REVIEW ARTICLE

Effect of physical manipulation on the oral pharmacokinetic profile of Xtampza® ER (oxycodone DETERx® formulation): A review of published studies

Jeffrey Gudin, MD

ARTICLE INFO

Keywords:
abuse
abuse-deterrent
extended-release
Oxycodone DETERx
OxyContin
opioid analgesics
tamper
Xtampza

DOI:10.5055/jom.2020.0559

ABSTRACT

Opioids can be an effective treatment option for appropriate patients with chronic pain for whom nonpharmacological or nonopioid treatment does not provide adequate pain relief. However, extended-release (ER) opioid formulations, because of their high drug content, are attractive options for nonmedical use and abuse. Xtampza® ER (oxycodone DETERx®) capsules, an ER abuse-deterrent formulation (ADF), contain microspheres that combine oxycodone with inactive ingredients to increase the difficulty of tampering with the ER mechanism. The aim of this article is to review five previously published studies highlighting the impact of physical manipulation (ie, crushing and chewing) on the pharmacokinetic (PK) properties of orally administered Xtampza ER compared with immediate-release (IR) oxycodone and/or reformulated OxyContin® (the first approved oxycodone ER ADF). Across five studies, manipulated (crushed or chewed) Xtampza ER retained an ER PK profile similar to that of intact Xtampza ER, with respect to maximum plasma concentration (C_{max}) and time to C_{max}. Additionally, bioequivalence was established between manipulated and intact Xtampza ER, based on C_{max} and area under the concentration-time curve values in healthy volunteers and nondependent recreational opioid users. In contrast, crushed OxyContin failed to retain the ER PK profile of intact OxyContin and was bioequivalent to IR oxycodone, based on C_{max} in healthy volunteers. The retention of ER PK properties when capsule contents are physically manipulated before oral administration suggests Xtampza ER has lower potential to be manipulated for oral abuse when compared with IR oxycodone or OxyContin.

INTRODUCTION

Chronic pain is a major public health problem that affects millions of adults in the United States.[1] Opioids can be an effective treatment option for appropriate patients with pain for whom nonpharmacological or nonopioid treatment is inadequate.[1-4] Extended-release (ER) opioids provide a longer duration of plasma exposure to the drug compared with immediate-release (IR) opioids, resulting in an extended period of analgesia over the dosing interval with less frequent dosing,[4] which may improve patient adherence to a prescribed opioid treatment regimen.[5] However, the high drug content of ER opioids makes these formulations attractive options for nonmedical misuse and abuse.[6] In addition, patients with chronic pain also may manipulate their ER opioids to facilitate swallowing of the medication for legitimate medical use[7] without recognizing the potential dangers.

Manipulation of an opioid medication can result in a rapid increase in drug exposure because the entire dose is released at one time (ie, "dose dumping"), which may increase the risk of morbidity

and mortality.[7,8] Misuse and abuse of prescription opioids contributed to a 153 percent increase in emergency department visits reported from 2004 to 2011.[9] Moreover, two-thirds of the more than 70,237 drug-related deaths reported in 2017 were attributed to opioids, of which more than 35 percent were attributed to prescription opioids (eg, oxycodone, hydrocodone, methadone).[10] This further attests to the severity of the opioid crisis.

To preserve the analgesic benefits and discourage misuse and abuse, abuse-deterrent formulations (ADFs) of opioid medications have been developed. They may include a physical barrier to prevent crushing and chewing, a chemical barrier to prevent extraction of the active ingredient, or an agonist–opioid antagonist combination to discourage manipulation of the medication.[11,12] Even with these approaches, ADF opioids may still be susceptible to manipulation and abuse.[7,13] Thus, although OxyContin® (Purdue Pharma, Stamford, Connecticut), the first approved oxycodone ER ADF, was associated with a 30-48 percent decrease in abuse among substance abusers in the first 3 years after introduction of the reformulated ADF opioid in 2010,[14] a survey of internet discussion boards representing drug abusers showed that OxyContin continued to be endorsed for oral abuse.[15] An observational study found that up to 42 percent of oral abusers reported manipulating (eg, chewing, dissolving) crush-resistant opioid medications, including reformulated OxyContin.[16] Moreover, postmarketing data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) system on the misuse and diversion of prescription opioids showed that 34 percent of abusers successfully defeated the ADF mechanism of reformulated OxyContin to inject or inhale the drug.[13]

The US Food and Drug Administration (FDA) considers the development of abuse-deterrent opioid formulations to be an important component of a multifaceted strategy for reducing opioid misuse and abuse. As a result, the FDA has recommended that evaluation of ADF opioids include in vitro manipulation and extraction studies (category 1), in vivo studies to assess the pharmacokinetics (PK) of manipulated drugs (category 2), studies of human abuse potential (category 3), and postmarketing studies after approval, to evaluate the impact of ADFs on abuse in the community setting (category 4).[17]

Xtampza® ER capsules (oxycodone DETERx®; Collegium Pharmaceutical, Inc., Stoughton, Massachusetts) contain microspheres that combine oxycodone with inactive ingredients to increase the difficulty of tampering with the ER formulation.[18,19] In vitro (category 1) studies showed that compared with reformulated OxyContin and IR oxycodone tablets, Xtampza ER capsule contents were less susceptible to physical manipulation (eg, crushing, grinding), chemical extraction, and passage through a needle when capsule contents were melted or suspended in water,[18-20] suggesting that when manipulated, Xtampza ER would be less susceptible to alterations in PK properties compared with OxyContin and IR oxycodone.

The purpose of this article is to review previous studies highlighting the impact of physical manipulation (ie, crushing and chewing) on the PK properties of orally administered Xtampza ER compared with OxyContin and/or IR oxycodone in healthy volunteers and nondependent recreational opioid users.

