LETTER TO THE EDITOR

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OXFORD

Response to Crudele et al. Commentary on Gudin et al. "Comparing the Effect of Tampering on the Oral Pharmacokinetic Profiles of Two Extended-Release Oxycodone Formulations with Abuse-Deterrent Properties"

Dear Editor,

We appreciate Crudele and colleagues taking the time to read our publication "Comparing the Effect of Tampering on the Oral Pharmacokinetic Profiles of Two Extended-Release Oxycodone Formulations with Abuse-Deterrent Properties" [1], in which the pharmacokinetic (PK) profiles of manipulated Xtampza extended release (ER) were compared with manipulated reformulated OxyContin. We are grateful to the editors for a chance to respond to their comments.

Crudele states that the paper "implies that these PK results are supported by comparative pharmacodynamic (drug liking effects) or human abuse potential study data, when such is not the case." The study in reference (Gudin et al. 2015) [1] did not collect comparative pharmacodynamic data as the differences of the PK results of the manipulated treatment groups were quite compelling and stand on their own: Crushed Xtampza ER (oxycodone) had a PK profile that was bioequivalent to Xtampza ER taken intact (Figure 1A) [1]. This was in contrast to the crushed OxyContin (oxycodone HCl) profile, which was significantly different than OxyContin taken intact and bioequivalent to crushed immediate-release oxycodone tablets (Figure 1B) [1]. The data presented in the referenced study have been recently duplicated in a second study [2] and are similar to previously published data showing that Xtampza ER crushed or chewed is bioequivalent to the intact formulation [3].

The PK studies comparing intact vs manipulated Xtampza ER are the reason the approved product label does not include language in the boxed warning that crushing, chewing, or dissolving can lead to rapid release and absorption of a potentially fatal dose of opioid. This is not the case for the approved OxyContin label, which contains within a boxed warning the statement "Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone" [4]. Both the Gudin et al. 2015 data and Purdue's own data [5], showing that manipulation of OxyContin was able to compromise its ER mechanism, support inclusion of such a statement in the label.

The Xtampza ER PK data for both oral and nasal manipulation are included within the drug abuse section of the Xtampza ER approved label [6]. Maintenance of the ER profile after manipulation has implications not only for abusers, but also for chronic pain patients who may unintentionally misuse their ER opioid medication for medical purposes, such as to facilitate swallowing [7].

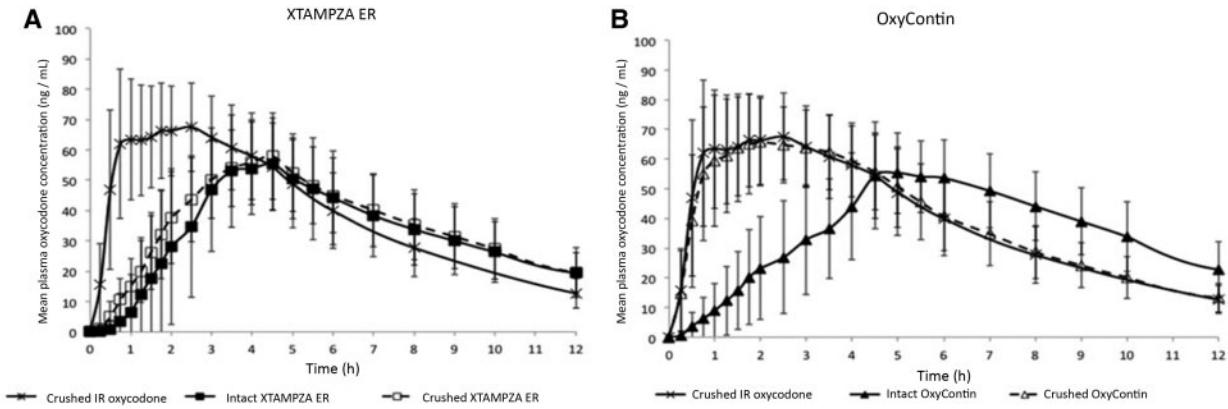

Figure 1 (A and B) Mean plasma concentration-time curve profiles compared with crushed IR oxycodone. Figure originally published in Gudin et al. Comparing the effect of tampering on the oral

The PK results in our paper were anticipated based on results of previously published in vitro data assessing the impact of physical manipulation on both Xtampza ER and OxyContin [3]. Multiple crushing methods were effective in reducing particle size and increasing oxycodone release from OxyContin; of the seven tools capable of reducing the particle size of OxyContin, six resulted in dissolution profiles that were different from control [3]. This study demonstrated a 60% increase in oxycodone release from manipulated OxyContin at 15 minutes, compared with 10% for Xtampza ER, when using the most effective manipulation tool for each product (the most effective tool was different for each product). These tools were selected from 10 common household tools based on their ability to reduce particle size and subsequent dissolution of each formulation.

Crudele points out, "The difficulty in or time and effort required to crush OxyContin tablets is only one impediment to preparing OxyContin for abuse." However, as we know from published studies, opioid abusers seek out formulations that can be manipulated with little effort and time [8]. Further, Crudele and colleagues note that "only real-world epidemiological studies can adequately demonstrate whether a product with ADP results in meaningful reductions in abuse, misuse, and related adverse outcomes." While it is true that this data does not yet exist for Xtampza ER, real-world data supports the fact that opioid abusers continue to abuse OxyContin by manipulation, whether for IV, IN, or oral abuse [9]. Respectfully, this data points to the need for access to ER oxycodone and other opioid formulations that better resist product manipulation.

