

# Likeability and Abuse Liability of Commonly Prescribed Opioids

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## Abstract

**Introduction** Nonmedical use of prescription opioid analgesics is associated with epidemic levels of morbidity and mortality. There are several factors that affect the abuse liability of the various opioids, including likability or the pleasurable subjective effects. Due to rising public health concerns over escalating prescription opioid abuse, we sought to examine the literature about abuse liability with a specific focus on likability studies.

**Methods** A search of EMBASE and MEDLINE databases identified articles that described the comparative likeability and/or abuse potential of hydrocodone and oxycodone relative to each other and/or of either one to morphine. After an assessment of study quality using the Oxford/Jadad scale, relevant details such as demographics, study design, and outcome measures were compiled into an evidence table.

**Results** We identified nine studies that met inclusion criteria. All were double-blinded, randomized, placebo-controlled crossover studies and scored 5 out of 5 Jadad scale. There was no consistent clinically significant difference between abuse liability of morphine and hydrocodone. Oxycodone demonstrated high abuse liability on the basis of its high likability scores and a relative lack of negative subjective effects.

**Conclusion** Oral oxycodone has an elevated abuse liability profile compared to oral morphine and hydrocodone.

**Keywords** Oxycodone · Hydrocodone · Morphine ·  
Likeability · Abuse liability

## Introduction

The USA is witnessing a burgeoning epidemic of nonmedical prescription opioid use associated with escalating rates of addiction, mortality, and economic loss [1]. Prescription opioids are a group of morphine-like analgesics that share clinical effects despite distinct pharmacological properties. The term “nonmedical users” refers to patients who use opioids in ways not directly intended by the prescriber and includes those who abuse the opioids for recreational purposes.

With the current options and ready availability of opioids, factors beyond availability become relevant to the evaluation of user preference. Such characteristics comprise a drug's pharmacological properties including onset or duration; mode of administration; adverse effects, such as nausea or flushing; or the desired psychoactive effects. The abuse liability of a drug characterizes its net positive and negative subjective effects and thus the likelihood of being used for recreational purposes. The term “likeability” generally represents the positive psychoactive component of a drug's subjective effects.

Although nearly all mu opioid receptor agonists are euphorogenic, select opioids are preferred among the abusing population. Therapeutically relevant pharmacological classifications, such as potency or duration of action, are not completely predictive of abuse liability. However, abuse liability can be inferred based on street price, pharmacy theft rates, drugs leading to treatment access [2], and overdose morbidity and mortality data [3]. For example, although threefold more hydrocodone than oxycodone tablets are sold [4], the latter is proportionally responsible for a much greater incidence of ED visits associated with nonmedical use

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[3]. This suggests that oxycodone is preferentially used for recreational purposes.

Due to rising public health concerns over escalating prescription opioid abuse, we sought to examine the literature about abuse liability with a specific focus on likability studies. We chose to compare two of the most widely prescribed oral opioids, hydrocodone and oxycodone, to each other and/or to morphine in order to assess abuse liability.

## Methods

A search of the English language medical literature was performed using MEDLINE and EMBASE databases to identify empirical literature using the independent terms “opioid likeability” and “opioid abuse liability.” Both terms were included due to the inconsistency in the design and terminology among relevant studies. This was supplemented by a manual review of the reference lists to identify gray literature, which include publications and other documents from federal offices, government agencies, and professional societies. The search results were subsequently limited to articles that specifically described the comparative likeability and/or abuse potential of hydrocodone and oxycodone relative to each other and/or of either one to morphine. Relevant articles were screened in a structured iterative process and additional literature search performed based on citations from pertinent articles. All articles used in the formulation of this clinical policy were graded by at least two authors using the Oxford/Jadad scoring system [5]. This system was applied to assess blinding, randomization, and withdrawal/dropouts and was used to assess the general quality of the selected research. Agreement was met among the reviewers on the score given to each respective publication.