XTAMPZA ER ORAL PK PROFILE

Pharmacokinetic (category 2) studies evaluate whether deliberate manipulation by abusers or accidental misuse by patients would increase the maximum plasma concentration (C_{max}) of the drug or shorten the time to C_{max} (T_{max}), both of which are indicators of abuse potential.[21] Therefore, the most aggressive tampering methods with the most significant impact on in vitro drug release rates (established in category 1 studies) are used for manipulation of the drug in PK studies.[17]

The effects of drug manipulation on the PK profile of Xtampza ER after oral administration were evaluated in five studies (Table 1).[8,20,22-24] The effects of crushing (based on the most effective crushing methods using household utensils [common household items that crush, cut, or grate by manual or mechanical means] that could be easily accessed by abusers) and chewing (one of the most common prescription opioid tampering methods[16]) on the PK profile of Xtampza ER capsule contents were compared with the PK profile of IR oxycodone solution in one category 2 study.[20] In addition, the effects of chewing on the PK profile of Xtampza ER were compared with that of crushed IR oxycodone as part of two category 3 (human abuse potential) studies in nondependent, recreational opioid users.[23,24] Two additional category 2 studies compared the effects of crushing on the PK profile of Xtampza ER capsule

Table 1. Studies evaluating the PK profile of physically manipulated Xtampza ER after oral administration

Study	Study Design	Study Population	Treatments[a]
Kopecky et al.[20]	Open-label, randomized, active-controlled, single-dose, crossover study (category 2)	Healthy, naltrexone-blocked volunteers	• Xtampza ER 40 mg (HFHC fed): intact, chewed, and crushed • IR oxycodone solution 40 mg (fasted)
Kopecky et al.[23]	Double-blind treatment phase of the randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, abuse-liability study (category 3)	Nondependent recreational opioid users	• Xtampza ER 40 mg (fasted and HFHC fed): intact and chewed • IR oxycodone 40 mg (fasted): crushed • Placebo
Meske et al.[24]	Double-blind treatment phase of the randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, abuse-liability study (category 3)	Nondependent recreational opioid users	• Xtampza ER 40 mg (fasted and HFHC fed): intact and chewed • IR oxycodone 40 mg (fasted): crushed • Placebo
Gudin et al.[8]	Open-label, randomized, active-controlled, single-dose, five-treatment, crossover study (category 2)	Healthy, naltrexone-blocked volunteers	• Xtampza ER 40 mg (HFHC fed): intact and crushed • OxyContin 40 mg (HFHC fed): intact and crushed • IR oxycodone 40 mg (HFHC fed): crushed
Brennan et al.[22]	Open-label, randomized, active-controlled, single-dose, five-treatment, crossover study (category 2)	Healthy, naltrexone-blocked volunteers	• Xtampza ER 40 mg (HFHC fed): intact and crushed • OxyContin 40 mg (HFHC fed): intact and crushed • IR oxycodone 40 mg (HFHC fed): crushed

[a]Xtampza ER dose assessed in these studies is 36 mg, which is equivalent to 40 mg oxycodone HCl.[19]
Abbreviations: ER, extended-release; HFHC, high-fat, high-calorie; IR, immediate-release; PK, pharmacokinetic.

contents with the PK profile of crushed IR oxycodone and crushed reformulated OxyContin.[8,22]

Because food consumption may alter drug availability, FDA guidance recommends modified-release drugs be evaluated under fasted and fed conditions when characterizing bioequivalence.[25] The Xtampza ER PK profile was therefore assessed in fasted[23,24] and fed[8,20,22-24] conditions in these studies, in line with FDA guidance.

ORAL XTAMPZA ER VERSUS IR OXYCODONE

Study in healthy volunteers

An open-label, randomized, active-controlled, crossover study was conducted to evaluate the PK profile of intact and manipulated oral Xtampza ER capsules (containing the equivalent of 40 mg oxycodone HCl) compared with the PK profile of IR oxycodone solution.[20] Healthy naltrexone-blocked volunteers were fed a high-fat, high-calorie (HFHC) meal 30 min before oral administration of intact, crushed (by the most effective tampering method), or chewed Xtampza ER 40 mg capsules with 240 mL of water, or received 2 mL of a 20 mg/mL IR oxycodone solution administered as a 240 mL solution in the fasted state.[20] Xtampza was dosed with food and IR oxycodone solution was dosed in a fasted state because these administration conditions were previously shown to maximize C_{max} for the respective formulations.[19,26]

After oral administration, both crushed and chewed Xtampza ER exhibited a gradual rise in plasma oxycodone concentration that was consistent with retention of the ER profile exhibited by the PK of intact Xtampza ER. These PK results contrasted with those for IR oxycodone solution, which exhibited a rapid rise in plasma oxycodone concentration (Figure 1)[20] with higher C_{max} values and faster T_{max} times. The IR oxycodone solution findings were in contrast with those for crushed and chewed Xtampza ER, whose values were relatively