Xtampza ER capsules are indicated to be taken with approximately the same amount of food with every dose in order to ensure consistent plasma levels are achieved. This is not the "carefully modulated, complete food intake" or "stringent procedure" Crudele states. An analysis of data collected in the primary efficacy and safety study of Xtampza ER, presented at the Xtampza US Food and Drug Administration (FDA) Advisory Committee meeting, showed no impact of type of food or timing of food intake on efficacy end points or adverse event reporting, even with inconsistent adherence to the "take with food" instruction [10]. Although the products are not bioequivalent, the label includes instruction on how to transition patients from other oral oxycodone formulations, stating, "Patients receiving other oral oxycodone formulations may be converted to Xtampza ER, using the same total daily dose of oxycodone, by administering one-half of the patient's total daily oral oxycodone dose as Xtampza ER every 12 hours with food" [6].

As noted in the Crudele letter, OxyContin was the first opioid to receive FDA-approved abuse-deterrence labeling. However, technology and drug development continue to improve. None of the abuse-deterrent products currently have data within their product label from postmarketing, epidemiologic studies evaluating the real-world impact of the abuse-deterrent properties. Collegium agrees with the importance of these studies and is currently working with the FDA to gather this data specific to Xtampza ER.

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LETTER TO THE EDITOR

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OXFORD

Sonographic Diagnosis and Treatment of Posterior Paralabral Cyst in the Hip Joint

Dear Editor,

A 36-year-old lady was seen for pain at the right lateral hip and thigh lasting for the last two months. She mentioned that the discomfort usually occurred after prolonged walking, and it was most painful when walking on the stairs. There was no weakness or paresthesia over her thigh or leg. She had a sedentary job and denied any antecedent injury as well. Physical examination showed slightly limited passive range of motion of the right hip flexion, internal and external rotation. Patrick test produced lateral hip and groin pain at the right side. Neurological examination was unremarkable. Anti-inflammatory medication was prescribed for a likely diagnosis of arthritis, but it did not cause significant improvement of her symptoms. Radiography of the right hip was noncontributory, and thus ultrasonography (US) was arranged.

US was performed by a physiatrist who specialized in musculoskeletal US with five years' experience, using the Acuson S2000 ultrasound system (Siemens, Munich, Germany) equipped with a 7–9 MHz linear transducer (9L4; Siemens). Any effusion or synovial hypertrophy was not observed at the anterior hip recess. On further investigation, a clearly demarcated anechoic cyst sized 12.3 mm x 7.2 mm extending from a cleft on the labrum at posterior hip joint was identified (Figure 1A). The patient was diagnosed with a paralabral cyst

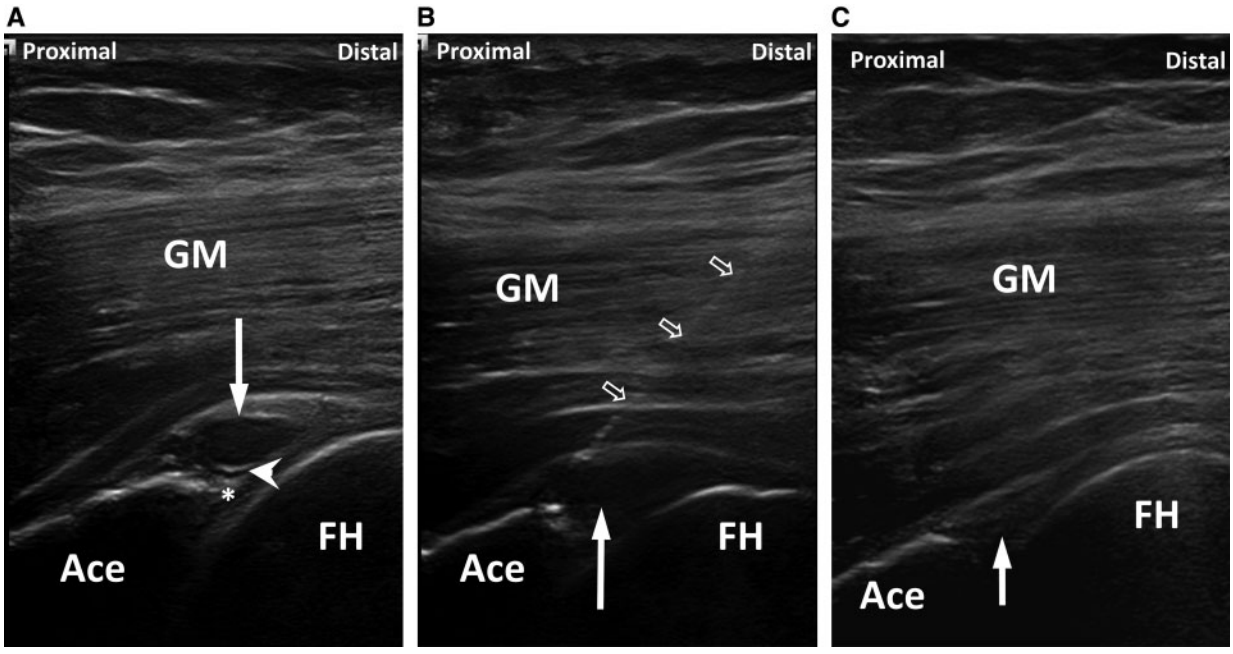

Figure 1 Ultrasonographic imaging of the posterior hip in the longitudinal axis (Ace = acetabulum; FH = femoral head; GM = gluteus maximus). The transducer was placed between the sciatic foramen and the greater trochanter, above the posterior hip joint. (A) A clearly-demarcated anechoic cyst (arrow)