Information from relevant articles was manually entered into a spreadsheet that contained details of target population demographics, study design typology, outcome measures (such as likeability), and funding source (Table 1). We collected data on formulation (e.g., immediate release vs. sustained release), route of administration (oral (PO) vs. intravenous (IV)), reported positive and negative effects, physiological effects when mentioned, method of evaluating abuse potential or likeability (e.g., visual analogue scales (VAS), the Addiction Research Center Inventory (ARCI), adjective opioid ratings scales, subjective questionnaires involving drug effect/liking/take again, breakpoint values drug vs. money, drug preference questionnaires), and funding source. Due to the lack of standardization of research studies and instrumentation, a meta-analysis was not feasible. Data were interpreted across a heterogeneous group of publications; thus, an integrated approach towards findings

and objectives were extracted from the manuscript to form a review.

Because the definition of positive and negative effects varied by study, we included as positive effects terms such as: euphoria, feel good, feeling high, carefree, coasting, dreamy, mellow, social, stimulated, pleasant thoughts, and pleasant bodily sensations. Similarly, terms defined as negative effects included: dysphoria, dislike, feeling irritable, dizzy, difficult to concentrate, headache, dry mouth, flushing, gastrointestinal distress, feeling heavy, sluggish, and unpleasant thoughts and bodily sensations. Outcome measures of increased abuse liability were based on high subjective ratings for positive effects (e.g., likeability) and low subjective ratings for negative effects. The reinforcing effect of an opioid was variably defined and quantified, in different methodologies, as either the desire to “take again” or was based on participant willingness to pay a specified amount (in dollars) for a drug.

## Results

Seventeen studies were found initially that met search criteria, and further review identified that nine met inclusion criteria. The primary reason for exclusion of a study was lack of an active comparator group to either the other semi-synthetic opioid or to morphine. All identified studies were double-blinded, randomized, control crossover studies. All scored 5 out of 5 on the Oxford/Jadad scale for quality (Table 1). Seven of the studies used exclusively subjects who had a history of opioid use or abuse. The studies varied in the dose form used and route of administration (PO vs. IV), as well as the other opioids included in the assessment (Table 1).

Subjective effects of opioid products were determined using VAS, ARCI, and the adjective opioid ratings scales. Some studies included questionnaires involving reinforcement data including drug effect, liking, and take again [6–9]. One study directly assessed breakpoint values of participants' desire for drug vs. money [10]. Additionally, studies included objective physiologic data and performance batteries to assess timing of onset, duration, and extent of opioid affects (Table 1).

Multiple studies, largely from a single research group, found no clinically significant difference between abuse liability of morphine and hydrocodone. Both hydrocodone and morphine demonstrated similar subjective positive and negative effects [6, 8]. This same pattern was identified when comparing extended-release morphine and immediate-release hydrocodone preparations [11]. In these studies, hydrocodone did not demonstrate reinforcing effects or statistically significant abuse liability. Moreover, oxycodone demonstrated high subjective attractiveness

**Table 1** Target population demographics, study design typology, outcome measures (such as likeability), and funding source