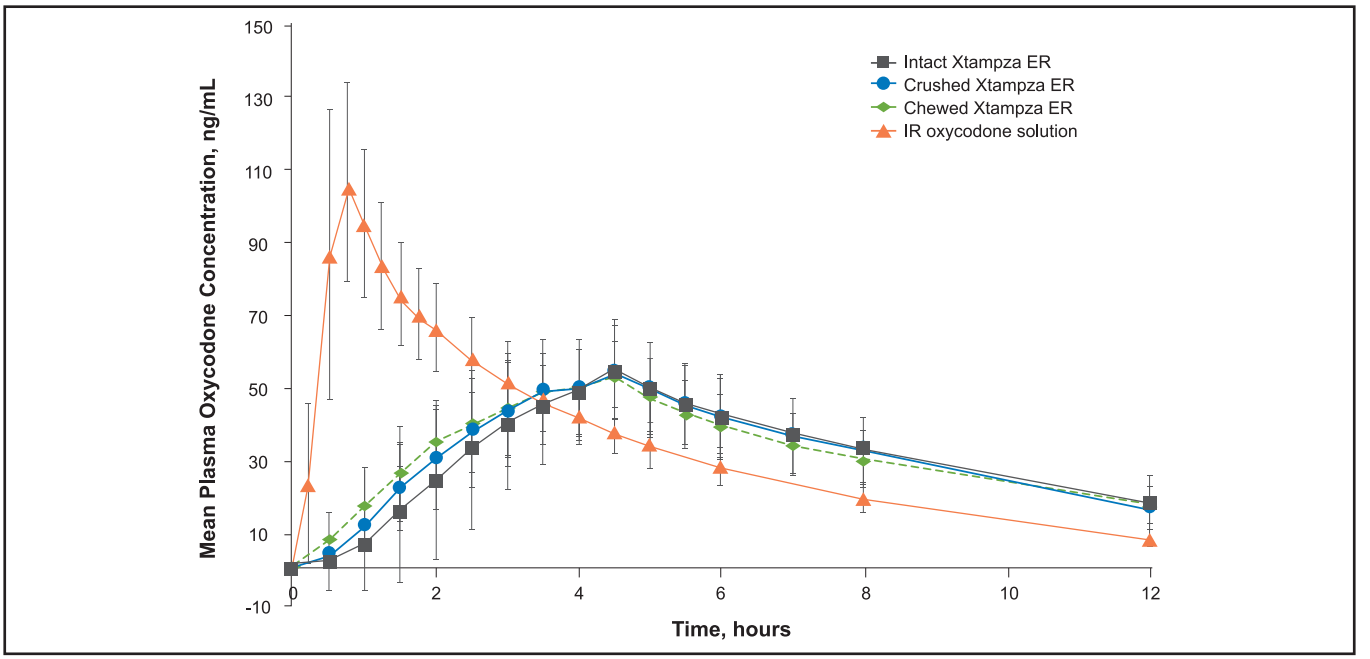

Figure 1. Mean oxycodone plasma concentration over time for intact, crushed, and chewed Xtampza ER compared with IR oxycodone solution in healthy volunteers.[20]* Error bars represent standard deviation.

unchanged compared with those for intact Xtampza ER capsules (Table 2).[20] This profile is consistent with maintenance of an ER profile after manipulation of Xtampza ER.

Although observed (area under the plasma concentration-time curve [AUC] from time 0 to the time of the last measurable plasma concentration [AUC_{0-t}]) and total plasma exposure to oxycodone (AUC from time 0 to infinity [$AUC_{0-\infty}$]) were similar for all Xtampza ER treatments and IR oxycodone solution, the partial AUC (pAUC) values over 2 h for all Xtampza ER treatments overlapped and were much lower compared with those for IR oxycodone solution, indicating that the early, slow rise in plasma oxycodone exposure was not altered by crushing or chewing Xtampza ER capsule contents.[20]

After oral administration, bioequivalence was demonstrated between crushed and chewed versus intact Xtampza ER capsules, based on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Table 2),[20] substantiating that manipulation of Xtampza ER by crushing or chewing does not increase the peak plasma exposure of oxycodone or the overall extent of exposure. In addition, the ER plasma oxycodone concentration-time profile was not changed when Xtampza ER capsule contents were crushed or chewed before administration.[20]

The mean abuse quotient (AQ) score (defined as C_{max}/T_{max}) reflects the rate of increase in plasma opioid concentration.[27] A higher AQ score is hypothesized to predict the likelihood of experiencing the rapid drug euphoria commonly sought by abusers.[20] In this study, AQ scores were substantially lower for all Xtampza ER treatments compared with IR oxycodone solution, and scores for crushed and chewed Xtampza ER were similar to those for intact Xtampza ER capsules, suggesting that an increase in euphoric effect is unlikely to be achieved by crushing and chewing Xtampza ER capsule contents before administration.

Studies in recreational opioid users

The effects of chewing on the PK profile and abuse potential of Xtampza ER compared with IR oxycodone were also evaluated in two randomized, double-blind, triple-dummy, active-, and placebo-controlled crossover studies in non-dependent recreational opioid users.[23,24] Both of these studies were conducted in non-naltrexone-blocked volunteers with a history of nondependent opioid use.[23,24] Volunteers who met eligibility

*Xtampza ER treatments were administered after a high-fat, high-calorie meal, and IR oxycodone solution was administered in the fasted state. ER, extended release; IR, immediate-release. Figure reprinted with permission from Kopecky EA, et al. *J Opioid Manage.* 2014; 10(4): 233-246.[20]

Table 2. Comparison of pharmacokinetic and bioequivalence parameters for Xtampza ER and IR oxycodone in healthy volunteers[20a]

Parameter	Intact Xtampza ER n = 42	Crushed Xtampza ER n = 42	Chewed Xtampza ER n = 38	IR Oxycodone Solution n = 40
PK parameter, mean (SD)				
C_{max}, ng/mL	62.3 (13.0)	57.6 (12.6)	55.6 (10.9)	115 (27.3)
T_{max}, h[b]	4.0 (1.5-6.0)	4.5 (2.5-6.0)	4.5 (2.5-8.0)	0.75 (0.5-2.0)
AUC_{0-t}, ng·h/mL	552 (123)	537 (140)	550 (112)	480 (77.9)
$AUC_{0-\infty}$, ng·h/mL	561 (124)	553 (134)	559 (113)	489 (80.2)
$t_{½}$, h	7.2 (2.4)	5.4 (1.0)	6.0 (1.4)	4.5 (0.5)
Bioequivalence[c], LS mean ratio (90 percent CI)				
Versus intact Xtampza ER				
C_{max}	–	**92.5 (86.0-99.5)**	**89.7 (83.2-96.8)**	–
AUC_{0-t}	–	**96.8 (91.6-102.4)**	**101.6 (95.8-107.6)**	–
$AUC_{0-\infty}$	–	**97.8 (92.7-103.3)**	**101.4 (95.9-107.3)**	–
Versus IR oxycodone solution				
C_{max}	54.5 (50.6-58.7)	50.4 (46.8-54.3)	48.9 (45.4-52.7)	–
AUC_{0-t}	**113.8 (107.5-120.5)**	**110.2 (104.1-116.7)**	**115.6 (108.8-122.8)**	–
$AUC_{0-\infty}$	**113.5 (107.4-119.9)**	**111.0 (105.1-117.4)**	**115.2 (108.6-122.2**)	–
AQ, mean (SD), ng/mL/h	19.7 (8.7)	14.4 (4.5)	14.0 (4.5)	167.8 (75.9)

Abbreviations: AQ, abuse quotient; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration; CI, confidence interval; C_{max}, maximum plasma concentration; ER, extended-release; IR, immediate-release; LS, least-squares; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal elimination half-life; T_{max}, time to C_{max}.
[a]Xtampza ER treatments were administered after a high-fat, high-calorie meal, and IR oxycodone solution was administered in the fasted state.
[b]Median (range).
[c]Bioequivalence was concluded (data in bold font) if the 90 percent CI of the estimated mean ratio was entirely within the 80 percent to 125 percent limits.
Table reprinted with permission from Kopecky EA, et al. *J Opioid Manage.* 2014;10(4):233-246,[20] with additional data from data on file.

requirements received single oral doses of Xtampza ER (equivalent to 40 mg oxycodone hydrochloride, administered as intact capsules and chewed capsule contents) 30 min after an HFHC meal or in the fasted state; crushed 40 mg IR oxycodone after an HFHC meal or in the fasted state; and placebo after an HFHC meal.

