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.

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Mania is a mood state characterized by poor judgment, marked impulsivity, and psychosis often resulting in hospitalization, arrest, or incarceration.[1] Repeated episodes of mania may be associated with progressive neuroanatomic change, functional change, or both.[2,3] There is increasing convergence and research focused on neuroanatomic (insula activation), genomic (catechol-*O*-methyltransferase, serotonin transporter), inflammatory (arachidonic acid up-regulation), and neuroendocrine markers of incipient mania or the switch process.[4–6] The public and personal health impact of markers that would allow primary prevention, early treatment intervention, or secondary prevention of mania is substantial.[7]

Incident estimates of antidepressant-induced mania (AIM) vary by study design. A recent registry of more than 3,200 bipolar patients reported an increased risk of "treatment-emergent mania" when prescribed antidepressants (HR = 2.83, 95% CI = 1.12–7.19); while the risk was confined only to antidepressants prescribed, the group represented 35% of the original study cohort.[8] While more than 40% of subjects from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) self-reported retrospective manic/hypomanic switch associated with antidepressant use,[9] controlled trials report significantly lower rates. A random-effects meta-analysis[10] of 35 clinical trials of bipolar depressed patients reported a switch rate of 12.5% with and 7.5% without antidepressant use. Other short-term clinical trials suggest the placebo or course-of-illness switch rate may be as low as 4%–7%.[11,12] In the largest trial to date, the EMBOLDEN II (Efficacy of Monotherapy Seroquel in bipolar Depression II), incidence of treatment-emergent mania/hypomania for placebo (n = 126) was 8.9% with a higher and lower switch rate for the selective serotonin reuptake inhibitor (SSRI) paroxetine (n = 122, 10.7%) and quetiapine (n = 245, 3%), respectively.[13] It is important to remember that with current contemporary trial design for bipolar I depression, subjects enrolled in trials of antidepressant monotherapy are carefully selected and the risk of a switch to mania in these study populations may be lower than the risk in clinical practice.[7]

Although based on small or retrospective studies, a number of demographic and clinical risk factors for AIM have been reported, including tricyclic versus SSRI antidepressants, absence versus presence of mood stabilizer, female gender, younger age, bipolar I versus II disorder subtype, rapid versus non–rapid cycling, mixed depressive symptoms, subclinical hyperthyroidism, substance abuse comorbidity, and psychosis.[14–19] There is still a need to further confirm whether these risk factors increase the risk of AIM in larger samples. Phenomenologically, a number of clinical terms (*antidepressant-induced mania*, *treatment-emergent mania*, *switch*) have been used to describe this mood shift from depression to mania, bypassing euthymia. The

International Society of Bipolar Disorder Task Force Report on Nomenclature[20] recommended the term *treatment-emergent manic switch* to account for potential confounds related to course of illness risk factors.

Genetic variation is known to contribute to individual response to many drugs including antidepressants,[21] and thus, genetic predisposition to AIM has also been considered.[22] The serotonin transporter gene, solute carrier family 6 (neurotransmitter transporter), member 4 (*SLC6A4*), which encodes the protein that transports the reuptake of synaptic serotonin, has 2 well-known polymorphisms: a 44-base pair (bp) insertion/deletion in the promoter region (5-HTTLPR) with long (L) and short (S) allele variants and a second intron variable number of tandem repeats (VNTR). Furthermore, the single nucleotide polymorphism (SNP) rs25531 has been reported to influence the association of the 5-HTTLPR alleles with expression of the *SLC6A4* gene, such that the combination of the 5-HTTLPR L allele with the rs25531 A allele results in higher levels of expression, whereas the 5-HTTLPR L allele combined with the rs25531 G allele results in expression levels similar to those of the 5-HTTLPR S allele.

The 5-HTTLPR polymorphism is by far the most commonly studied variation in the gene and has been shown to be associated with differential gene expression,[23] SSRI response rates,[24] side effects,[25] and AIM.[26,27] Two meta-analyses, with different study inclusion criteria, have evaluated the evidence for the pharmacogenetic association with AIM and have reached different conclusions; while 1 of the studies reported significant evidence of association,[28] the other suggested only a trend.[29]

Conclusions that could be drawn from the prior studies on *SLC6A4* and AIM were limited because most of the prior studies did not evaluate potential confounding factors and investigated the role of only 1 genetic variant in the *SLC6A4* gene.[26,27,30–33] This study was conducted to evaluate the association between a narrowly defined AIM phenotype and potential clinical risk factors as well as 3 common variations of the serotonin transporter gene.