Study	Year	Design	Patient population	Outcome measures	Results	Jadad score	Pharm funding
Comer SD, et al. [10]	2008	Inpatient randomized double-blind, placebo-controlled, crossover study testing physiological, subjective, and performance effects IV fentanyl, oxycodone, morphine, buprenorphine, and heroin each at placebo and 4 doses	IV heroin users on PO morphine maintenance	VAS, Opioid Symptom Checklist, Subjective Opioid Withdrawal Scale, Drug Effect Questionnaire, Drug vs. Money Breakpoint Comparison	Oxycodone appears to have substantial abuse liability due to its high positive subjective ratings and lack of negative effects. Oxycodone produced robust reinforcing effects similar to heroin and morphine with no subjective ratings of bad effects.	5	Janssen Pharmaceuticals (Johnson and Johnson), Schering-Plough Corporation
Stoops WW, et al. [12]	2010	Inpatient randomized double-blind, placebo-controlled, crossover study testing physiological, subjective, and performance effects of IV oxycodone, morphine, and hydrocodone (5, 10, and 20 mg/10 ml) and placebo	Recreational IV opioid users	VAS, ARCI, 17 Item Adjective Checklist	IV potency analysis revealed that IV oxycodone is more potent than hydrocodone and morphine. Oxycodone had lower scores for bad effects than morphine and hydrocodone. Oxycodone had the highest “street value” rating. Peak effects of oxycodone were of greater magnitude, but not significantly different when compared to morphine and hydrocodone (supported by relative potency analysis).	5	NIDA
Walsh SL, et al. [13]	2008	Outpatient randomized double-blind, randomized, placebo-controlled crossover trial testing relative abuse potential and potency oral oxycodone (10, 20, 40 mg), hydrocodone (15, 30, 45 mg), hydromorphone (10, 17.5, 25 mg), and placebo by assessing subjective, observer-rated, and physiological effects.	Recreational opioid users	VAS, ARCI, Subject and Observer-rated Adjective Scale, 17 Item Adjective Checklist	Relative potency analysis hydrocodone: hydromorphone 0.772:1, oxycodone: hydromorphone 0.85:1 - suggestive that abuse liability potency and analgesic potency different. Patients had no bad effect for any drug/dose. All three drugs increased ratings of euphoria (liking drug, good effects, high, and MBG score). No difference in time to peak subjective effects oxycodone, hydrocodone, hydromorphone. No substantial differences in subjective effects particularly as related to abuse liability discernable between 3 formulations tested.	0	NIDA
Wilsey BL, et al. [11]	2009	Outpatient randomized, double-blind, crossover, placebo-controlled trial assessing abuse liability of PO ER morphine 15 mg, hydrocodone 30 mg/acetaminophen 975 mg, and placebo	Chronic pain patients with hx opioid abuse	VAS, ARCI, cue reactivity	Drug liking/abuse liability does not differ substantially between hydrocodone/apap and morphine ER. Cue reactivity did not differ among drugs tested and placebo, but was uniformly high.	5	NCRR/NIH
Zacny JP and Gutierrez S [7]	2003	Outpatient double-blind randomized placebo-controlled crossover trial testing subjective and objective physiological effects of PO doses oxycodone (10, 20, 30 mg), morphine (40 mg), 2 mg lorazepam, and placebo	Healthy volunteers with a history of drug use	VAS, ARCI, Adjective Rating Scale, questionnaire drug liking/drug effect/take again, 24-h post-session sequelae questionnaire	Oxycodone produced a profile of subjective effects that include abuse liability-related effects and unpleasant effects. Oxycodone at the 20 and 30 mg doses increased the MBG scores (described as euphoria) on the ARCI, 40 mg morphine did not cause an increase in MBG score. Peak liking and “want to take drug again” ratings were	5	NIDA

Table 1 (continued)