In both studies, all Xtampza ER treatment conditions (chewed and intact after fasted and fed states) produced more gradual increases in plasma oxycodone concentrations over time compared with crushed IR oxycodone, which was consistent with maintenance of an ER profile after physical manipulation of Xtampza ER (Figure 2).[23,24] Similar to studies in healthy volunteers, whether administered in the fed or fasted state, in both studies of recreational opioid users all Xtampza ER treatments produced a substantially lower C_{max} and delayed T_{max} compared with those for crushed oxycodone IR (Table 3).[23,24] However, plasma exposure to oxycodone

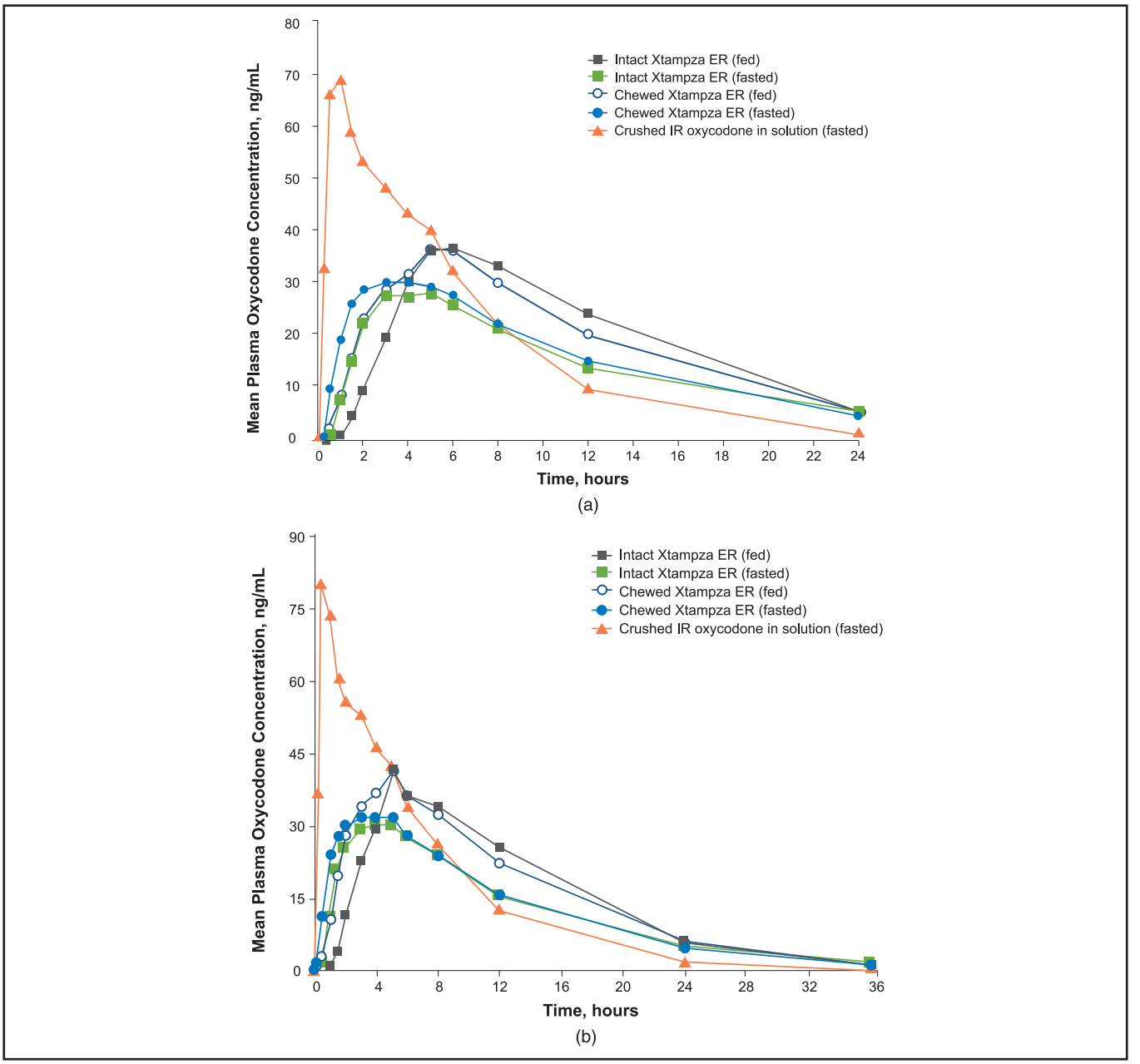

Figure 2. Mean oxycodone plasma concentration over time for intact and chewed Xtampza ER (fed [HFHC] and fasted treatments) compared with crushed IR oxycodone (fasted treatment) in recreational opioid users.[23,24†]

was similar across all Xtampza ER treatments based on AUC_{0-t} and $AUC_{0-\infty}$, whether in the fed or fasted state, and did not differ from crushed IR oxycodone.

In these studies in recreational opioid users, bioequivalence was demonstrated between chewed and intact Xtampza ER treatments in the fed state and between chewed and intact Xtampza ER treatments in the fasted state, based on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Table 3).[8,22] In contrast, based on C_{max}, bioequivalence was not demonstrated between any of the Xtampza ER treatments and IR oxycodone.

