Published in final edited form as:
Bipolar Disord. 2012 February ; 14(1): 90–98. doi:10.1111/j.1399-5618.2012.00983.x.

Pollen-specific immunoglobulin E positivity is associated with worsening of depression scores in bipolar disorder patients during high pollen season

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Abstract

Objective—An association between allergic disease and depression has been consistently reported, but whether the key mediating ingredients are predominantly biological, psychological, or mere artifacts remains unknown. In the current study, we examine the hypothesized relationship between allergen-specific immunoglobulin E (IgE) status and changes in allergy symptoms with worsening in depression scores in depressed sensitized individuals.

Methods—In patients with recurrent mood disorders, we individually coupled sensitization to specific seasonal aeroallergens (as assessed by allergen-specific IgE) with temporal windows of exposure to aeroallergens (low versus high tree or ragweed pollen counts measured according to the National Allergy Bureau guidelines). We compared Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD) depression score changes in 41 patients with mood disorders [25 with major depression and 16 with bipolar I disorder, diagnosed by Structured Clinical Interview for DSM (SCID)] seropositive for tree or

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Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

ragweed pollen-specific IgE antibody versus 53 patients with mood disorders (30 with major depression and 23 with bipolar I disorder) seronegative for aeroallergen-specific IgE.

Results—Worsening in total depressive scores from low to high pollen exposure was greater in allergen-specific IgE positive patients as compared to allergen-specific IgE antibody negative patients ($p = 0.01$). When stratified by polarity, the association was significant only in patients with bipolar I disorder ($p = 0.004$). This relationship was resilient to adjustment for changes in allergy symptom scores.

Conclusion—To our knowledge, this is the first report of coupling a molecular marker of vulnerability (allergen-specific IgE) with a specific an environmental trigger (airborne allergens) leading to exacerbation of depression in patients with bipolar I disorder.

Keywords

allergen; allergen-specific IgE antibody; allergy; bipolar disorder; depression; ragweed pollen; tree pollen

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Epidemiological studies have previously shown an association between allergy and depression. For instance, in a series of articles, Timonen and colleagues (1–4) reported that the frequency of depression is greater in those with a history of allergic disease, particularly in women and in those with a family history of allergies in first degree relatives (5). Seasonal allergic rhinitis is among the most common allergic disorders (6, 7); with pollen being a common seasonal aeroallergen (8, 9). We have previously reported an association between seasonal changes in mood and self-reported sensitivity to high atmospheric pollen counts in college students (10). Marshall and colleagues (11) reported that sensitized individuals suffering from allergic rhinitis reported lower positive-affect scores during ragweed seasons.

Studying the association between allergies and recurrent mood disorders may be important for reasons beyond just the high prevalence of both conditions. Depression [whether it is major depressive disorder (MDD) or part of a bipolar I or II disorder] is an important risk factor for suicide (12–16). Allergen exposure, allergy, and suicide have been previously linked in large epidemiological studies (17, 18). More importantly, a marked tree pollen peak during spring and a lesser peak in weed pollen in the late summer and fall overlap with a highly consistent (across countries and continents) peak in suicide in spring and a somewhat less consistent and smaller peak in the fall (19, 20). In a study of 1,585 victims of suicide, Timonen and colleagues (18) reported that while the rate of completed suicide among non-atopic individuals was evenly distributed throughout the year, a considerable seasonality of suicide was present in atopic individuals. Consistent with this finding, we have reported a doubling of non-violent suicide rates in women during the peak tree pollen season (17, 21). Suicide is also related to prior history of allergy in interaction with a history of mood disorders (22). Moreover allergic, particularly upper respiratory allergic, disorders impair sleep (23), which is an important risk factor for instability in recurrent mood disorders and suicidal behavior (24).

