Comment on: Evaluation of a Food and Drug Administration Mandate to Limit Acetaminophen in Prescription Combination Products

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Dear Editor,

Drs. Goldberger and Vearrier offer several possible explanations for their finding that the frequency of treatment with acetylcysteine and the incidence of hepatotoxicity were both low and unchanged in the year before and after the FDA limitation on acetaminophen (APAP) content of combination products in their recent study published in JMT [1].

One explanation for the lack of noticeable improvement is that the incidence of hepatotoxicity was already so low. In the 2015 AAPCC NPDS report, outcomes of unintentional exposures to APAP-opioid combination product were “no effect” in 64.5%, “minor” in 18.3%, “moderate” in 7.7%, and “major” in 1.8% [2]. In the same report, the outcomes for exposures to adult products containing only APAP (regardless of intention) were “no effect” in 52.7%, “minor” in 27.5%, “moderate” in 15.3%, and “major” in 4.0% [2]. “Moderate” and “major” outcomes appear to be twice as likely for APAP

alone than for APAP-opioid combinations, although the differences may be due to the exclusion of intentional exposures.

Over a decade ago, we undertook a prospective crossover trial in which volunteers ingested 5 g of APAP alone or in combination with diphenhydramine or oxycodone (in commercially available combinations). We measured APAP concentrations hourly for 8 h after ingestion and again at 24 h [3]. The time course for APAP concentrations was flatter and lower for the APAP-oxycodone treatment arm with a 27% lower area under the curve and a 35% lower maximum concentration (Fig. 1). These parameters reflect a lower bioavailability of APAP in the combination product.

The lower APAP bioavailability may explain why unintentional overdoses of APAP-opioid combination products seldom lead to serious toxicity and why a well-intentioned effort to improve safety appears to have no effect in unintentional overdose outcomes.

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Fig. 1 Hourly serum acetaminophen (APAP) concentrations 0 through 8 h after ingestion of 5 g APAP alone or in combination with diphenhydramine (DPH) or oxycodone (OXY) [3]

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Conflicts of Interest None

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