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Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania.

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Abstract

INTRODUCTION:

Identifying clinical and genetic risk factors associated with antidepressant-induced mania (AIM) may improve individualized treatment strategies for bipolar depression.

METHOD: From 2009 to 2012, bipolar depressed patients, confirmed by DSM-IV-TR-structured interview, were screened for AIM. An AIM+ case was defined as a manic/hypomanic episode within 60 days of starting or changing dose of antidepressant, while an AIM- control was defined as an adequate (≥ 60 days) exposure to an antidepressant with no associated manic/hypomanic episode. 591 subjects (205 AIM+ and 386 AIM-) exposed to an antidepressant and a subset of 545 subjects (191 AIM+ and 354 AIM-) treated with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were used to evaluate the association of AIM with phenotypic clinical risk factors previously published. 295 white subjects (113 AIM+ cases, 182 AIM- controls) were genotyped for 3 SLC6A4 variants: the 5-HTTLPR, single nucleotide polymorphism (SNP) rs25531, and the intron 2 variable number of tandem repeats (VNTR). Tests of association with AIM were performed for each polymorphism and the haplotype.

RESULTS: The only clinical risk factors associated with AIM in the overall and the SSRI + SNRI analysis was bipolar I subtype. The S allele of 5-HTTLPR was not significantly associated with AIM; however, a meta-analysis combining this sample with 5 prior studies provided marginal evidence of association (P = .059). The L-A-10 haplotype was associated with a reduced risk of AIM (P = .012).

DISCUSSION: Narrowly defined, AIM appears to be at greatest risk for bipolar I patients. Our haplotype analysis of SLC6A4 suggests that future pharmacogenetic studies should not only focus on the SLC6A4 promotor variation but also investigate the role of other variants in the gene.