In both studies, oral administration of crushed IR oxycodone produced AQ scores that were approximately 10-fold higher for crushed IR oxycodone

†Figures represent data as reported in (A) Kopecky 2017 and (B) Meske 2018.[23,24] ER, extended-release; HFHC, high-fat, high-calorie; IR, immediate-release. (A) Reprinted from Kopecky EA, et al. *J Clin Pharm.* 2017;57(4):500-512, under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License (*http://creativecommons.org/licenses/by-nc-nd/4.0/*). (B) Reprinted from Meske D, et al. *J Opioid Manag.* 2018; 14(5): 359-372, under Creative Commons CC-BY-NC-ND-4.0 (*http://creativecommons.org/licenses/by-nc-nd/4.0/*).[23,24]

Table 3. Comparison of PK parameters for Xtampza ER and IR oxycodone in recreational opioid users

Parameter	Intact Xtampza ER Fed	Chewed Xtampza ER Fed	Intact Xtampza ER Fasted	Chewed Xtampza ER Fasted	Crushed IR Oxycodone Fasted
Kopecky et al.[23]	**n = 38**	**n = 38**	**n = 38**	**n = 38**	**n = 38**
PK parameter, mean (SD)					
C_{max} ng/mL	41.9 (12.4)	40.3 (12.2)	30.9 (9.9)	35.5 (12.5)	77.7 (24.5)
T_{max}, h[a]	5.1 (1.6-12.1)	5.1 (2.1-12.1)	4.1 (1.6-8.1)	3.1 (1.1-6.2)	1.1 (0.2-5.1)
AUC_{0-t}, ng·h/mL	511 (155)	498 (123)	408 (113)	433 (123)	468 (106)
$AUC_{0-\infty}$, ng·h/mL	553 (131)	515 (122)	469 (107)	469 (126)	476 (106)
$t_{½}$, h	5.2 (0.9)	5.3 (0.7)	8.8 (2.6)	7.4 (2.3)	3.6 (0.5)
Bioequivalence[b], LS mean ratio, percent (90 percent CI)					
Versus intact Xtampza ER HFHC fed					
C_{max}, ng/mL	—	**96.0 (88.3-104.4)**	—	—	54.1 (49.8-58.8)
AUC_{0-t}, ng·h/mL	—	**101.7 (90.5-114.3)**	—	—	**110.4 (98.2-124.0)**
$AUC_{0-\infty}$, ng·h/mL	—	**96.9 (91.5-102.7)**	—	—	**109.0 (103.1-115.3)**
Versus intact Xtampza ER fasted					
C_{max}, ng/mL	—	—	—	**113.2 (104.1-123.1)**	40.4 (37.2-43.9)
AUC_{0-t}, ng·h/mL	—	—	—	**105.9 (94.2-119.0)**	**94.4 (84.0-106.0)**
$AUC_{0-\infty}$, ng·h/mL	—	—	—	**99.5 (94.0-105.4)**	**96.5 (91.4-101.9)**
Versus crushed IR oxycodone					
C_{max}, ng/mL	—	51.9 (47.9-56.4)	—	45.8 (42.2-49.6)	—
AUC_{0-t}, ng·h/mL	—	**112.3 (100.1-125.9)**	—	**99.9 (89.3-111.7)**	—
$AUC_{0-\infty}$, ng·h/mL	—	**105.7 (100.3-111.4)**	—	**96.1 (91.3-101.1)**	—
AQ, mean (SD), ng/mL/h	7.8 (4.9)	8.1 (4.3)	8.2 (4.0)	13.0 (8.2)	108.0 (84.1)
Meske et al. 2018[24]	**n = 61**	**n = 66**	**n = 67**	**n = 67**	**n = 64**
PK parameter, mean (SD)					
C_{max} ng/mL	45.4 (11.6)	44.3 (10.9)	33.9 (9.8)	37.6 (11.5)	91.1 (26.6)
T_{max}, h[a]	5.1 (2.1-12.1)	5.1 (1.5-8.1)	4.1 (1.5-8.1)	3.1 (0.5-8.1)	0.5 (0.3-5.2)
AUC_{0-t}, ng·h/mL	541 (127)	553 (149)	447 (119)	466 (145)	543 (131)
$AUC_{0-\infty}$, ng·h/mL[c]	546 (134)	568 (138)	478 (122)	480 (126)	549 (132)
$t_{½}$, h	5.3 (0.7)	5.4 (0.8)	8.1 (2.5)	7.6 (2.5)	4.2 (0.6)
Bioequivalence[b], LS mean ratio, percent (90 percent CI)					
Versus intact Xtampza ER HFHC fed					
C_{max}, ng/mL	—	—	—	**90.4-102.1**	—
AUC_{0-t}, ng·h/mL	—	—	—	**94.2-105.3**	—
$AUC_{0-\infty}$, ng·h/mL	—	—	—	**96.7-106.3**	—

Table 3. Comparison of PK parameters for Xtampza ER and IR oxycodone in recreational opioid users (continued)

Parameter	Intact Xtampza ER Fed	Chewed Xtampza ER Fed	Intact Xtampza ER Fasted	Chewed Xtampza ER Fasted	Crushed IR Oxycodone Fasted
Versus intact Xtampza ER fasted					
C_{max}, ng/mL	—	—	—	**104.4-117.5**	—
AUC_{0-t}, ng·h/mL	—	—	—	**100.1-111.5**	—
$AUC_{0-\infty}$, ng·h/mL	—	—	—	**97.4-106.0**	—
AQ, mean (SD), ng/mL/h	8.9 (5.3)	10.6 (5.7)	10.5 (4.9)	17.6 (14.8)	138 (84.5)

Abbreviations: AQ, abuse quotient; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last measurable plasma concentration; CI, confidence interval; C_{max}, maximum plasma concentration; ER, extended-release; HFHC, high-fat, high-calorie; IR, immediate-release; LS, least-squares; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal elimination half-life; T_{max}, time to reach C_{max}.
[a]Median (range).
[b]Bioequivalence was concluded (data in bold font) if the 90 percent CI of the estimated mean ratio was entirely within the 80 percent to 125 percent limits.
[c]n = 52 for intact Xtampza ER fed, n = 54 for chewed Xtampza ER fed, n = 63 for intact Xtampza ER fasted, n = 63 for chewed Xtampza ER fasted, and n = 63 for crushed IR oxycodone fasted.
Table reprinted from Kopecky EA, et al. *J Clin Pharm.* 2017;57(4):500-512,[23] under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License (*http://creativecommons.org/licenses/by-nc-nd/4.0/*), and Meske D, et al. *J Opioid Manag.* 2018;14(5):359-372,[24] under Creative Commons CC-BY-NC-ND-4.0 (*http://creativecommons.org/licenses/by-nc-nd/4.0/*).

than scores for chewed and intact Xtampza ER fasted and fed treatments.[23,24] This finding was consistent with retention of an ER PK profile after administration of all Xtampza ER treatments and indicates that oral administration of manipulated Xtampza ER may have a lower potential for abuse compared with crushed IR oxycodone.

