Suicide and Prescription Rates of Intranasal Corticosteroids and Nonsedating Antihistamines for Allergic Rhinitis: An Ecological Study

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ABSTRACT

Objective: To estimate the relationship between antiallergy drug prescription rates and suicide across the United States and over time. The relationship between allergy, allergens, and suicidal behavior and suggestions of a possible immune mediation led us to hypothesize that intranasal corticosteroids, known to reduce local airway production of T-helper cell type 2 cytokines, may be associated with reduced risk of suicide relative to antihistamines, which only secondarily affect cytokine production.

Method: The authors evaluated the relationship of suicide rates at the county level in the United States (N = 120,076 suicides) with prescriptions for intranasal corticosteroids and nonsedating antihistamines, in interaction with antidepressant prescriptions and other socioeconomic variables, for the period from 1999 to 2002. Suicide rate data were derived from state vital record systems based on local death certificate registries, and county-level allergy and antidepressant prescription data were obtained from IMS Health Incorporated (Plymouth Meeting, Pennsylvania).

Results: The prescription volume of intranasal corticosteroids was associated with a lower suicide risk ($P = .0004$), while that of antihistamines was associated with a modestly greater suicide risk ($P = .0001$). Adjustment for antidepressant prescriptions did not affect these relationships.

Conclusions: This is the first study, to our knowledge, to find a possible association between *completed* suicide and medications for allergic rhinitis and also the first report of an association of intranasal corticosteroid use with a lower suicide rate. This association should be considered preliminary and deserving of further investigation.

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Suicide is a prevalent public health problem, with almost a million people dying annually.[1] It is the tenth leading cause of death worldwide[2] and the eleventh in the United States.[3] In victims of suicide, postmortem, an increased gene expression of T-helper cell type 2 (Th2) (ie, allergy mediating) cytokines has been reported in the orbitofrontal cortex,[4] a region of the prefrontal cortex that modulates emotion, behavior, and suicidal behavior.[5] This is consistent with recent findings linking allergy with suicide[6] and with previous reports linking atopy with seasonality of suicide,[7] allergen exposure with suicide,[8] and allergy with major depression[9]—the most common psychiatric condition associated with suicide. Moreover, intranasal allergic sensitization and exposure in rodents results in anxiety,[10] aggressive behaviors,[11] and impaired social interactions,[10] as well as an increase in Th2 cytokine gene expression in the brain.[10,11]

Thus, we hypothesized that the treatment of allergic rhinitis, a common manifestation of allergy that affects an estimated 20 to 40 million people in the United States,[12] may modulate or mediate, at least in part, the relationship between allergic rhinitis and suicide. As a first step before future studies, we now estimate ecologically a possible association between suicide and common medications for allergic rhinitis.

METHOD

This is an ecological study of suicide and drug prescription trends at the county level in the United States from 1999 to 2002. In order to analyze associations between use of allergy medications and county-level mortality data, we adopted a methodology that was originally developed by 2 of our coauthors (R.D.G. and J.J.M.)[13] to analyze associations between use of antidepressant medications and suicide rates. We adjusted for the possible effect of antidepressants on the association of suicide and allergy medications, as well as a number of socioeconomic variables.

Data Source

Monthly suicide rate data were derived from state vital record systems based on local death certificate registries for the years 1999 to 2002 for each US county. Suicide is coded as *U03, X60–X84, or Y87.0, based on the *International Classification of Diseases, Tenth Revision* (1992). Suicide rates were subdivided by year (1999–2002), age group (1 = 0–14 years, 2 = 15–24 years, 3 = 25–44 years, 4 = 45–64 years, 5 = 65+ years), sex (1 = male, 2 = female), and race (1 = black, 2 = nonblack) for 3,087 counties. Each county therefore has $4 \times 5 \times 2 \times 2 = 80$ unique suicide rates. The total number of suicides was 120,076. County-level allergy and antidepressant prescription data were obtained from IMS Health Incorporated, Plymouth Meeting, Pennsylvania (source: IMS Xponent, January 1999–December 2002). This database uses the collected data from about 70% of all prescriptions filled in community pharmacies to project nationally representative data and is used by the US Food and Drug Administration (FDA) and other government agencies. Because sedating antihistamines tend to be used for other indications than allergy (insomnia, for instance) and because we wanted to have equipoise for antihistamines relative to intranasal corticosteroids (prescription medications), we limited ourselves to data on prescribed nonsedating

antihistamines before they became over-the-counter medications. For each county, the number of prescriptions from 1999 to 2002 was obtained for antihistamines alone, antihistamines/decongestants, intranasal corticosteroids, and antidepressants.