The early phase of an allergic response is predominately mediated by Th2 cytokines, such as interleukin (IL)-4 and IL-6; however, a cascade of pro-inflammatory agents including Th1 immunoactive molecules (e.g., cytokines and chemokines) are also released (25). There is substantial evidence that some of these pro-inflammatory cytokines play a role in the pathophysiology of depression (26–30) and bipolar disorders (31–33).

MDD and bipolar depression are very similar in presentation, however, some differences exist (34, 35). For instance, atypical depression (36, 37) is more common in bipolar

disorders (38). As opposed to typical (melancholic) depression, atypical depression is characterized by reactive mood along with laden paralysis and increase in sleep, increase in appetite, weight gain rather than weight loss, and sensitivity to rejection (36). Atypical depression is common, starts early on in life, and it may result in higher disability (37) and higher risk of suicidal behavior (39).

In the current study we have hypothesized that in patients with recurrent mood disorders, a biological marker of allergic sensitization (i.e., allergen-specific IgE status) will be associated with exacerbation of depression scores during exposure to allergens, even when adjusted for changes in allergy symptoms. Additionally we hypothesized that change in depression scores from pre- and post-peak pollen intervals will positively correlate with changes in allergy symptom scores.

Methods

Patients

After approval by the Institutional Review Boards (IRB) of the University of Maryland School of Medicine and of the Sheppard Pratt Health Systems (Baltimore, MD, USA), 100 subjects ages 18 to 65 years old with a previous diagnosis of either MDD or bipolar I disorder, were recruited through radio and newspaper advertisements and from referral from local clinical and research sites in Washington, D.C. and Maryland. In summary: (i) patients were prescreened for inclusion and exclusion criteria via a phone interview, Structured Clinical Interview for DSM Disorders (SCID) (40) and Phadiatop™ (ImmunoCAP 250™, Phadia, Uppsala, Sweden) multi-allergen screen; (ii) allergen-specific IgE positive individuals were group-matched with the allergen-specific IgE negative group; (iii) real-time measurements of tree and ragweed pollen in the area were obtained; (iv) the patients were interviewed during the peak pollen window of taxa to which they were allergic, tree taxa in spring and ragweed in fall; (v) mood and allergy symptoms were evaluated by trained raters; (vi) blood samples were drawn at each interview and C-reactive protein (CRP) was measured to adjust for nonspecific inflammation; and (vii) collected data were analyzed for associations.

Screening

Subjects were prescreened by phone to exclude those with major medical illnesses such as cancer, HIV infection, lupus, rheumatoid arthritis; a prior history of psychotic disorders, winter-type seasonal affective disorders, drug and alcohol dependence; and women who were pregnant or were not using proper contraception methods and could potentially become pregnant. Those who passed the prescreen criteria were invited for an in-person interview during which time we used the SCID as a screening tool to confirm the inclusion diagnosis of MDD or bipolar I disorder, and to exclude patients with history of psychotic or cognitive disorders and substance abuse and dependence. At the time of the screening visit, 6 ml of blood was drawn and serum was analyzed for aeroallergen-specific IgE using the Phadiatop™ at the Johns Hopkins University Dermatology, Allergy, and Clinical Immunology (DACI) Reference Laboratory (Baltimore, Maryland, USA). The Phadiatop™ is a single, qualitative multi-allergen screen that detects IgE antibody in a panel of aeroallergen specificities that represent those primarily involved in inducing aeroallergen-related allergic disease in adults and children (41). Phadiatop™ results are reported as positive or negative with a positive result being > 0.35 kU_A/L of IgE antibody. Results of the test are highly predictive for individual IgE antibody measures obtained by a panel of separate skin tests or *in vitro* IgE antibody tests (41–45). The Phadiatop™ has a negative predictive value of 89.9% that exceeds individual total and allergen-specific IgE serological analyses. Its positive predictive value for atopic status (IgE antibody positivity) is reported

to be 72.6%. The diagnostic sensitivity of the test ranges from 75–95% and diagnostic specificity from 85–95%. These characteristics make the Phadiatop™ the single most desired test for assessing the state of atopy and ruling out IgE-mediated allergic disease in study subjects. In individuals with a low probability of atopic disease, this test minimizes the need for multiple *in-vivo* or *in-vitro* allergen-specific IgE measurements.