ORAL XTAMPZA ER VERSUS OXYCONTIN

Studies in healthy volunteers

Two similarly designed, open-label, randomized, active-controlled, crossover studies were conducted to evaluate the PK profile of intact and manipulated oral Xtampza ER capsules compared with intact and crushed reformulated OxyContin tablets.[8,22] In these studies, healthy naltrexone-blocked volunteers were fed an HFHC meal 30 min before study drug administration. Volunteers then received single oral 40-mg doses of intact or crushed Xtampza ER capsules, intact or crushed OxyContin tablets, and crushed IR oxycodone tablets administered with 240 mL of water. While crushed Xtampza ER and IR oxycodone were prepared using the same tampering method, crushed OxyContin was prepared with a different method, such that the crushed study drugs were prepared with the most effective method of tampering identified in previous studies.[8,20,22]

In both clinical studies, crushed and intact Xtampza ER capsules produced a similar gradual rise in plasma oxycodone concentrations over time, with no differences in C_{max} and T_{max}.[8,22] In contrast, compared with intact OxyContin, crushed OxyContin tablets exhibited a more rapid rise in plasma oxycodone concentration over time, which was reflected in a higher C_{max} and shorter T_{max}, indicating that crushed OxyContin failed to retain an ER PK profile and instead resembled the attractive abuse quotient/potential of crushed IR oxycodone (Figure 3 and Table 4).[8,22]

In one of these studies,[8] the median T_{max} for crushed versus intact Xtampza ER capsules was not statistically different; however, the median T_{max} for crushed Xtampza ER was significantly longer than that for crushed IR oxycodone ($p < 0.0001$). In contrast, the median T_{max} for crushed OxyContin tablets did not differ from that for crushed IR oxycodone

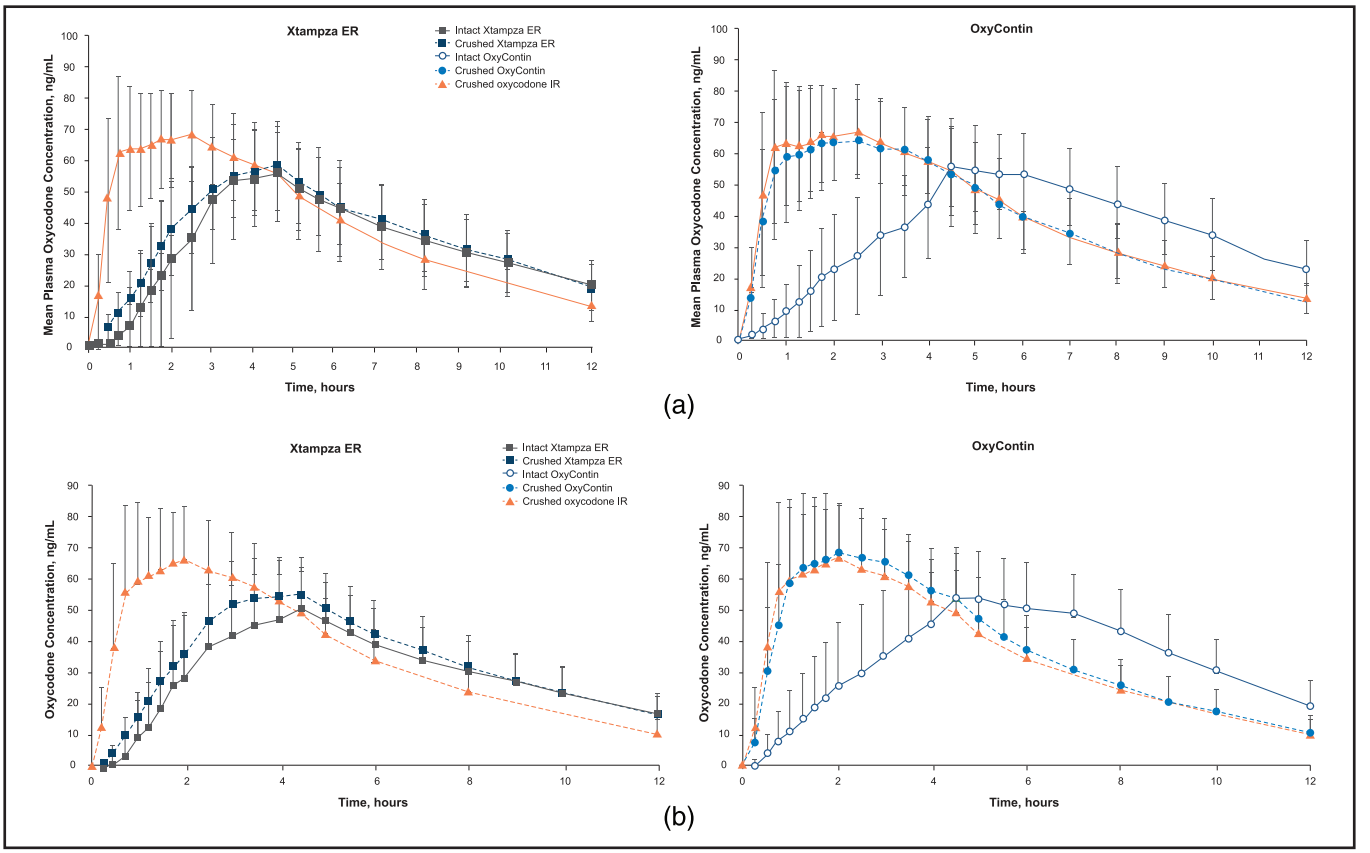

Figure 3. Mean oxycodone plasma concentration over time for intact and crushed Xtampza ER and OxyContin compared with crushed IR oxycodone in healthy volunteers.[8,22‡] Error bars represent standard deviation. ER, extended-release; IR, immediate-release.

tablets and was significantly shorter than that for intact OxyContin tablets ($p < 0.0001$).[8]

Although the values for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were similar in both studies for each of the Xtampza ER and OxyContin treatments, cumulative pAUC values over the first 1.75 h after treatment were substantially lower for intact and crushed Xtampza ER capsules compared with crushed OxyContin tablets, and the OxyContin values resembled those for crushed IR oxycodone.[8,22] These findings indicated that, unlike Xtampza ER, manipulated OxyContin did not retain its ER plasma oxycodone exposure profile.

