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A Flawed Design Produces Flawed Results

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Dear Dr. Saitz

A recent study (Chu et al., 2017) in *The Journal of Addiction Medicine* indicated that ondansetron administration did not reduce naloxone-precipitated opiate withdrawal (NPOW) symptoms in chronic opiate users with chronic back pain (COU/CBP). However, a study design flaw is responsible for the lack of efficacy, which prevents drawing any conclusions from its results.

The COU/CBP results are in stark contrast to two prior studies (Chu et al., 2009; Erlandson et al., 2017), which demonstrated that treatment of healthy volunteers with either of two structurally distinct 5-HT₃ antagonists substantially reduced (and often eliminated) NPOW symptoms. In these studies, the 5-HT₃ antagonists were administered 2.5 hours before naloxone; but naloxone was administered only 0.5 hour after ondansetron in the COU/CBP study. This difference had a critical effect on outcome. The anti-emetic effect of ondansetron has a rapid onset (<0.5 hour) because it is mediated at sites (5-HT₃ receptor⁺ vagal afferent nerves in the gastrointestinal tract and brainstem) outside of the CNS (Tyers, 1992; Tyers and Freeman, 1992). This was cited (Chu et al., 2017) as a justification for administering naloxone 0.5 hour after ondansetron treatment. However, ondansetron's effect on NPOW occurs within the CNS (Chu et al., 2009); a peripheral acting opioid antagonist (methylnaltrexone) does not precipitate withdrawal (Portenoy et al., 2008; Thomas et al., 2008). Ondansetron has an unexpectedly slow rate of CNS entry; CNS penetration is marked even reduced at 1.5 hour after oral administration (Simpson et al., 1992). Even when administered intravenously, 0.5 hour is not enough time for ondansetron to equilibrate across the blood brain barrier. Any drug that does not have time to reach its receptor cannot have a therapeutic effect. This design element in the COU/CBP study significantly reduced its potential for observing a treatment effect. Properly designed clinical studies are required to assess a drug's treatment potential.

Although we cannot draw any conclusions from the COU/CBP study, a critically important question remains: *will ondansetron be effective in treating populations affected by chronic opioid use disorders?* Populations with different characteristics may have a different treatment response. The COU/CBP population is impacted by many confounding factors (chronic opioid exposure, long-term effects of pain on nociception, anticipatory withdrawal symptoms, possible mood disorders) that are not present in the healthy controls, and the

increased withdrawal scores observed in COU/CBP population are indicative of this. Therefore, it is important during the early stages of clinical testing to carefully consider the population studied. For example, an ongoing, multi-center clinical study [NCT01965704] examines the ability of ondansetron to ameliorate the incidence of the neonatal abstinence syndrome (NAS) in babies born to mothers with opioid use disorders. These neonates do not have many of the confounding features present in COU/CBP population; but they were exposed to opiates over a several month period. However, animal model results (Chu et al., 2009) indicate that ondansetron could ameliorate opiate withdrawal symptoms after exposure to multiple opioid doses. Thus, we have reason to hope ondansetron treatment will have a beneficial effect in preventing NAS.

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