METHOD

The Mayo Clinic Bipolar Disorder Biobank was established in 2009 with a primary goal to collect data and biospecimens from patients with bipolar disorder to enable future biomarker studies of disease risk and treatment response. Enrollment sites, each with site-specific institutional review board approval, included Mayo Clinic Rochester, Lindner Center of HOPE/University of Cincinnati College of Medicine, and University of Minnesota, Minneapolis.

Initial participation in the biobank required *DSM-IV-TR* diagnostic confirmation of bipolar I or II disorder or schizoaffective bipolar disorder.[34] Patients enrolled in the Bipolar Biobank from 2009 to 2012 were screened for AIM. While the International Society for Bipolar Disorders has recommended the term *treatment-emergent manic switch* to account for potential confounds in causality,[20] we have continued to use the term *AIM* given our plan to add these study data to the prior meta-analysis, which,[29] in addition to 5 individual studies, used AIM nomenclature. Moreover, the narrow phenotype definition in this study controlled for potential illness confounders, identified in the International Society for Bipolar Disorders nomenclature, to better assess the risk of antidepressant exposure and drug-associated switch to mania.

Clinical Points

- Patients with bipolar I disorder have higher rates of antidepressant-induced mania than patients with bipolar II disorder.
- Antidepressants have an inherent risk for destabilization in bipolar disorder.
- The serotonin transporter and associated areas of potential genetic variation may be associated with antidepressant-induced mania.

An AIM+ case was defined as a manic/hypomanic episode by *DSM* criteria within 8 weeks (60 days) of starting an antidepressant treatment or increasing an antidepressant dose. In addition to confirmation of bipolar I versus II subtype from the SCID,[34] clinical correlates ascertained by review of medical record for each AIM+ case included antidepressant class (particular interest in SSRI or serotonin-norepinephrine reuptake inhibitor [SNRI]), lifetime Axis I comorbidity, presence or absence of concurrent mood-stabilizing treatment (ie, therapeutic dose of lithium, carbamazepine, divalproex, or atypical antipsychotic), and rapid cycling status at time of AIM. Adequate (≥ 60 day) exposure to an antidepressant with no associated adverse event (AIM) was considered as an AIM– control (AIM–, n = 354). All AIM+ and AIM– phenotypes were confirmed by site senior psychiatrist principal investigators (M.A.F., S.L.M., S.C.). Logistic regression models were used to test various demographic and clinical characteristics as predictors of AIM.

A subset of 332 subjects with available AIM phenotypic data (129 AIM+ cases, 203 AIM– controls) was genotyped. To control for the potential confound of population stratification[35] (ie, ancestry-dependent differences in genetic polymorphism frequencies and ancestry-dependent differences in phenotype distributions, leading to confounded associations between genotypes and phenotypes), we included 295 self-reported white subjects (113 AIM+ cases, 182 AIM– controls) in the genetic association analysis.

Three *SLC6A4* variants were genotyped: the 5-HTTLPR (long [L] and short [S] alleles), SNP rs25531 (A/G), and the intron 2 VNTR (9, 10, 12 repeat alleles). The 17-bp VNTR region of the second intron of *SLC6A4* was polymerase chain reaction (PCR)–amplified from genomic DNA as described by Battersby and colleagues.[36] Amplicons were separated using the Agilent 1000 DNA system (Agilent Technologies; Waldbronn, Germany). Fragment sizes of 250, 271, and 302 bp correspond to 9, 10, and 12 repeats, respectively. The simultaneous determination of the long and short form of the 5-HTT promoter region and rs25531 was performed

Table 1. Demographics of Bipolar Depressed Subjects Screened for Antidepressant-Induced Mania (AIM)[a]