In each study, both Xtampza ER treatments (intact and crushed) were bioequivalent to one another but not to IR oxycodone solution based on C_{max} values (Table 4), demonstrating that the ER plasma oxycodone exposure profile was not changed when Xtampza ER capsule contents were crushed before administration.[8,22] In contrast, bioequivalence was demonstrated between crushed OxyContin tablets and crushed IR oxycodone tablets based on C_{max}, and the crushed and intact forms of OxyContin were not bioequivalent on C_{max} (Table 4) in either study, indicating that orally administered, crushed OxyContin did not retain its ER profile.

The higher AQ scores observed in these studies for crushed OxyContin resembled scores for IR oxycodone, consistent with the more rapid rise in C_{max} and shorter T_{max} after oral administration of these formulations.[8,22] However, all Xtampza ER treatments produced substantially lower AQ scores compared with crushed OxyContin and IR oxycodone, consistent with retention of an ER PK profile and indicating a lower potential for abuse by manipulation with Xtampza ER.

‡Figures represent data as reported in (A) Gudin 2015 and (B) Brenner 2017.[8,22] All treatments were administered after a high-fat, high-calorie meal. (A) Reprinted from Gudin J, et al. *Pain Med.* 2015; 16: 2142-2215, under Creative Commons CC-BY-NC license (*https://creativecommons.org/licenses/by-nc/4.0/*). (B) Adapted from Brennan MJ, et al. *Pain Manag.* 2017;7(6):461-472, under Creative Commons Attribution-Non-Commercial-NoDerivatives 4.0 Unported License (*http://creativecommons.org/licenses/by-nc-nd/4.0/*) with additional permission from *Pain Management* as agreed by Future Medicine Ltd.[8,22]

Table 4. Comparison of PK and bioequivalence parameters for Xtampza ER and OxyContin in healthy volunteers[a]

Parameter	Intact Xtampza ER	Crushed Xtampza ER	Intact OxyContin	Crushed OxyContin	Crushed IR Oxycodone
Gudin et al. 2015[8]	**n = 38**	**n = 38**	**n = 40**	**n = 39**	**n = 40**
PK parameter, mean (SD)					
C_{max}, ng/mL	67.5 (17.6)	62.9 (12.6)	64.9 (13.8)	78.4 (12.9)	79.4 (17.1)
T_{max}, h[b]	3.5 (1.2-6.0)	4.0 (2.0-7.0)	5.0 (2.0-10.0)	1.8 (0.5-5.0)	1.8 (0.5-4.0)
AUC_{0-t}, ng·h/mL	569 (139)	587 (151)	598 (146)	579 (130)	548 (140)
$AUC_{0-\infty}$, ng·h/mL	581 (138)	597 (149)	611 (145)	587 (132)	561 (146)
$t_{½}$, h	5.7 (0.9)	5.0 (0.6)	4.3 (0.6)	4.5 (0.7)	4.2 (0.6)
Bioequivalence, LS mean ratio, percent (90 percent CI)[c]					
Versus intact Xtampza ER					
C_{max}, ng/mL	—	**94.4 (89.3-99.7)**	—	—	—
$AUC_{0-\infty}$, ng·h/mL	—	**101.7 (98.1-105.5)**	—	—	—
Versus crushed IR oxycodone					
C_{max}, ng/mL	—	77.4 (73.5-81.5)	—	**101.7 (95.8-107.9)**	—
$AUC_{0-\infty}$, ng·h/mL	—	**103.7 (100.6-106.9)**	—	**106.4 (99.0-114.5)**	—
Versus intact OxyContin					
C_{max}, ng/mL	—	—	—	121.2 (113.8-129.0)	—
$AUC_{0-\infty}$, ng·h/mL	—	—	—	**95.9 (93.0-98.9)**	—
AQ, mean (SD), ng/mL/h	20.9 (11.2)	16.5 (5.4)	14.0 (6.4)	58.1 (42.7)	62.3 (47.5)
Brennan et al. 2017[22]	**n = 38**	**n = 39**	**n = 38**	**n = 39**	**n = 37**
PK parameter, mean (SD)					
C_{max}, ng/mL	56.9 (13.4)	61.2 (13.1)	63.7 (14.8)	79.9 (17.9)	78.1 (22.0)
T_{max}, h[b]	3.5 (1.0-5.5)	3.5 (2.5-5.5)	4.5 (1.8-8.0)	1.8 (0.5-4.5)	1.5 (0.5-4.5)
$AUC_{0-\infty}$, ng·h/mL	534 (142)[d]	549 (143)	574 (150)	540 (142)	497 (143)
Bioequivalence, LS mean ratio, percent (90 percent CI)[c]					
Versus intact Xtampza ER					
C_{max}, ng/mL	—	**107.0 (99.2-115.4)**	—	—	—
AUC_{0-t}, ng·h/mL	—	**104.8 (98.1-111.9)**	—	—	—
$AUC_{0-\infty}$, ng·h/mL	—	**103.1 (96.6-110.1)**	—	—	—
Versus crushed IR oxycodone					
C_{max}, ng/mL	—	80.1 (74.2-86.5)	—	**104.7 (97.0-112.9)**	—

Table 4. Comparison of PK and bioequivalence parameters for Xtampza ER and OxyContin in healthy volunteers[a] (continued)

Parameter	Intact Xtampza ER	Crushed Xtampza ER	Intact OxyContin	Crushed OxyContin	Crushed IR Oxycodone
Gudin et al. 2015[8]	**n = 38**	**n = 38**	**n = 40**	**n = 39**	**n = 40**
AUC_{0-t}, ng·h/mL	—	**113.5 (106.2-121.4)**	—	**110.8 (103.7-118.4)**	—
$AUC_{0-\infty}$, ng·h/mL	—	**112.9 (105.8-120.5)**	—	**110.6 (103.7-118.0)**	—
Versus intact OxyContin					
C_{max}, ng/mL	—	—	—	126.0 (116.8-135.8)	—
AUC_{0-t}, ng·h/mL	—	—	—	**93.4 (87.5-99.8)**	—
$AUC_{0-\infty}$, ng·h/mL	—	—	—	**93.5 (87.7-99.7)**	—
AQ, mean (SD), ng/mL/h	19.1 (9.7)	17.4 (6.1)	13.6 (6.0)	56.1 (33.7)	63.1 (47.5)

