"Effect of the putative lithium mimetic ebselen on brain myo-inositol, sleep and emotional processing in humans"

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**Background:** Ebselen has been tested in clinical trials for other disorders, enabling us to determine for the first time the effect of a blood-brain barrier penetrant IMPase inhibitor on human central nervous system (CNS) function. In this paper the authors report that in a double-blind, placebo-controlled trial with healthy participants, acute oral ebselen reduced brain myo-inositol in the anterior cingulate cortex, consistent with CNS target engagement. Ebselen decreased slow-wave sleep and affected emotional processing by increasing recognition of some emotions, decreasing latency time in the acoustic startle paradigm and decreasing the reinforcement of rewarding stimuli. In summary, ebselen affects the phosphoinositide cycle and has CNS effects on surrogate markers that may be relevant to the treatment of bipolar disorder, which can be tested in future clinical trials.

**Feedback:** this is a well-written paper with a strong rationale, innovative design and findings with clinically relevant implications. I support the publication of this manuscript in Neuropsychopharmacology pending a few revisions.

1. Could the authors provide additional information on the pharmacokinetics of ebselen, e.g.half-life, duration of effects, expected waiting time before effects on mood and cognition can be detected.
2. Based on this kind of information could the authors explain the duration of the treatment (1 week), lack of washout period and potential carry-over effects.
3. Did the authors control for learning effects since the tasks were presented within such a short period of time (1 week).
4. Did the authors expect changes in mood in these participants? I would refer to lack of mood changes shown in Table 1 and would add a few comments focusing on this topic in the discussion.
5. Also, since the authors include 1. A facial recognition task and 2. Acoustic startle paradigm in response to pleasant, unpleasant and neutral stimuli I would include a paragraph on affective processing in the introduction and a better interpretation of such findings in the discussion.
6. In line with my previous comment, it would be important to highlight the fact that despite the lack of mood changes participants showed changes in these emotional tasks.
7. Could the authors clarify whether they had apriori regions of interest for their MRS analyses and why. This could be developed further in the discussion.
8. I would also recommend a better explanation of how the changes in sleep architecture may be linked to changes in emotional processing (regardless of current mood state).
9. Minor details: typos such as “vomitting” (Figure 1j)