	Overall		All Drugs (n = 591; 205 AIM+ cases/ 386 AIM– controls)			SSRIs and SNRIs (n = 545; 191 AIM+ cases/ 354 AIM– controls)		
Demographic	n	%	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Male gender	243	41.1	1.42	1.01–2.02	.48	1.38	0.96–1.98	.085
Bipolar I disorder	465	78.7	2.15	1.36–3.41	.0011	2.13	1.33–3.42	.0016
Rapid cycling	328	55.8	1.41	0.99–1.99	.050	1.34	0.93–1.91	.12
Clinical diagnosis								
PTSD	150	26.0	1.10	0.75–1.64	.59	1.11	0.74–1.67	.60
Anxiety disorder	400	68.5	1.58	1.08–2.31	.018	1.31	0.88–1.96	.18
Eating disorder	94	16.0	1.42	0.90–2.23	.13	1.61	1.00–2.58	.0496
Alcohol abuse/dependence	224	38.1	1.11	0.78–1.57	.56	1.05	0.73–1.51	.82
Nicotine dependence	196	33.6	0.92	0.64–1.32	.65	0.94	0.64–1.38	.76
Any ADHD	162	28.2	1.41	0.97–2.05	.076	1.30	0.87–1.92	.20
Adult ADHD	127	22.0	1.46	0.97–2.19	.068	1.39	0.91–2.12	.13
Child ADHD	94	16.5	1.53	0.98–2.41	.063	1.32	0.82–2.11	.26

[a]An AIM+ case was defined as a manic/hypomanic episode by *DSM* criteria within 60 days of starting an antidepressant treatment or increasing an antidepressant dose. An AIM– control was defined as adequate (≥ 60 day) exposure to an antidepressant with no associated adverse event.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, PTSD = posttraumatic stress disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

by PCR amplification of the promoter region of 5-HTT followed by Haemophilus parainfluenzae II digestion of the resulting amplicon as described by Wendlend and coworkers.[37] Digested fragment sizes of 512 and 469 bp correspond to LA and SA (L or S allele with "A" present at rs25531), respectively. The presence of "G" at rs25531 is indicative of a digested fragment of 402 bp and an additional fragment of 69 or 100 bp for the S and L allele, respectively.

Secondary genetic analyses were restricted to a subset of subjects that took SSRIs or SNRIs (105 AIM+ cases, 167 AIM– controls) or that included only AIM+ cases that were not taking mood stabilizers at the time of AIM (n = 72). Logistic regression was used to evaluate the association of each genotyped variant with AIM. Log-additive allele effects as well as a dominant effect of S (recessive effect of L) were considered. The analyses of a dominant S allele effect compared subjects with the S/S or S/L genotype with those with the L/L genotype. For the combined 5-HTTLPR/rs25531 genotypes, additive and recessive effects of the LA allele were considered, with analyses of a recessive LA effect by comparing those with the LA/LA genotype with all remaining subjects. For the intron 2 VNTR, log-additive effects of the 10-repeat allele and log-additive effects of the 12-repeat allele were considered by coding the genotype as the number of 10-repeat alleles or number of 12-repeat alleles, respectively.

Haplotype analysis was performed to investigate the role of haplotypes composed of the 3 *SLC6A4* polymorphisms that were genotyped: 5-HTTLPR, rs25531, and intron 2 VNTR. Haplotype association tests were performed using the score statistic proposed by Schaid and colleagues[38] and implemented in the HaploStats R package. Log-additive haplotype effects were assumed, and haplotypes with frequencies below 0.02 were excluded.

Finally, a meta-analysis of the log-additive allele effects of the S allele was performed by adding our new results to a previously published meta-analysis.[29] The meta-analysis combined the results of the individual studies using the DerSimonian-Laird method,[39] assuming random effects to account for the previously described between-study variation.[29] The meta-analysis was performed using the R package rmeta (http://cran.r-project.org/web/packages/rmeta/index.html).

RESULTS

As presented in Table 1, 591 bipolar subjects were included in this study, including 205 AIM+ cases and 386 AIM– controls; a subset restricted to just SSRI or SNRI antidepressants included 191 AIM+ cases and 354 AIM– controls. For the 191 AIM+ cases, 57.1% of AIM occurred at starting dose, while 16.2% occurred after dose increase, and for 26.7% this information was unknown. Concomitant mood stabilization at the time of AIM was absent in 58.6%, present in 19.9%, and unknown in 21.5% of AIM+ cases. Rapid cycling at the time of AIM was reported in 35.6% of AIM+ cases (64.4% absent or unknown).

As presented in Table 1, for the overall group, bipolar I subtype, female gender, and current rapid cycling with anxiety disorder comorbidity were associated with AIM+. Only bipolar I subtype and history of eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder) were associated with AIM+ in the SSRI + SNRI analysis.