Study	Year	Design	Patient population	Outcome measures	Results	Jadad Pharm funding score
Zacny JP and Lichtor SA [9]	2008	Outpatient double-blind randomized placebo-controlled crossover trial testing subjective and objective physiologic effects of PO doses oxycodone (10, 20 mg), morphine (30, 60 mg), and placebo	Healthy volunteers with a history of drug use	VAS, ARCI, Adjective Rating Scale, questionnaire drug liking/drug effect/take again, 24-h post-session sequelae questionnaire	increased by all three doses oxycodone and 40 mg of morphine. Oxycodone 20 mg has more abuse liability-related effects and fewer aversive effects than morphine 60 mg. High dose oxycodone ratings of feel bad were zero, whereas for morphine 60 mg feel bad ratings were 12.4. Morphine had increased SE dry mouth. No dry mouth reported by any participants given any dose oxycodone.	5 NIDA
Zacny JP. [6]	2003	Outpatient double-blind, randomized placebo-controlled crossover study testing subjective and objective effects of PO hydrocodone/homatropine (5/1.5, 10/3, 20/6 mg), morphine (40 mg), 2 mg lorazepam, and placebo	Healthy volunteers with a history of drug use	VAS, ARCI, Adjective Rating Scale, questionnaire drug liking/drug effect/take again, 24-h post-session sequelae questionnaire	20 mg hydrocodone/homatropine and morphine had a similar profile of subjective effects. Peak liking between morphine and hydrocodone were similar. Both morphine and hydrocodone had pleasant and unpleasant effects noted. Post-session ratings for "drug liking" and "want to take again" were not significant for hydrocodone or morphine. Additionally, there was no significant increase in MBG score for hydrocodone or morphine.	5 NIDA
Zacny JP and Gutierrez S [14]	2009	Outpatient randomized, double-blind, placebo-controlled, crossover study evaluating subjective and objective effects PO doses acetaminophen plus oxycodone (10, 20) or hydrocodone (15 and 30), and acetaminophen alone, placebo.	Healthy volunteers with a history of drug use	VAS, ARCI, Adjective Rating Scale, questionnaire drug liking/drug effect/take again, 24-h post-session sequelae questionnaire and drug liking/take again	In non-drug-abusing volunteers, peak rating of "drug liking" elevated for both doses oxy/acetaminophen, but only for the higher dose hydrocodone/acetaminophen. Peak ratings of "take again" were elevated for oxycodone/acetaminophen at low dose only. Overall, oxycodone was found to have greater abuse liability and does not have dry mouth SE present with hydrocodone.	5 NIDA
Zacny JP, et al. [8]	2005	Outpatient randomized, double-blind, placebo-controlled crossover study assessing subjective and objective effects of PO hydrocodone/acetaminophen (5/500, 10/500, 20/1,000), morphine (40 mg), and placebo	Recreational opioid users	VAS, ARCI, Adjective Rating Scale, questionnaire drug liking/drug effect/take again, 24-h post-session sequelae questionnaire, and drug liking/take again	Hydrocodone/acetaminophen had several subjective effects related to abuse liability, but only at the 20 mg dose. Peak MBG scores for hydrocodone approaches, but did not reach, significance. Several subjects reported liking and wanting to take hydrocodone again, but 24 h ratings of "drug liking" and "take again" were not statistically significant. Peak rating of liking was increased for hydrocodone 20 mg and morphine 40 mg, but morphine had significantly decreased trough ratings of "drug liking" (dislike) and take again at 24 h.	5 NIDA

ratings and a paucity of negative ratings across the majority of studies assessed [7, 9, 10, 12]. Oxycodone also demonstrated significantly increased reinforcing characteristics. “Take again” ratings were consistently higher for oxycodone than morphine [6, 10].

One study found no substantial difference in subjective effects related to likability of oxycodone, hydrocodone, and hydromorphone, but did demonstrate increased risk of abuse over placebo for all three opioid products assessed [13]. A similar study comparing oxycodone and hydrocodone to placebo found that peak liking ratings were significantly greater with oxycodone compared to placebo, and those of hydrocodone were not [14]. Most studies that included morphine used morphine as a gold standard opioid and differentiated the abuse potential of morphine vs. the newer opioid drugs. None of the randomized controlled trials that included morphine found statistically significant abuse potential or reinforcing effects of morphine [6, 8, 9]. At high doses, morphine was found to have predominantly dysphoric effects and increased negative side effects including dry mouth and flushing [8, 9]. Mean 24-h “take again” ratings in one study indicated that in recreational drug users, morphine was less likely to be “wanted” or taken again than placebo [8].

## Discussion

At a national level, hydrocodone and oxycodone are the most frequently prescribed opioid analgesics and have the highest level of abuse of any prescription medication [3, 4]. Our literature review demonstrated that oxycodone has a substantially elevated abuse liability profile due to high likability scores and far fewer negative subjective effects. Our findings are consistent with previous epidemiologic and ethnographic studies that suggest that oxycodone is favored over hydrocodone. When patients with a history of abuse are queried about their choice of opioids, abusers preferred oxycodone over other opioids [15].

