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CYP2D6 function moderates the pharmacokinetics and pharmacodynamics of 3,4-methylene-dioxymethamphetamine in a controlled study in healthy individuals

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The role of genetic polymorphisms in cytochrome (CYP) 2D6 involved in the metabolism of 3,4-methylene-dioxymethamphetamine (MDMA, ecstasy) is unclear. Effects of genetic variants in CYP2D6 on the pharmacokinetics and pharmacodynamic effects of MDMA were characterized in 139 healthy individuals (70 men, 69 women) in a pooled analysis of eight double-blind, placebo-controlled crossover studies. In CYP2D6 poor metabolizers, the maximum concentrations (Cmax) of MDMA and its active metabolite 3,4-methylene-dioxyamphetamine were +15 and +50% higher, respectively, compared with extensive metabolizers and the Cmax of the inactive metabolite 4-hydroxy-3-methoxymethamphetamine was 50-70% lower. Blood pressure and subjective drug effects increased more rapidly after MDMA administration in poor metabolizers than in extensive metabolizers. In conclusion, the disposition of MDMA and its effects in humans are altered by polymorphic CYP2D6 activity, but the effects are small because of the autoinhibition of CYP2D6.

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