As presented in Table 2, separate analyses of 5-HTTLPR, 5-HTTLPR/rs25531, and intron 2 VNTR variation in AIM+ cases versus AIM– controls were not statistically significant. However, estimates indicate a trend for the S allele to be associated with higher risk of AIM (OR = 1.31, *P* = .12 for an additive allelic effect; OR = 1.49, *P* = .14 for a dominant S allele effect), a finding consistent with earlier studies of the 5-HTTLPR–AIM association.[29] Additionally, 5-HTTLPR/rs25531 LA allele recessive effect was marginally significantly associated with a reduced risk of AIM.

Table 2. *SLC6A4* Variation in 295 Self-Reported Caucasian Subjects[a]

	All Drugs (113 AIM+ cases vs 182 AIM– controls)			SSRIs and SNRIs (105 AIM+ cases vs 167 AIM– controls)		
Variant	OR	95% CI	*P* Value	OR	95% CI	*P* Value
5-HTTLPR						
S allele additive effect	1.31	0.94–1.84	.12	1.31	0.92–1.87	.13
S allele dominant effect	1.49	0.87–2.54	.14	1.49	0.85–2.59	.16
5-HTTLPR/rs25531						
LA allele additive effect	0.77	0.55–1.08	.12	0.74	0.53–1.06	.097
LA allele recessive effect	0.60	0.34–1.07	.084	0.56	0.31–1.03	.062
Intron 2 VNTR						
10 allele additive effect	0.78	0.55–1.11	.17	0.80	0.56–1.15	.23
12 allele additive effect	1.14	0.81–1.60	.46	1.11	0.78–1.58	.57

[a]An AIM+ case was defined as a manic/hypomanic episode by *DSM* criteria within 60 days of starting an antidepressant treatment or increasing an antidepressant dose. An AIM– control was defined as adequate (≥ 60 day) exposure to an antidepressant with no associated adverse event.
Abbreviations: AIM = antidepressant-induced mania; OR = odds ratio; *SLC6A4* = solute carrier family 6 (neurotransmitter transporter), member 4; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; VNTR = variable number of tandem repeats.

Table 3. Haplotype Analysis in 295 Self-Reported Caucasian Subjects (AIM+ cases [n = 113] vs AIM– controls [n = 182])[a]

Haplotype	Frequency	Score	Simulation *P*	Maximum Statistic Simulation *P*	Global Simulation *P*
L-A-10	0.344	–2.448	.012	.047	
L-G-12	0.027	–1.555	.14	…	
S-A-10	0.214	0.144	.86	…	.020
L-A-12	0.136	0.965	.31	…	
S-A-12	0.225	1.034	.28	…	

[a]An AIM+ case was defined as a manic/hypomanic episode by *DSM* criteria within 60 days of starting an antidepressant treatment or increasing an antidepressant dose. An AIM– control was defined as adequate (≥ 60 day) exposure to an antidepressant with no associated adverse event.
Abbreviation: AIM = antidepressant-induced mania.

As presented in Table 3, the haplotype analysis was significant for association of the 5-HTTLPR, rs25531, and intron 2 VNTR haplotypes with AIM ($P = .02$ for global test of haplotype association). In particular, the L-A-10 haplotype was shown to be associated with reduced risk of AIM ($P = .012$; maximum statistic simulation P that accounts for testing of multiple haplotypes: $P = .047$). Secondary haplotype analyses for SSRI + SNRI antidepressants only (105 AIM+ cases, 167 AIM– controls) and AIM+ cases without concurrent mood stabilization therapy (72 AIM+ cases, 182 AIM– controls) achieved similar results (SSRI + SNRI: $P = .02$, global $P = .033$; no concurrent mood stabilization: $P = .048$, global $P = .028$).