The route of administration in the reviewed studies was generally oral. Prior work has shown that abusers of hydrocodone and oxycodone typically took medication orally, the route intended for use, whereas morphine abusers more often injected PO morphine formulations [16]. Since progression to intravenous use is not uncommon among prescription opioid users, we included the two studies that evaluated the comparative effects of the selected opioids administered intravenously. Results of one study suggested that all three opioids produce subjectively similar effects and are all of equal abuse potential when given by this route [12]. Both semisynthetic opioids produced markedly less negative effects than morphine. No studies could be found that compared the abuse potential of the same opioid agent via multiple routes.

Abuse liability of opioid analgesics reflects a combination of factors, but availability likely maintains the greatest impact on the opioid choice of abuse for an individual or population. For example, although opium has been abused for centuries, the isolation of morphine leads to its preferential widespread abuse. The subsequent derivatization of morphine to form heroin essentially displaced morphine abuse at the beginning of the twentieth century. Those intent on opioid abuse now have multiple options due to the development of additional semisynthetic, and fully synthetic, opioids that are in pharmaceutical grade drugs. Ultimately, healthcare providers are the source of most of these drugs, which has resulted in this new trend of prescription opioid misuse and abuse.

The data we reviewed suggest that there is less abuse potential associated with the use of hydrocodone and morphine than with oxycodone. This supports the recent implementation in Washington State and other regions of the “oxy-free” emergency department [17].

## Limitations

The studies were quite diverse, not standardized methodologically, using mixed approaches and distinct assessment tools. The studies reviewed compared different patient populations (e.g., recreational opioid users, abusers, and naïve subjects), using different routes of administration, with varying preparations (e.g., containing acetaminophen), and used varying assessments for physiological effects (e.g., pupil size). Only one of the studies reviewed addressed the use of opioid in patients with chronic pain [11]. The studies typically involved only a small sample size, and studies were performed under laboratory, not real-world, conditions. Additionally, since most patients had prior opioid exposure, adverse and negative effects of opioids are likely to be higher in opioid-naïve patients, so the relative negative effects of some of these opioids may be more significant in opioid-naïve patients and may highlight the “likeability” of drugs with fewer negative effects (e.g., oxycodone) with first-time exposure.

In this study, likability is equated with abuse liability. Outside the laboratory setting, abuse liability is not solely dependent on likability; factors such as price, availability, previous exposure, formulation, and route of administration also play a role in determining potential for abuse. The studies reviewed attempted to eliminate these outside factors to isolate likability and directly assess abuse liability. We primarily examined studies evaluating immediate-release formulations of the specified short-acting opioids, but many abusers use extended-release preparations of these opioids. However, until recently, some of these extended-release formulations could be converted to immediate-release formulations by mechanical means such as crushing. The use of tamper-resistant formulations, which are designed to

impede modification, should reduce use by this means [18]. A recent analysis of self-reported substance use by patients admitted to treatment facilities since the switch to tamper-resistant oxycodone ER (Oxycontin and generic) has demonstrated a change back to short-acting oxycodone and possibly heroin [19]. Interestingly, the FDA allows label claims for abuse deterrence based on several criteria, one of which is the relative likeability of one product compared to older formulations of the drug. However, no opioid analgesic to date has received approval to use this claim. Although 6/17 of the originally selected articles were funded by pharmaceutical companies, only one of the studies included had such funding [10]. Although this was not designed by intent, industry funding may have led to research methodologies that did not fit our specific criteria.

## Conclusion

Oral oxycodone has a substantially elevated abuse liability profile compared to oral morphine and hydrocodone due to high likability scores and a relative lack of negative subjective effects.

**Funding Sources** None

**Conflict of Interest** None

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