Allergen-specific IgE

Serum from each subject with a positive Phadiatop™ was re-analyzed by the ImmunoCAP-250 (Phadia, Uppsala, Sweden) to obtain a quantitative measure of IgE antibody levels specific for individual aeroallergens. IgE antibody levels were reported in kU_A/L to the following pollen allergen specificities: white ash (*Fraxinus americana*), American beech (*Fagus grandifolia/americana*), common silver birch (*Betula verrucosa*), elm (*Ulmus americana*), maple (*Acer saccharum*), poplar/cottonwood (*Populus deltoides*), sycamore (*Platanus occidentalis*), and oak (*Quercus alba*) trees, and common ragweed (*Ambrosia artemisiifolia/elatior*) pollen. Sensitization was defined as a specific IgE antibody level > $0.35kU_A/L$ (41).

Subjects were grouped based on their serological results; individuals who had a tree or ragweed pollen-specific IgE positive status were included in the *experimental* group. Those with a negative Phadiatop™ were matched by age and gender to the *experimental group* and included in the control group. To avoid confounding by non-seasonal allergy, especially to perennial home allergens, individuals who were positive by the Phadiatop™ multi-allergen screen but negative for tree or ragweed pollen-specific IgE antibodies were excluded.

At high and low pollen periods, blood samples were collected to measure CRP levels to permit later adjustment for nonspecific seasonal inflammation (e.g., including seasonal viral and bacterial upper respiratory infections, bacterial sinus infections, and dental inflammatory processes).

Pollen counting

Atmospheric sampling for pollen aeroallergens was performed using a volumetric rotating-arm impaction sampler (Model 40 Rotorod® Sampler, SDI Company, Plymouth Meeting, PA, USA) according to standards outlined by the National Allergy Bureau, American Academy of Allergy, Asthma and Immunology. At an elevation of 25 feet above ground level, the sampler is located on the roof of a two-story building at the United States Centralized Allergen Extract Laboratory, Walter Reed Army Medical Center in Silver Spring, Maryland. The suburban site location is well represented by area tree, weed, and grass species.

The Rotorod® sampler employs two polystyrene ‘I’ rods (1.52 mm wide × 32 mm long) that are coated with silicone grease adhesive and are placed in the fixed retracting head of the sampler. Rotation of each sampling period is performed at 2400 RPM. The Rotorod® sampling exposure time was set for a 10% sampling period (i.e., 60-second exposure time each 10-minute period). The total exposure time for a 24-hour period was 144 minutes. Sampling rods were removed at the end of a 24-hour collection period, mounted on a grooved stage adapter slide, and stained with Calberla’s solution (glycerol 16.0% vol/vol, ethyl alcohol 33.0% vol/vol, and basic fuchsin 0.02% vol/vol). The rods were then examined by a National Allergy Bureau, American Academy of Allergy, Asthma and Immunology certified counter using light microscopy and the various pollen grains were quantified at 400× magnification.

Daily atmospheric pollen concentrations were determined by dividing the *raw* pollen count, obtained microscopically from the collecting surfaces of the rods, by the volume of air

sampled over the 24-hour period. The daily pollen counts for tree, weed, and grass species were reported as the average number of pollen grains per cubic meter (grains/m^3) of air for each 24-hour sampling period.