Finally, a meta-analysis was performed to determine the overall evidence for the 5-HTTLPR–AIM association after combining these new study results with the results of prior studies. This 6-study meta-analysis demonstrated a marginally significant evidence of association of the S allele with AIM (OR = 1.35; 95% CI, 0.99–1.85; $P = .059$; Figure 1).[26,27,31–33]

DISCUSSION

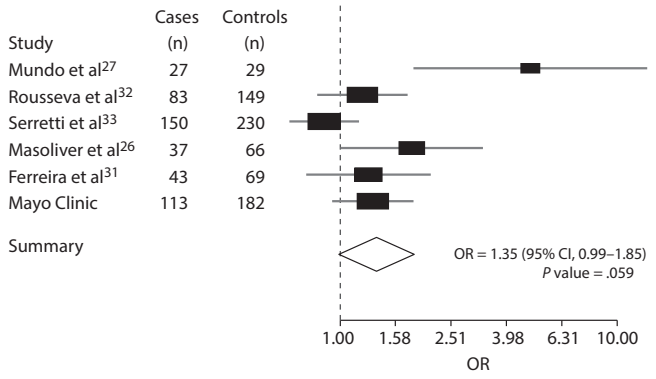
In summary, we have identified key clinical risk factors of bipolar I subtype and 1 lifetime comorbidity pattern that appear to be associated with a narrowly defined phenotype of AIM. While not demonstrating a statistically significant association with the 5-HTTLPR S allele polymorphism in *SLC6A4*, the 6-study meta-analysis provides marginally significant evidence of association with this antidepressant-associated adverse event. Furthermore, to our knowledge, this is the first report of the 5-HTTLPR–rs25531–intron 2 VNTR–L-A-10 haplotype being associated with a reduced risk of AIM.

This study has a number of strengths, foremost being a narrowly defined phenotype of AIM. By reducing the time duration of exposure to drug, we increased the actuarial risk of drug liability as opposed to risk from general course of illness or rapid cycling status. Furthermore, a number of potential confounds to risk identified in the prior meta-analysis[29] were controlled for in this study (ie, differential mania/hypomania diagnostic criteria for inclusion, inclusion of nonserotonin transporter antidepressants, time duration of AIM [1 study each for 1 month, 2 months, 3 months, and no time frame duration in 2 studies], and cases and controls matched for ethnicity).

The time duration of drug exposure for adverse event risk and causality is a relevant issue in bipolar study design given the inherent instability and cycling of the illness. The International Society for Bipolar Disorders Task Force Report on Nomenclature[20] recommended the term *treatment-emergent manic switch*, with parameters of strength of association based on time duration (up to 12 weeks) and level of diagnostic criteria met; an exception was made if the treatment switch was within the first 2 weeks of antidepressant medication exposure. This study, which is focused on drug liability and genomic variation at the serotonin transporter, utilized a narrow definition of 8, not 12, weeks, defined full syndromal *DSM* criteria for mania and hypomania and assessed for rapid cycling and absence of mood stabilization concurrent treatment at the time of AIM.

The identification of bipolar I subtype as a risk factor for AIM replicates previous findings[14,15] and even underscores with adjunct mood stabilization, which is typically more common in bipolar I versus bipolar II depression, the potential liability of antidepressants in this patient group. Recent review work by Baldessarini and colleagues[40] identifies a mood switch of ~ 8% in unipolar patients treated with an antidepressant; the risk was 2.6 times greater with versus without antidepressant treatment, with incidence rates 4.5 times greater in juvenile than adult populations. Furthermore, a recent registry reported an increased risk of "treatment-emergent mania" during the first 3 months of antidepressant monotherapy in the treatment of bipolar disorder, implying a window of liability for this drug-related event.[8] Given the retrospective nature of the study, we were unable to identify the age at onset of AIM, but as noted in previous work,[30,31] age is a risk factor for AIM. The eating disorder finding is new and needs replication.

Figure 1. Meta-Analysis of *SLC6A4* and AIM+[a]



[a]An AIM+ case was defined as a manic/hypomanic episode by *DSM* criteria within 60 days of starting an antidepressant treatment or increasing an antidepressant dose.
Abbreviations: AIM = antidepressant-induced mania, *SLC6A4* = solute carrier family 6 (neurotransmitter transporter), member 4.