Statistical Analysis

Study measures included (1) mean daily dose of intranasal corticosteroid and antihistamine medications along with antidepressant prescriptions per capita by county and (2) number of individuals in zip code area taking antihistamines alone, intranasal corticosteroids alone, or both medications concurrently. We obtained the Federal Information Processing Standard county codes, which are 5-digit codes assigned to each county in the United States, to handle the information, and we calculated medication usage rate per 100,000. To relate the use of allergy medications and antidepressants to suicide rate, we estimated a mixed-effects Poisson regression model, adjusting for county-specific case-mix. The mixed-effects Poisson regression model is suitable for rare-event data, as the observed number of suicides in a given county may be very small, while the population size may be quite large and vary from county to county. The model estimated overall suicide rate, and we estimated covariate-adjusted county-specific estimates of suicide rates. The model for estimation developed by 2 coauthors (R.D.G. and J.J.M.) was described in detail elsewhere.[13] The covariates adjusted for were age group, sex, and race at the subject level and rural/urban indicator (1 = metropolitan, 2 = non-metropolitan), number of psychiatrists, and logarithm of median household income at the county level. In terms of the use of allergy medications and antidepressants, we used the logarithm of number of prescriptions per person per year to account for differential population size of counties and skewness of the distribution. To decompose the overall relationship between suicide rate and drug use into between-county and within-county components, we specified the model using the county's mean drug use and yearly deviation from the mean for each class of drug use.

$$\lambda = \mathrm{Exp}[\Sigma_k \{\beta_k (\log D_k - X_k^m) + m_k X_k^m\} + \beta_0 + F_0]$$

where

λ = suicide rate,
D_k = number of prescriptions per person per year for drug class k,
$X_k = \log D_k$,
X_k^m = mean drug use for 1999–2002 for X_k,
$F_0 = \alpha_0$ (age group) + α_1 (sex) + α_2 (race) + α_3 (rural vs urban) + α_4 (number of psychiatrists) + α_5 (log income)

In the above equation, β_k is the estimate of the within-county drug effect on suicide rate, and m_k is the estimate of the between-county effect. The primary effect of interest is the within-county effect (adjusted for between-county differences), since the between-county effects may be produced by unmeasured confounders that complicate their interpretation.

In these data, the mean county prescription rates for the different drug classes are highly correlated. To avoid this multicollinearity, the mean for the 3 classes of allergy medications and the mean for the 4 classes of antidepressant drugs were used in place of the means for the individual drug classes. These within-county drug class deviations were then treated as random effects in the model, adjusted for the overall county mean–level drug class effects. As sensitivity analyses, we estimated the model separately for each allergy medication class and jointly for the 3 allergy medication classes and then compared these results to the full model that included joint estimation of all allergy and antidepressant medication classes.

Clinical Points

- Psychiatrists, allergists, and generalists should be mindful that allergy and suicide may be interconnected through pathophysiologic as well as iatrogenic effects.
- Clinicians should inquire about history of allergy and sensitization to allergens in patients at risk for suicide, and internists should inquire about history of depression, past suicide attempts, and individual behavioral reactions to allergy medication.
- This report is ecological, and thus its results should lead to future studies rather than be misunderstood as solid evidence for individual treatment decisions.