Abbreviations: AQ, abuse quotient; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration; C_{max}, maximum plasma concentration; CI, confidence interval; ER, extended-release; IR, immediate-release; LS, least-squares; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal elimination half-life; T_{max}, time to reach C_{max}.
[a]All treatments were administered after a high-fat, high-calorie meal.
[b]Median (range).
[c]Bioequivalence was concluded (data in bold font) if the 90 percent CI of the estimated mean ratio was entirely within the 80 percent to 125 percent limits.
[d]n = 37; one subject did not have enough data points in the terminal phase of the PK profile to calculate $AUC_{0-\infty}$ by extrapolation.
Table reprinted from Gudin J, et al. *Pain Med.* 2015;16(11):2142-2151,[8] under Creative Commons CC-BY-NC license (*https://creativecommons.org/licenses/by-nc/4.0/*); and Brennan MJ, et al. *Pain Manag.* 2017;7(6):461-472,[22] under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 Unported License (*http://creativecommons.org/licenses/by-nc-nd/4.0/*) with additional permission from *Pain Management* as agreed by Future Medicine Ltd, and additional data from data on file.

CLINICAL IMPLICATIONS

Based on the results from PK studies of the manipulated Xtampza microsphere-in-capsule ER technology, crushing and chewing had little effect on the oxycodone PK profile after oral administration (ie, there was a lack of dose dumping). This is important because nonmedical users of prescription opioid medications frequently resort to physical manipulation of the drug prior to oral administration to achieve more rapid drug release, resulting in heightened euphoria.[16,28] Furthermore, ER opioid formulations are more likely to be abused because a single dose of these formulations contains higher amounts of the drug compared with IR formulations.[6] Additionally, patients with chronic pain, or their caregivers, may manipulate opioids to facilitate swallowing of the medication for legitimate medical use,[7] unaware that cutting, crushing, or grinding medication can change the release mechanism of the drug, increasing potential dangers.[29]

Although manipulation of an opioid can result in a rapid increase in drug exposure, it is important to note that crushing or chewing Xtampza ER did not affect the time-release mechanism of the drug. In contrast, OxyContin failed to retain an ER profile, emulating instead the rapid rise in plasma oxycodone concentration observed with crushed IR oxycodone.[8,20,22] Consistent with the PK profile of manipulated OxyContin in these studies, recreational opioid abusers still abuse OxyContin by manipulating it prior to oral or other routes of administration (eg, by snorting or injecting).[30] Thus, the OxyContin prescribing information carries language in its boxed warning regarding the dangers of crushing, chewing, or dissolving, which can cause rapid release and absorption of a potentially fatal dose of oxycodone.[31] In contrast, the Xtampza ER

prescribing information does not carry this language in its boxed warning.[19]

Manipulating Xtampza ER capsule contents before oral administration in the fasted or fed state did not compromise the ER profile of the formulation in recreational opioid abusers, which was consistent with results observed in healthy volunteers.[23,24] Although these findings suggest that Xtampza ER may be less susceptible to abuse, assessment of Drug Liking is a more sensitive measure of the potential for abuse after the drug has been physically manipulated.[17,32] Consistent with the results from PK studies with oral administration of manipulated Xtampza ER, recreational opioid users reported lower Drug Liking scores after oral administration of crushed Xtampza ER compared with crushed IR oxycodone in category 3 abuse potential studies.[23,24] Similarly, recreational users reported lower willingness to take the drug again as measured by lower Take Drug Again scores after oral administration of Xtampza ER compared with crushed IR oxycodone, also a category 3 study.[24] In addition to the oral route of abuse, recreational opioid users also reported lower Drug Liking scores after intranasal administration of crushed Xtampza ER compared with crushed IR oxycodone.[33]

No currently marketed ADF opioid can prevent oral ingestion of more than the prescribed dose of the intact drug.[12] It is important to note that Xtampza ER is the only opioid formulation currently available without language in the boxed warning against the potential dangers of crushing or chewing.[19] Furthermore, based in part on these studies, the Xtampza ER prescribing information allows health care providers to choose the most appropriate mode of oral administration (eg, sprinkled on food, administration by nasogastric/gastric tube) in patients with swallowing difficulties.[7,19,34] The attributes of Xtampza ER discussed above, as well as its efficacy in pain relief, established in a phase 3 study of patients with moderate-to-severe chronic back pain requiring opioid analgesics, fit an unmet need for ADF opioids.[35]

CONCLUSIONS

Xtampza ER is indicated for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment when alternative treatment options fail to provide adequate relief. Xtampza ER PK properties were consistently retained across five independent studies. In clinical studies involving healthy volunteers, the ER PK properties of Xtampza ER were retained when capsule contents were chewed or crushed before oral administration. This was in contrast to OxyContin, which failed to retain its ER PK profile when the tablets were crushed before oral administration. This is important because it suggests that Xtampza ER has a lower potential to be manipulated for abuse, which was also demonstrated in clinical studies of recreational opioid users.

ACKNOWLEDGMENTS

Technical editorial and medical writing assistance was provided by Pratibha Hebbar, PhD, and Craig Albright, PhD, Synchrony Medical Communications, LLC, West Chester, Pennsylvania, under the direction of the author. Funding for this support was provided by Collegium Pharmaceutical, Inc., Stoughton, Massachusetts.

Disclosures: *Dr. Gudin reports serving as a consultant for Averitas, Hisumitsu, Mallinckrodt, Nektar, Purdue Pharma (manufacturer/marketer of OxyContin®), and Quest Diagnostics; as an advisory board member for AcelRx Pharmaceuticals and GlaxoSmithKline; and as a consultant and speakers bureau member for BioDelivery Sciences International, Collegium Pharmaceutical (marketer of Xtampza® ER), DSI, Salix Pharmaceuticals, and Scilex Pharmaceuticals.*

Jeffrey Gudin, MD, Clinical Associate Professor, Anesthesiology, Rutgers New Jersey Medical School, Newark, New Jersey.

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