We defined low pollen and peak pollen seasons based on a historical survey of pollen counts in the area (46, 47). Very sensitive people may become symptomatic when the pollen count for a particular taxon reaches 10 grains/m^3. Therefore, the time period when the tree or ragweed pollen counts were below these values was considered the low pollen season. The peak pollen season, which is when most or almost all who are sensitive to a particular taxon become symptomatic, was defined by counts greater than 90 grains/m^3 for trees and 50 grains/m^3 for ragweed. Individuals were invited for an in-person interview when the counts of pollens to which they were allergic were either low (low pollen season interview) or high (peak pollen season interview), but not in-between. For example, if a person was allergic to oak pollens, then the patient was invited for his/her low pollen season interview when the atmospheric oak pollen count was below an average pollen level that would trigger an allergic response (i.e., less than 10 grains/m^3). Such individuals were invited for the peak pollen interview when the pollen counting centers reported a peak in oak pollen (i.e., more than 90 grains/m^3). Since rain reduces the atmospheric pollen counts dramatically, if person allergic to oak pollen was scheduled to come for an interview during a rainy day, the interview was deferred to a day when the counting centers reported another peak in the oak pollen counts. If a patient was allergic to multiple tree taxa, then the patient was invited for the peak pollen interview during the pollination of the last taxon to pollinate. For instance, if a patient was allergic to pollen of maple, (first to pollinate), birch, and oak (last to pollinate), he/she was brought back for the high pollen evaluation during the oak high pollen interval. This meticulous procedure afforded us a quasi-experimental design. While the peak pollen period was determined by the concordance of allergen-specific IgE specificity and relevant pollen exposure, the low tree pollen rating was either before (for the majority of individuals) or after (for a minority) the peak pollen period rating. The order was convenience-based (i.e., non-random).

Mood and allergy severity assessments

The Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD) (48) was used to assess for symptoms of depression during each evaluation (low pollen and peak pollen seasons). A self-rated questionnaire, the Allergy Symptom Severity Assessment (ASSA) (49) was used to assess the severity of allergic symptoms. Both the SIGH-SAD raters and subjects were masked to the allergen-specific IgE positivity status. To rule out the presence of hypomanic-manic symptoms or medication changes, patients were both clinically evaluated and the Hypomania Interview Guide–Seasonal Affective Disorder version (HIGH-SAD) (50) scale was used approximately a week prior to high/low pollen season visits. The patients were informed about their specific allergy status only at the end of the study.

Statistical analyses

To determine outliers and identify extreme skewness, initial descriptive analyses were used. The change (delta) in variables for depression, anxiety, and allergy symptoms severity were computed as the difference between the scores (from the scales used) at the time of the peak pollen interval visit versus the low pollen period visit. For continuous variables, mean and standard deviation were calculated, while for categorical data (e.g., pollen-specific IgE positivity) proportions were computed. Means were compared using the *t*-test, while proportions were compared with the Pearson chi-square test.

Multivariate regression models were developed to examine potential association between high versus low pollen season changes in SIGH-SAD scores as a dependent variable and allergen-specific IgE status as main independent variable. The model also included the change in ASSA scores in order to adjust for psychological reaction to the effects of allergy symptoms on mood. To adjust for nonspecific inflammatory processes (e.g., variable degree of acute or residual inflammation due to upper respiratory infections that are known to cluster at the end of winter and the beginning of spring), CRP was used as an independent variable as well. Other variables that were included in final models for adjustment were gender, order of visit, and being on antidepressants. The data were analyzed for the entire sample and then stratified by diagnoses (MDD versus bipolar disorders) and re-analyzed. The same statistical models were used to analyze the association between changes in HIGH-SAD score in bipolar I disorder, and allergen-specific IgE status and ASSA.