Table 1. Association Between Within-County Changes in Allergic Rhinitis Medications and Suicide Rates[a]

	Coefficient Estimate (*P* value)		
Drug Class	Model 1[b]	Model 2[c]	Model 3[d]
Antihistamines alone	0.085 (.0001)	0.128 (.0001)	0.138 (.0001)
Antihistamines/decongestants[e]	0.036 (.1137)	0.023 (.4301)	0.010 (.7509)
Intranasal corticosteroids	−0.024 (.3684)	−0.146 (.0001)	−0.137 (.0004)

[a]Data obtained in part from IMS Health Incorporated, Plymouth Meeting, Pennsylvania (source: IMS Xponent, January 1999–December 2002).
[b]Individual medication classes.
[c]Joint estimation of all 3 allergy medication classes.
[d]Joint estimation of all allergy and antidepressant medication classes.
[e]Joint use of antihistamines and decongestants.

RESULTS

Within-county changes in antihistamine prescription volume were positively associated with suicide rates (estimated coefficient = 0.138, $P = .0001$), whereas intranasal corticosteroid prescription rates were inversely associated with suicide rates (estimated coefficient = −0.137, $P = .0004$). No significant effect of joint use of antihistamines and decongestants was found (estimated coefficient = 0.010, $P = .7509$).

Table 1 presents the estimated coefficient and corresponding probability value for each of the 3 allergy medication classes for the 3 models (model 1, individual medication classes; model 2, joint estimation of all 3 allergy

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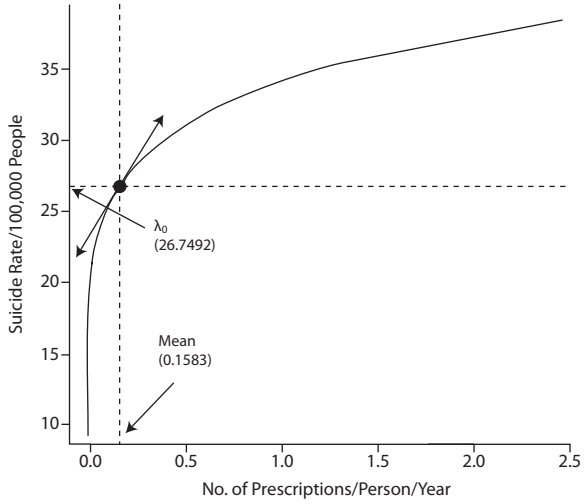
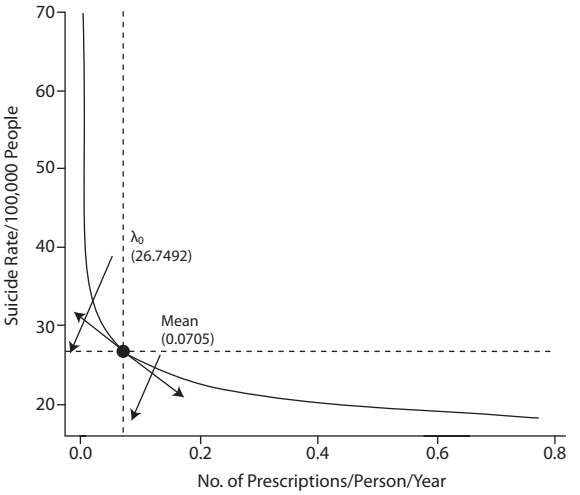
Figure 1. Nonsedating Antihistamines: Relationship of Prescription Volume to Suicide Rates (within-county)[a,b]



[a]Data obtained in part from IMS Health Incorporated, Plymouth Meeting, Pennsylvania (source: IMS Xponent, January 1999–December 2002).

[b]λ_0 Represents the national average estimated suicide rate/100,000 for a 25- to 44-year-old nonblack male living in a metropolitan area with national average levels of access to a psychiatrist, income, and medication use. *Mean* refers to the average county level of prescriptions/person/year. The tangent line in both directions at mean = 0.1583 and $\lambda 0 = 26.7492$ to the curve denotes the rate of change in suicide rate as a function of within-county change in prescription rate of nonsedating antihistamines.

Figure 2. Intranasal Corticosteroids: Relationship of Prescription Volume to Suicide Rates (within-county)[a,b]



[a]Data obtained in part from IMS Health Incorporated, Plymouth Meeting, Pennsylvania (source: IMS Xponent, January 1999–December 2002).

