a Web site (www.smokefree.gov) maintained by the US Department of Health and Human Services to provide information to download to make cessation easier.

Patients with chronic pain who express an interest in nicotine cessation may benefit from medications to assist with this. Bupropion is a prescribed polycyclic antidepressant that is also started prior to tobacco cessation and continued for 3–6 months of therapy.[87] Bupropion has been shown to be effective for neuropathic pain[88] as well as smoking cessation and depression, all of which may be present concurrently among patients with chronic nonmalignant pain. Awareness of nicotine use and patient level of interest in quitting can help with selection of therapeutic options, especially those that may be effective for multiple conditions.

RESEARCH DIRECTIONS

Currently, the extant literature suggests that important and clinically significant interactions exist between opioids, cigarette smoking, and pain. However, multiple areas of this relationship clearly need further investigation. First and foremost, a clearer picture between the relationship between LTOT use and cigarette smoking is needed. High rates of comorbidity would not be surprising given the documented relationship among methadone-maintained individuals and other populations such as those with cocaine use disorders[41,42,89–94] and problem drinking.[95–99] Once this information is gathered, researchers can begin to better understand how smoking affects the analgesic effects of opioids. Although the current review highlights some of these findings, there is a lack of knowledge regarding the effects of smoking on the analgesic effects on the vast majority of commonly prescribed opioids.

Another important area of future research is how ENDS use may affect opioid analgesia. Growing evidence supports that ENDS can transmit a number of biologically relevant substances beyond just nicotine.[100,101] This area of study will likely face substantial challenges given the general lack of regulation regarding ENDS devices and the rapidly growing variety of ENDS products and their uses.[75]

Finally, a number of clinically important areas also exist that would benefit from further exploration. For example, there has been growing awareness that smoking cessation prior to surgery can improve a number of important surgical outcomes such as wound healing.[102] However, little is known how this might affect the efficacy and appropriate dose of opioids used during and following surgery. Given the case report on methadone toxicity following smoking cessation reported above and general lack of knowledge regarding opioid and smoking interactions, there may be important clinical risks that have yet to be discovered. Also, an interesting relationship between chronic smoking and higher susceptibility to developing back pain has been repeatedly reported.[10] However, the exact mechanism of this relationship is still unknown. For example, do smokers simply engage in unhealthy behaviors (poor posture,

other unhealthy behaviors) that affect the development of back pain, or does cigarette smoking somehow inhibit the healing or even directly damage the spine and related muscle groups?

Overall, evidence strongly suggests that cigarette smoking and opioid use are intimately intertwined and that dual use may have clinically significant effects on opioid analgesia. However, it is also clear that important details of this relationship have not been directly explored, and the field would benefit from direct and targeted investigations.

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