Results

A total of 94 out of 100 individuals met the full criteria for inclusion in the study. Table 1 presents the characteristics of the 94 individuals who were included in the analysis. There were 41 individuals with an allergen-specific IgE status and 53 subjects who were IgE antibody negative [of the 55 individuals with unipolar depression, 25 (45.5%) were IgE positive, while 16 (41.0%) of the 39 individuals with bipolar depression were IgE positive]. Forty percent of the participants were male. Despite efforts to match the groups by gender, age, and allergen-specific IgE status, the seropositive group was younger than the seronegative group (39.9 years SD = 9.7 and 46.8 years SD = 9.9, respectively; $p = 0.001$), and significant differences were present in the medications that patients were taking. There were no other differences in other characteristics of individuals with a positive versus negative allergen-specific IgE status (Table 1). The means of ASSA scores, while not significantly different at low pollen intervals, were significantly higher in the allergen-specific IgE positive group compared to the seronegative group during peak pollen season (6.5 SD = 4.15 and 4.6 SD = 3.2, respectively; $p = 0.03$).

Primary outcome

In the final multiple regression models for the primary hypotheses of the study, we evaluated the effect of allergen-specific IgE status to tree or ragweed pollens and changes in the ASSA scores as independent variables on changes in SIGH-SAD (as the dependant variable) corrected for change in CRP, age, order of visit, and taking antidepressants. The results of the multiple regression analysis, using the entire sample, confirmed the hypothesis of change in total SIGH-SAD scores from low to high pollen periods being significantly higher in allergen-specific IgE status group ($p = 0.01$) and significantly correlated with worsening in allergy severity symptoms ($p = 0.02$).

Typical and atypical SIGH-SAD scores

Changes in *typical* SIGH-SAD scores from low pollen season to high pollen season were significantly associated with a worsening in the subject's ASSA score ($p = 0.004$) but only marginally for pollen-specific IgE status ($p = 0.065$) However, changes in *atypical* SIGH-SAD scores were significantly associated with allergen-specific IgE status ($p = 0.01$) but not changes in the ASSA scores ($p = 0.43$).

Stratification by depression polarity

In patients with MDD, no statistical significance was observed in either total SIGH-SAD scores (Table 2, column 1), typical SIGH-SAD scores (Table 2, column 2), or atypical SIGH-SAD scores (Table 2, column 3) from low to high pollen season in allergen-specific IgE status and IgE negative groups. In patients with a diagnosis of bipolar I disorder,

however, changes in total SIGH-SAD scores (Table 3, column 1) from low to high pollen seasons were significantly associated with allergen-specific IgE status ($p = 0.03$) and changes in allergy severity symptoms ($p = 0.003$). In bipolar disorder patients, changes in *typical* SIGH-SAD scores (Table 3, column 2) were only significant for changes in ASSA scores ($p = 0.004$) while changes in *atypical* SIGH-SAD scores (Table 3, column 3) from low to high pollen seasons were significantly correlated to both IgE status ($p = 0.004$) and changes in ASSA scores ($p = 0.02$).

Changes in HIGH-SAD scores were not significantly correlated with allergen-specific IgE status and changes in ASSA scores ($p = 0.42$) in the entire sample or in bipolar patients alone ($p = 0.16$).

CRP—Changes in CRP values were negatively associated with changes in depression scores in patients with unipolar depression [significant association with change in total ($p = 0.01$) and atypical ($p = 0.02$) scores, and a trend in typical scores ($p = 0.07$); Table 2] and bipolar I disorder patients (significant for atypical $p = 0.02$, and trend for the total depression scores $p = 0.08$)

Discussion

To our knowledge, this is the first study to examine the relationship between allergen-specific IgE positivity (allergic sensitization) and a worsening of depression scores during peak pollen periods in patients with recurrent mood disorders. Two primary hypotheses of the study were confirmed. First, allergen-specific IgE status was associated with a greater increase in depressive scores during exposure to aeroallergens ($p = 0.01$). Second, the exacerbation of allergic symptoms correlated significantly with a worsening in the depression scores ($p = 0.02$).

When stratified by diagnoses, the difference was seen only in bipolar depression. Although neuroimmune system dysregulation has previously been suggested to play a role in bipolar disorder (24, 31, 32), to our knowledge, this is the first study to link allergens, allergy, and bipolar depression.