[b]λ_0 Represents the national average estimated suicide rate/100,000 for a 25- to 44-year-old nonblack male living in a metropolitan area with national average levels of access to a psychiatrist, income, and medication use. *Mean* refers to the average county level of prescriptions/person/year. The tangent line in both directions at mean = 0.1705 and $\lambda 0 = 26.7492$ to the curve denotes the rate of change in suicide rate as a function of within-county change in prescription rate of nonsedating intranasal corticosteroids.

medication classes; model 3, joint estimation of all allergy and antidepressant medication classes).

The results were generally consistent across the 3 model specifications, and we base our final inferences on model 3, which contains joint estimation of all allergy medication classes adjusted for antidepressant prescriptions. Adjusting for antidepressants did not change the results.

Results of this analysis are displayed graphically in Figures 1 and 2. The graphs display the change in suicide rate as a function of change in the number of prescriptions per person per year in a given county. To produce these estimated curves, we anchored covariates in the model to the following values: age group = 25–44 years, sex = male, race = nonblack, and rural/urban index = metropolitan and the national averages for the number of psychiatrists and log income level. For these values of covariates, a county with national average use for each medication has an estimated suicide rate of $\lambda_0 = 26.7492/100{,}000$. The suicide rate differs depending on the values of covariates as well as prescription rates. As an example, if the age group is changed to 65 years and older, and the analysis is restricted to females, the background suicide rate decreases to $\lambda_0 = 7.3113/100{,}000$. Figures 1 and 2 show that as antihistamine prescription rates increase so do suicide rates, but as intranasal corticosteroid prescription rates increase, suicide rates decrease.

Table 2 presents the within-county effects on suicide rate evaluated at age group = 25–44 years, sex = male, race = nonblack, and rural/urban index = metropolitan and the national averages for the number of psychiatrists and log income level for each drug class based on the estimated model. The suicide rates are adjusted for the effects of age, but prescriptions are for the county as a whole. The first row of the first medication group in Table 2, "antihistamines alone," can be read as follows: If drug consumption of antihistamines alone rises from the current mean level of 0.158 prescriptions/person/year by 1%, which equals 1.583×10^{-3} prescriptions/person/year, then the suicide rate would increase by 0.134%, or approximately 0.04 suicides per 100,000 people (95% CI, 0.025 to 0.047). Similarly, for the first row of the last medication, intranasal corticosteroids, in the table, if drug consumption of inhaled steroids rises by 1%, which equals 7.05×10^{-4} prescriptions/person/year, then the suicide rate is estimated to decrease by 0.16%, or approximately 0.04 suicides per 100,000 people (95% CI, –0.06 to –0.026).

DISCUSSION

Our findings from this analysis are consistent with the hypothesis that treatment with intranasal corticosteroids may be associated with a lower risk of suicide. In our analysis, we focused on within-county effects over time, which, unlike between-county effects, are less likely to be attributed to nonspecific factors such as the accessibility to quality health care or physician training because these change quite slowly over time and should be relatively constant within counties during the short time window that we have investigated. Recently, the FDA raised concerns about an

Table 2. Within-County Effects of Allergic Rhinitis Medications on Suicide Rate[a,b]

Drug	Point of Evaluation	Percent Change in No. of Prescriptions (change in no. of prescriptions/person/y)	Resulting Percent Change in No. of Suicides (change in no. of suicides/100,000 people)	Confidence Interval
Antihistamines alone	$\lambda_0 = 26.7492/100{,}000$	1% (1.583×10^{-3})	0.1342% (0.0359)	0.0254 to 0.0465
		10% (1.583×10^{-2})	1.342% (0.3590)	0.2535 to 0.4646
		100% (1.583×10^{-1})	13.42% (3.5897)	2.5348 to 4.6463
Antihistamines/ decongestants	$\lambda_0 = 26.7492/100{,}000$	1% (5.22×10^{-4})	0.0246% (0.0066)	−0.0073 to 0.0204
		10% (5.22×10^{-3})	0.246% (0.0658)	−0.0728 to 0.204
		100% (5.22×10^{-2})	2.46% (0.6580)	−0.7276 to 2.041
Intranasal corticosteroids	$\lambda_0 = 26.7492/100{,}000$	1% (7.05×10^{-4})	−0.1602% (−0.0429)	−0.0597 to −0.0260
		10% (7.05×10^{-3})	−1.602% (−0.4285)	−0.5973 to −0.2560
		100% (7.05×10^{-2})	−16.02% (−4.2852)	−5.9730 to −2.5992

