clinical pharmacology of GABAmimetics has been slowly developing, largely because of the antiepileptic properties of GABA agonists. GABAmimetics have relatively potent antidyskinetic actions in tardive dyskinesia[9] and may have antidepressant action. Perhaps these potential clinical applications will encourage additional pharmaceutical development in the area of GABAmimetics. Then, we can anticipate more GABAmimetic tools for GABA studies. Systematic studies to explore the putative role of GABA in depression are needed to address this therapeutic potential further and uncover its biologic correlates.

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Second Thoughts on 3,4-Methylenedioxymethamphetamine (MDMA) Neurotoxicity

To the Editor.—Recent attention has been drawn to the purported neurotoxic dangers associated with 3, 4-methylenedioxymethamphetamine (MDMA). Price et al[1] have attempted to assess possible serotonergic neurotransmitter damage by contrasting serum prolactin response to the challenge with intravenous L-tryptophan in subjects with a history of MDMA use vs control subjects. Their primary finding was a blunted rise in the expected serum prolactin level in MDMA users, but not to a statistically significant degree. The importance of this finding appears to be questionable and perhaps misleading. Even if the data had yielded a statistically significant result, would such a correlation necessarily imply causation?

A methodological limitation to the study would appear to be that subjects were not adequately screened on selection to exclude those who were using other psychotropic drugs. There is no mention that toxicology screens were ever performed. In fact, three subjects (33%) admitted to marijuana use during the 3-week supposed drug-free interval prior to the testing. As marijuana is known to affect dopaminergic function (and, consequently, prolactin secretion),[2] the implications for MDMA effect on serotonergic function are further questioned. One additional point regarding this study is that even if one could demonstrate that MDMA users had diminished serotonergic function compared with control subjects, what does this imply? Without data as to baseline serotonergic functioning prior to the first ingestion of MDMA, such findings are of limited significance.

Numerous animal studies have been performed over the past several years that were designed to evaluate the neurotoxic potential of MDMA. Until recently, most have examined short-term degeneration of serotonin neurons in animal brain following repeated systemic administration of MDMA. Battaglia et al[3] have examined the brains of rats treated with massive subcutaneous dosages of MDMA (cumulatively up to 100 times the usual human oral dose) over time, and have noted complete regeneration 1 year after administration of the drug. This, together with the fact that there have yet to be documented clinical cases of MDMA-induced serotonergic neurotoxicity (ie, there have been no reports of sleep, mood, appetite, aggressive, or sexual dysregulation), may indicate that concerns over long-term neuropsychiatric damage have been overstated.

The related controversy over fenfluramine hydrochloride has some relevance here. During the last 25 years, approximately 50 million people have been clinically treated with fenfluramine.[4] Fenfluramine has been utilized primarily as a weight-reducing agent and has also been used in clinical trials for the treatment of infantile autism and childhood attention-deficit disorder with hyperactivity. However, animal studies have demonstrated that fenfluramine has a serotonergic neurotoxic capability three times that of MDMA.[5] Yet despite such findings, fenfluramine has accepted clinical indications, has a history of widespread use, and is without the known induction of neurological side effects.

Claims have been made that MDMA enhances the processes of psychotherapy by facilitating empathy, heightening introspection, and lowering defensive anxiety.[6] Because of concerns of possible neurotoxicity, however, rigorous clinical trials designed to validate these claims have not been performed. The data reviewed suggest that fears of MDMA neurotoxicity may have been exaggerated and it may well be significantly less toxic than a very widely used medication, fenfluramine. In view of its purported unique psychoactive properties, it may be appropriate to pursue clinical trials of MDMA. Alternatively, the search for a nontoxic analogue should be encouraged.

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