Our current results are consistent with our previous studies reporting behavioral and neuroimmune changes in laboratory animals sensitized and exposed to aeroallergens (51, 52). Of particular importance, increased gene expression for Th2 cytokines overexpressed in sensitized and exposed rodents (53) was also found overexpressed in victims of suicide as compared with individuals who died of other causes (54).

Since symptoms of allergies, especially upper respiratory allergies, impair quality of life (7, 55, 56), psychological distress associated with allergic exacerbation may appear to be the logical link between worsening in mood and exposure to allergens. However, in our study, after adjustment for allergy symptom severity (measure of physical discomfort), the changes in depression scores remained significant. The findings of our current study suggest that worsening of depression in sensitized individuals during peak pollen seasons is not related only to severity of physical symptoms in allergic reaction, thus unlikely to be a mere reaction to a physical illness or methodological artifact (57). CRP values were included in the multivariable model as an overall surrogate of inflammation. The significant negative relationship between changes in CRP and changes in certain depression scores between high pollen and low pollen conditions is unprecedented, unexpected, and for a better understanding would require replication in larger samples with measurement of inflammatory mediators and markers of physical health.

Exacerbation in bipolar disorder has also been linked to photoperiodic changes (58); therefore, it could be theoretically possible that changes in mood ratings from low to high pollen season can be accounted for by the difference in photoperiod and result in a spurious relationship between allergy and depression. However, our results being robust to adjustment to order of visit (with implicit differences in photoperiod) reduced the possibility of the observed association being secondary to change in daylength.

Limitations of our study include non-random order of high versus low pollen visit and lack of information on meteorological condition of the days patients were evaluated (however, patients were not interviewed during rainy days when pollen counts would be low). A major limitation is not evaluating health behaviors of the participants. Although our data suggest a biological, probably immunological, relationship between allergen exposure, allergy, and depression, we did not measure cytokines locally or systemically. The levels of total IgE were not measured, and would have been potentially interesting to evaluate relationships between total IgE and medications, and depression scores. Finally, we excluded those patients who had suicidal ideations, were psychotic, or were using illicit drugs, potentially reducing generalizability of our results.

Our study had considerable strengths which included substantiation of diagnoses by standardized tools (SCID); measurement of symptoms by rater with semistructured scales previously used in seasonal depression (SIGH-SAD, HIGH-SAD); determination of allergen-specific IgE status by state-of-the-art laboratory evaluation; and finally, careful coupling between sensitivity and exposure.

In conclusion, as hypothesized, from low to high pollen exposure, worsening of depression scores was positively associated with allergic sensitization even after adjustment for changes in allergy symptoms. These results, if replicated in larger and better designed studies, suggest a potential for developing personalized interventions to prevent a specific (i.e., allergen-induced) form of environmentally driven exacerbation of mood disorders, in particular in patients with bipolar disorder. Future studies should focus on patients with bipolar I disorder in larger numbers, randomize the order of visit and mood ratings, and measure potential molecular mediators in plasma as well as nasal secretions.

Acknowledgments

This study was supported by grant R21 MH075891-01A1 from the National Institute of Mental Health (TTP: Principal Investigator) and by research funds from the Johns Hopkins University Dermatology, Allergy, and Clinical Immunology (DACI) Reference Laboratory (RGH: Principal Investigator). The execution of this study was also supported by the University of Maryland General Clinical Research Center Grant M01 RR 16500, General Clinical Research Centers Program, National Center for Research Resources (NCRR), NIH. TTP was additionally supported by R01MH074891, a grant from the American Foundation for Suicide Prevention, and a NARSAD Independent Investigator Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.

The authors thank Drs. Hirsh Komarow and Alkis Togias for their conceptual support for the study. The authors also thank Jessica McDonald, Evan R. Sander, Bernadine Postolache, Belzora Joppy, and Nancy Furst for their help with recruitment.