[a]Data obtained in part from IMS Health Incorporated, Plymouth Meeting, Pennsylvania (source: IMS Xponent, January 1999–December 2002).
[b]In the first row of data, for example, if drug consumption of inhaled steroids rises by 1%, which equals 1.583×10^{-3} prescriptions/person/year, then the suicide rate is estimated to increase by 0.13%, or approximately 0.04 suicides per 100,000 people (95% CI, 0.025–0.047).

association of montelukast, approved for the treatment of allergic rhinitis, with suicidal behavior, although this relationship is controversial.[14] However, to our knowledge, no investigation of the relationship of suicide to more common medications for allergic rhinitis, such as intranasal corticosteroids and antihistamines, has taken place to date. These medications are considered standard of care in the treatment of allergic rhinitis according to current standards of care.[15,16]

Inflammatory mediators released during allergic reaction in the nasal cavity are capable of bypassing the blood-brain barrier and reaching brain regions involved in behavioral modulation via axonal, periaxonal, vascular, and perivascular connections.[17] We thus postulate that certain molecular signals of inflammation produced during allergic reactions, including Th2 and Th1 cytokines, may affect functioning in specific areas of the brain such as the orbitofrontal cortex, induce or exacerbate affective dysregulation, and impair behavioral restraint, leading to suicidal behavior. An alternative hypothesis is that nonspecific psychological effects of sickness would act as triggers for suicidal behavior. If indeed cytokines produced as the result of allergic inflammation in nasal mucosa reach and affect the behavioral modulating role of the orbitofrontal cortex, medications that decrease production of cytokines (ie, intranasal corticosteroids)[16,18] may be associated with a decreased suicide rate.

Given the well-known potential role of systemic corticosteroids in aggravating mental illness,[19] the yet unknown possible protective effect of intranasal corticosteroids warrants discussion. Intranasal corticosteroids are applied directly to nasal mucosa and are designed to achieve localized effects with minimal systemic effects, and it is generally assumed that intranasal corticosteroid treatment in recommended doses does not significantly suppress hypothalamic-pituitary-adrenal axis function.[20,21] In contrast, however, some systemic adverse effects of topical intranasal steroids have nevertheless been reported.[22] Recent data collected by the International Pharmacovigilance Program suggested that intranasal corticosteroids may produce various neuropsychiatric disturbances such as nervousness, anxiety, agitation, insomnia, emotional lability, depression, somnolence, confusion, convulsion, and migraine, thus pointing toward a possible central nervous system effect.[23,24]

Intranasal corticosteroids reduce intranasal production of cytokines,[16] while antihistamines do so only secondarily.[25,26] Intranasal corticosteroids are thought to reverse the exaggerated Th2-related cytokine response that is related to the pathophysiology of allergic rhinitis.[27,28] Our hypothesis connecting allergic rhinitis with suicidal behavior is based on the model of allergy-related cytokines affecting brain regions previously implicated by the histopathology[29] and the functional neuroimaging[30] of suicidal behavior. In animal models, we have reported an increased expression of Th1 cytokines in response to intranasal lipopolysaccharides[31] and Th2 cytokines in response to intranasal allergens.[10] Of relevance for modeling suicide risk factors, these experimental molecular changes have been paralleled by depressive-like behaviors[31] and anxiety-like behaviors,[10] as well as social interaction impairments.[10]

