No Evidence of Decrease in Cognitive Function in Users of Low-Dose Ecstasy

Unlike nearly all previous research on the issue of potential long-term effects of Ecstasy use, the Netherlands XTC Toxicity team used a prospective study design, assessing people before and after they decided to take Ecstasy. It is precisely because Schilt and colleagues[1] are engaged in conducting one of the most ambitious and carefully thought out programs of research that seeks to overcome the problems of retrospective study designs that we remark on the serious problems with this report. Schilt and colleagues overstate the findings of their nonrandomized study when they conclude that their data show that "even a first low cumulative dose of Ecstasy is associated with decline in verbal memory."[1(p728)] All 12 cognitive test scores in both groups were within the normal range, and no decreases were demonstrated in the Ecstasy group over time.

Schilt and colleagues describe an increase in verbal memory scores in the nonuser group as a relative decrease in the Ecstasy users. They argue that an increase in scores is to be expected because of retest effects, but retest effects of word list recall tests disappear within a month,[2] so there is no reason to expect a retest effect after a variable follow-up period of up to 3 years.

While Schilt and colleagues state that the sample of Ecstasy users represents people with "low" Ecstasy use, with an average cumulative use of 3.2 tablets, 1 or more subjects reported cumulative use of 30 tablets. This dose is lower than those reported in heavy Ecstasy users but does not qualify as low use. To reach conclusions specific to low Ecstasy use, Schilt and colleagues should have repeated their analyses after excluding subjects who used more than 10 tablets of Ecstasy. They do not report the maximum dose of Ecstasy consumed on any 1 occasion, so the use of large doses per use cannot be ruled out. Average dose per use is likely to highly influence the effects of the drug because MDMA (3,4-methylenedioxymethamphetamine [Ecstasy]) has nonlinear pharmacokinetics.[3]

Taken together, Schilt and colleagues did not demonstrate a decrease in verbal memory function in Ecstasy users and not all participants reported low Ecstasy use. Furthermore, a difference in verbal memory performance may have arisen because subjects who took Ecstasy may have experienced anxiety about confirming beliefs on the harms of Ecstasy use. Subjects were informed at the beginning of the Netherlands XTC Toxicity study that Ecstasy use may cause cognitive deficits, and the name of the project itself contains the word *toxicity*. Such priming has been shown to impair performance in Ecstasy users, specifically on tests of verbal memory.[4] This effect fits with current models of test anxiety in which task-related thoughts and worries interfere with phonological aspects of working memory.[5]

The question of the long-term cognitive harms of minimal MDMA use is important not only for public health but also for psychiatric treatment development. There are currently 4 active randomized, double-blind, placebo-controlled clinical trials (clinicaltrials.gov identifiers NCT00252174, NCT00090064, NCT00402298, and NCT00353938) involving a few low doses of MDMA administered as an augment to therapy for anxiety disorders. It is important to distinguish between controlled clinical use of MDMA and use of illicit drug preparations termed *Ecstasy* of unknown purity and dosage, in uncontrolled settings, and without health precautions. As with any other medication, the differences in risk between medically controlled use of MDMA and illicit use of Ecstasy can and must be communicated clearly.

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Additional Information: Mr Johansen is director of Evidence Knowledge Exchange (www.evidence.no), a Norwegian nonprofit offering continuing education courses.

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In reply

Krebs and Johansen raise some questions concerning the conclusions of our article "Cognition in Novice Ecstasy Users With Minimal Exposure to Other Drugs."[1] We interpret the absence of a retest effect on a verbal memory task in Ecstasy users as a decrease in verbal memory. This is based on the fact that the Ecstasy-naive subjects showed an increase in performance between the initial and follow-up ex-