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Table 1

Characteristics of the experimental (tree or ragweed pollen antigen-specific IgE positive status) and control (IgE negative status) groups are presented

Characteristic	All patients (n = 94)	IgE positive (n = 41)	IgE negative (n = 53)	p-value
Age, years, mean (SD)	43.8 (10.4)	39.9 (9.7)	46.8 (9.9)	0.001
Gender, male, n (%)	40 (42.6)	19 (46.3)	21 (39.6)	0.52
Race, n (%)				0.62
Caucasian	30 (31.9)	14 (34.2)	16 (30.2)	
African American	61 (64.9)	25 (61.0)	36 (67.9)	
Other	3 (3.2)	2 (4.9)	1 (1.9)	
Diagnosis, n (%)				0.21
Major depression	55 (58.5)	25 (45.5)	30 (54.5)	
Bipolar I disorder	39 (41.5)	16 (41.0)	23 (59.0)	
Order of visit, n (%)				0.045
First visit during low pollen season	81 (86.2)	32 (34.0)	49 (52.1)	
First visit during high pollen season	13 (13.8)	9 (9.6)	4 (4.3)	
Medications, n (%)				
Mood stabilizers	33 (35.0)	12 (29.3)	21 (39.6)	0.3
Antidepressants	72 (76.6)	27 (65.9)	45 (84.9)	0.03
Antipsychotic medications	23 (24.5)	8 (19.5)	15 (28.3)	0.33
Anxiolytic medications	20 (21.3)	8 (19.5)	12 (22.6)	0.71
Hypnotic medications	26 (27.7)	7 (17.1)	19 (35.9)	0.044
Antihistamines	10 (10.6)	5 (12.2)	5 (9.4)	0.67
Thyroid hormone	14 (14.9)	3 (7.3)	11 (20.8)	0.07
Stimulants	7 (7.5)	0 (0)	7 (13.2)	0.016
Opioid (pain control)	4 (4.3)	2 (4.9)	2 (3.8)	0.8
Others	46 (49.0)	17 (41.5)	29 (54.7)	0.2

Table 2

Multivariable regression models in patients with unipolar recurrent major depression with SIGH-SAD (total, typical, and atypical) changes as dependant variable, and as independent variables: allergen-specific IgE, allergy severity symptoms, and CRP, adjusted for gender, order of visit, and antidepressant treatment.

	Δ SIGH-SAD total			Δ SIGH-SAD typical			Δ SIGH-SAD atypical		
Variable	**Coefficient**	**SE**	**p-value**	**Coefficient**	**SE**	**p-value**	**Coefficient**	**SE**	**p-value**
Δ CRP	−0.14	0.05	0.01	−0.07	0.04	0.07	−0.07	0.03	0.02
IgE positive	4.75	3.80	0.22	3.08	2.77	0.28	1.67	1.91	0.39
Δ Allergy symptoms	0.38	0.44	0.40	−0.08	0.32	0.80	−0.29	0.22	0.20

SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version; SE = standard error.

Table 3

Multivariable regression models in patients with bipolar I disorder with SIGH-SAD (total, typical, and atypical) change as dependant variable, and as independent variables: allergen-specific IgE, allergy severity symptoms, and CRP, adjusted for gender, order of visit and antidepressant treatment.

	Δ SIGH-SAD total			Δ SIGH-SAD typical			Δ SIGH-SAD atypical		
Variable	**Coefficient**	**SE**	**p-value**	**Coefficient**	**SE**	**p-value**	**Coefficient**	**SE**	**p-value**
Δ CRP	−0.33	0.18	0.08	−0.50	0.13	0.26	−0.90	0.08	0.02
IgE positive	11.95	5.21	0.03	4.70	3.63	0.21	7.25	2.21	0.004
Δ Allergy symptoms	1.80	0.54	0.003	1.21	0.38	0.004	0.58	0.23	0.02

SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version; SE = standard error.