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Letter to the Editor

The need for studies of acetaminophen's impact on risk-taking in daily life; reply to Ross and Holstege (2021)

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We appreciate the opportunity raised by Drs Ross and Holstege to discuss the potential behavioral effects of acetaminophen beyond a controlled laboratory environment. In their letter to the editor, they "recommend that more research is needed prior to concluding that acetaminophen use is an acute danger to tasks of daily living". We heartily agree. We respectfully disagree, however, about the reasonableness of hypothesizing in the 'Potential Implications' section of a manuscript that acute acetaminophen consumption could have effects on behavior and decision-making that go beyond conventionally accepted reductions in pain and fever. Indeed, proposing such hypotheses is a critical component of motivating future studies to better understand the risks and benefits of consuming this drug. Millions of individuals in the USA take acetaminophen each day, and the behavioral effects of this drug are largely unstudied. We simply do not know if, when or for whom acute acetaminophen might have influences on thought, emotions or behavior in daily life. Ross and Holstege cite no data to indicate otherwise. Without such data, it is impossible to know what effects and effect size, if any, acetaminophen might have in daily life.

We should note that a growing body of literature from large, prospective studies exists in Europe (Liew *et al.*, 2014), North America (Rifas-Shiman *et al.*, 2020) and Asia (Chen *et al.*, 2019) linking acetaminophen use during pregnancy with later expression of risk-taking-related phenotypes in the offspring such as ADHD and externalizing behavior. In a recent study, acetaminophen levels in meconium (the first feces of newborn infants) predicted hyperactivity levels at age 10. The relationship between in utero exposure and hyperactivity was mediated by alterations in dorsolateral prefrontal connectivity (Baker *et al.*, 2020)—a region implicated in performance on the risk-taking task used in our study (Schonberg *et al.*, 2012). Naturally, if acetaminophen is identified in these correlational studies as the causal agent for these developmental effects, this finding would not necessarily mean that acute acetaminophen exerts any behavioral effects via the same pathways. But, the phenotypic overlap points to the potential for acetaminophen not being as inert as previously thought.

Because our study was laboratory-based basic research, it is indeed premature to make clinical recommendations based on these data. As hypothesized in our manuscript, acetaminophen could have the opposite behavioral effect, decreasing risk-taking, with only a subtle alteration of the experimental conditions. Similarly, the medical condition for which acetaminophen was consumed (e.g. headache; cold symptoms) also could fundamentally change the drug's psychological effects. Thus, as we have demonstrated (Roberts *et al.*, 2019), acetaminophen's psychological and behavioral effects are likely state- and context-dependent, defying the simple categorization of a newspaper headline.

Ultimately, like Ross and Holstege, we too hope that acetaminophen does not influence risk-related decisions in daily life and appreciate their furthering discussion of this important issue. However, we believe it is an important research endeavor to uncover its effects, whether positive or negative, large or small, so that individuals and clinicians can make more informed decisions about it.

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Conflict of interest

The authors declare no conflict of interest.

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