In allergic rhinitis, although the initial events are Th2 mediated, the Th1 cytokine activation also plays a significant role, especially in more sustained and chronic allergic inflammation.[32] It is important to mention that, while the rates of symptomatic improvement of allergic rhinitis with intranasal corticosteroids and antihistamines are similar, the molecular and cellular effects of the two medication types are different.[33,34] In addition, intranasal corticosteroids may have a more potent effect on mitigating sleep disruption induced by allergic rhinitis.[35,36] It is well known that Th2 cytokines may have a potential to impair sleep,[37] and sleep impairment has been reported to be a possible suicide risk factor.[38,39] In considering possible explanations for the positive association of antihistamine prescription volume with suicide rates, it is important to note that we evaluated nonsedating antihistamines requiring a prescription. Such newer generation antihistamines, in contrast with the older sedating antihistamines, rarely cause nonspecific cognitive deficits[40] that could potentially disinhibit behaviors in vulnerable individuals. There is a possibility that antihistamines are in fact pharmacologically neutral in terms of suicide risk, with their prescription serving as just a "marker" of diagnosed allergy. Recently, allergy was reported to be associated

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with a higher rate of completed suicide, in particular in the absence of history of diagnosed mood disorder,[6] and seasonal allergy was found to be associated with suicidal ideation.[41]

Decongestants are effective in ameliorating nasal congestion from allergic rhinitis; however, they can cause psychiatric disturbances related to their stimulating effect, such as elevated arousal level, impaired sleep, loss of appetite, and excessive nervousness.[42,43] We hypothesized an increase in suicide rates with the joint use of decongestants, considering their potential arousal effects, but our results did not support that hypothesis.

Contrary to our expectations, the relationship between suicide rates and allergy medications was not modified significantly by use of antidepressants. It has been reported that SSRI prescription volumes correlated negatively with suicide rates and tricyclic antidepressant prescription volumes correlated positively.[12] When we analyzed differentially the interaction with allergy medication of volumes of tricyclic versus SSRI antidepressants in this study, we did not find statistically significant interactions with allergy medications.

Limitations of the study include the following: (1) General limitations of ecological models. Ecological models are based on the information measured at the aggregate level and thus provide information on groups of individuals in a geographically determined area. Incorrect inferences can be made about individual-level associations. (2) We cannot exclude the potential bias from confounding by indication—ie, the possibility of attributing to the medication effects that might be associated to the condition being treated. (3) Prescriptions for admitted patients and over-the-counter volume of antihistamines are not covered by this analysis. However, as there are very limited number of patients admitted to the hospital due to allergic rhinitis, our estimates may still hold true. Moreover, we purposefully analyzed data for years in which the nonsedating antihistamines required a prescription, as did the intranasal corticosteroids. However, we should acknowledge that the overall indications for intranasal corticosteroids and newer generation antihistamines are not fully overlapping, because second-generation antihistamines are used to treat other atopic diseases like atopic dermatitis, urticaria, mastocytosis, and asthma, while intranasal corticosteroids are exclusive to nasal symptoms. Thus, it is possible that conditions such as chronic urticaria known to have a strong impact on quality of life[44] might elevate suicide risk preferentially with newer generation antihistamine prescription volume rather than intranasal corticosteroids. (4) We had no information about actual use as opposed to filling a prescription. (5) No information regarding rates of allergy and mental illness was available.

The strength of this study is its coverage of the entire population of the continental United States as well as a biologically based, hypothesis-driven approach to pharmacoepidemiology. Considering that allergy is a very prevalent condition and allergy medications are used in relatively high volume, and that suicide has major public health relevance with a relatively stagnating arsenal of interventions, our study may have a major clinical impact if future studies confirm its findings. The recently published FDA communication[14] about the safety of montelukast addressed possible behavior/mood changes, suicidality, and suicide. An analysis of the relationship of suicidal behavior and ideation to the use of new-generation nonsedating antihistamines, similar to analyses that were conducted for clinical trials of antiepileptic drugs, would be of importance.

An inverse association between intranasal corticosteroid prescription volume and suicide is consistent with previously reported associations of markers of inflammation with suicide attempts[45,46] and completion.[47] The public health implications of suicide, the high prevalence of allergies, and the potential for preventive interventions highlight the need for more systematic studies of the relationship of allergies and their pharmacologic treatments to the risk for suicide and nonfatal suicide attempts.

Drug name: montelukast (Singulair).

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