This study has a number of limitations, foremost of which is the retrospective nature of phenotypic classification, initial recruitment of bipolar I subjects for the first year of study enrollment, and inability to assess for depressive symptom severity or presence of mixed depression.[16] While the phenotype is narrowly defined and has addressed a number of potential confounds in the literature,[20] the retrospective nature of the phenotype classification does not fully clarify induced versus associated risk. Furthermore, AIM+ cases and AIM– controls were not matched for dates of assessment. In contrast to the AIM+ cases, the absence of mood-stabilizing treatment and presence of rapid cycling status at time of antidepressant trial for the AIM– controls was not quantified. Although a prospective, randomized controlled trial (controlling for potential confounding factors) would provide ideal data for assessing pharmacogenomic risk for AIM, a well-designed retrospective study can also provide high-quality data, with larger sample size, in shorter timeframe, and at lower cost. This is the second-largest genomic risk study, with a sample size of 295 white subjects. Improvements can be made by collecting detailed information to precisely define AIM outcomes in a well-defined population of bipolar subjects. Pharmacogenomic studies need to collect information regarding other potential moderators and mediators to AIM and take those factors into account in genetic association analyses.

In addition to the narrow clinical phenotype, this study has a number of strengths in the genomic analysis. Although most of the previous studies of *SLC6A4* and AIM used homogeneous white cohorts, 1 study[32] did not report racial demographic details of cases and controls, and a pediatric study[30] had substantial differences in the ethnic distribution of cases versus controls. Knowing that frequencies of the studied polymorphisms are population dependent, we limited our analysis to subjects with self-reported white ancestry to minimize the potential confounding by population stratification. While residual population structure cannot be entirely ruled out, it has been shown that self-reported ancestry can be a reliable method to control for population stratification in candidate gene studies.[41,42] While not able to show statistically significant association between AIM and the S allele (additive or dominant), the trends were in the direction of previous research; when entered into existing meta-analysis from our group,[29] the larger sample size was associated with a narrower 95% CI (0.94–2.12 to 0.99–1.85), with a commensurate increase in statistical significance from $P = .10$ to $P = .059$. It is important, when finalizing impressions of the role of *SLC6A4* genetic variation in AIM, to recognize the potential limitation of potential publication bias as a result of unreported negative studies evaluating *SLC6A4*.

In addition to the frequently studied 5-HTTLPR L/S variant, our study included the rs25531 SNP that is believed to modify the effect of the 5-HTTLPR variant, as well as the intron 2 VNTR, which is known to be associated with differential expression of the *SLC6A4* gene. Prior meta-analyses[29] identified significant heterogeneity between studies of the 5-HTTLPR pharmacogenetic effect on AIM and did not conclusively demonstrate a significant pharmacogenetic effect. Here we have provided additional evidence for the potential role of the 5-HTTLPR genetic variation in risk of AIM. More importantly, our results suggest that a haplotype that includes both the promoter polymorphism and the intron 2 VNTR of the serotonin transporter gene may be a better predictor of the risk of AIM than the promoter polymorphism alone. Thus, further effort into understanding the relationship between *SLC6A4* variation and risk of AIM should be made to evaluate the role of the intron 2 VNTR as well as other variants in *SLC6A4*, rather than focusing exclusively on the promoter long/short variant.

Few pharmacogenetic studies of antidepressant effectiveness in bipolar depression or antidepressant-associated–induced mania have been published. Future studies will need to be adequately powered and to investigate the role of potential confounders such as age, circadian rhythm (ie, established pattern of winter depression and spring vernal equinox mania), concurrent use of mood stabilizers, and rapid cycling. Large samples with well-characterized response to treatment with specific antidepressants are needed to enable pharmacogenomic genome-wide association studies that will allow the identification of genetic variants involved in both the pharmacokinetics and pharmacodynamics of the medications and thus predict treatment response. The identification of pharmacogenomic predictors of treatment response is expected to aid in the development of pharmacogenomically based treatment algorithms that will enhance outcome and reduce the occurrence of ineffective or suboptimal treatment trials.

Given the "striking incongruity"[43] between the widespread use of antidepressants versus lack of evidence base for their therapeutic intervention, future pharmacogenomic studies will have very high potential clinical impact to best individualize treatment for the depressed phase of bipolar disorder. This could be for therapeutic benefit, particularly

for depressive predominant bipolar disease,[44] which has a significantly reduced pharmacopeia compared with acute mania. Pharmacogenomic testing may also allow future focus on primary (prevention of mania in at-risk depressed young adults with family history of bipolar disorder), secondary (established bipolar depression diagnosis with consideration of genomic testing ± concomitant mood stabilization prior to antidepressant treatment), and tertiary (minimize the oftentimes chaotic consequences in the aftermath of mania, providing better long-term care) prevention strategies to more optimally reduce the disease burden of bipolar disorder.

Drug names: carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), lithium (Lithobid and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others).

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