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Association between asthma medications and suicidal ideation in adult asthmatics

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Summary

Background: Asthma has been associated with suicidal ideation (SI), though the mechanisms remain poorly understood. Some asthma medications (e.g., theophylline and beta-2 adrenergic agonists) have been shown to provoke feelings of anxiety, fear, and irritability, but their link to SI among asthmatics has not been examined, which was the purpose of the present study.

Methods: 664 adult asthma outpatient (39% male, M age = 49 ± 14.3) underwent a sociodemographic, psychiatric, and medical history interview. Patients reported asthma medication use, which was verified by chart review. All patients underwent spirometry and completed questionnaires including the beck depression inventory-II (BDI-II) which includes an item that assesses SI in the past two weeks.

Results: 11.5% of patients reported having SI in the past two weeks. After adjusting for age, sex, smoking, asthma severity, and depressive disorders, analyses indicated that theophylline use was associated with an increased likelihood of SI (OR = 2.67, 95% CI = 1.07–6.65). Sensitivity analyses including asthma control levels and benzodiazepine use as additional covariates did not alter this association (respectively: OR = 2.54, 95% CI = 1.04–6.37; OR = 2.71, 95% CI = 1.09–6.78), though adding cohabitation rendered it no longer statistically significant (OR = 2.34, 95% CI = 0.90–6.09). There were no associations between SI and LABA use.

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Conclusions: Findings suggest that theophylline but not LABA use may be associated with an increased risk of SI among adult asthmatics independent of depressive disorders, asthma control levels, and asthma severity, but not cohabitation, suggesting that cohabitation may be important for SI in this population. Physicians should be cautious when prescribing theophylline or similar agents to asthmatics, and ensure adequate follow-up.

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Introduction

Suicide is the fourth leading cause of death in Canada among adults aged 45–54, after cancer, cardiovascular diseases, and unintentional injuries.¹ Multiple factors may explain suicidal behavior (an inclusive term used to refer to the spectrum of behaviors related to suicide including suicidal ideation, attempted suicides, and completed suicides). Notably, chronic illness has been identified as an important risk factor for suicidal behavior.^{2–5} Among several chronic illnesses (cardiovascular disease, hypertension, asthma, chronic bronchitis, cancer, arthritis, diabetes, gout, lupus, thyroid, liver and renal disorder) pulmonary diseases (including asthma) have been shown to have the strongest association with suicidal behavior.^{3,6} Surprisingly, major depression, drug and/or alcohol dependence, and sociodemographic characteristics such as age, sex, ethnicity, income, and years of education, do not seem to alter the association between pulmonary disease and suicidal behavior,^{3,6,7} despite the fact that these variables are generally identified as risk factors.^{8–13} These perplexing results highlight the importance of understanding how patients with asthma can manifest suicidal behavior.

Asthma is associated with sometimes unpredictable and potentially life-threatening attacks. Financial losses may be incurred as a result of treatment (e.g., medication expenses, hospitalization) and/or asthma-related work absenteeism. Aside from the impact of these psychosocial factors, other variables may explain increased suicidal behavior among asthmatics. Significant adverse psychological effects, including agitation, anxiety, and depression have been shown to be associated with sustained use of theophylline^{14–18} and beta-2 adrenergic agonists,^{14,17,19} both of which are bronchodilator medications. However, the potential mechanisms linking asthma to suicidal behavior remain poorly understood. To our knowledge, no study has ever explored the association between daily use of bronchodilators (i.e., theophylline and long-acting beta-2 adrenergic agonists, LABA) and suicidal behavior in this population.

The aim of the present study was to evaluate the risk for suicidal ideation (SI) associated with bronchodilator medications that are prescribed on a daily basis (theophylline and LABA's), in a large sample of Canadian adult patients with asthma. It was hypothesized that theophylline and LABA use would be associated with a significantly increased risk of SI among adult asthmatics, independent of covariates.

Method

Sample

This is a sub-analysis of a larger prospective cohort study (PAL Study: Psychological factors in Asthma Longitudinal

Study), which was designed to assess psychological and behavioral risk factors for asthma morbidity. For the main study, a total of 801 consecutive adults with physician-diagnosed asthma were recruited from the outpatient asthma clinic of Hôpital du Sacré-Cœur de Montréal between June 2003–January 2007. Asthma was confirmed by chart evidence of a reversibility of bronchial obstruction (increase in FEV₁ of $\geq 15\%$ after inhaled salbutamol) or bronchial hyperresponsiveness to methacholine challenge.²⁰ Patients were eligible if they were between the ages of 18 and 75 years and were French or English speaking. Patients were excluded if they had occupational asthma, a comorbid medical condition that significantly impacted health outcomes (e.g., chronic obstructive pulmonary disease, cardiovascular disease), evidence of severe psychopathology (e.g., psychosis), current substance abuse, or cognitive deficits such that they were not able to give consent. Of 801 patients recruited, 137 patients had missing data for both the independent and dependent variables and were thus excluded from the analyses, leaving a final sample of 664 patients. This project was approved by the Ethics Committee of Hôpital du Sacré-Cœur de Montréal, and written consent was obtained from all participants.

Procedure

A single clinical research assistant recruited patients following their clinic visit in the outpatient asthma clinic of Montreal's Sacré-Cœur Hospital. All patients underwent a sociodemographic and medical/asthma history interview, as well as standard pulmonary function tests (spirometry). As part of the medical/asthma history interview, patients self-reported medication use, which was verified by chart review. Patients then underwent a brief structured psychiatric interview using the Primary Care Evaluation of Mental Disorders,²⁴ and completed a series of self-report questionnaires assessing psychological factors, including depression (which included an assessment of SI) and levels of asthma control.

Measures

Sociodemographic and medical/asthma history

At the time of recruitment, patients provided information about their sociodemographic characteristics and their medical and asthma history. The following information was collected: age, sex, ethnicity, whether they were cohabitating (living with a partner), employment status, level of education, smoking history, body mass index (BMI), presence of medical comorbidities, date of initial asthma diagnosis, presence of atopy, and current asthma medication prescriptions. Asthma severity was assessed according

to GINA guidelines.²¹ All medical history information and prescription data were verified by chart review in consultation with the treating physician.

Primary care evaluation of mental disorders (PRIME-MD)

The PRIME-MD is a brief, structured psychiatric interview that evaluates a range of psychiatric disorders that tend to present in primary care settings (i.e., mood, anxiety, somatoform, eating, and substance abuse disorders). For the purposes of this sub-study, only the mood disorders module,²⁴ which was administered by a trained, clinical research assistant and was supervised by a licensed clinical psychologist (KL), is considered. The PRIME-MD has good psychometric properties. It uses Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R)²² criteria to generate diagnoses that have been shown to be of comparable reliability ($\kappa = 0.71$), sensitivity (83%) and specificity (88%) for diagnoses of mood disorders as longer structured interviews such as the Structured Clinical Interview for DSM (SCID).^{23–25}

Suicidal ideation: question 9 of the Beck Depression Inventory-II (BDI-II)

The BDI-II^{26,27} is a self-report questionnaire containing 21 items designed to measure the intensity of depressive symptoms over the past two weeks. Question 9 on the BDI-II evaluates SI. For this question, the patient chooses the response that best describes how he or she has been feeling during the past two weeks including the day on which the questionnaire is completed. The response options for question 9 include: 0 = "I don't have any thoughts of killing myself," 1 = "I have thoughts of killing myself, but I would not carry them out," 2 = "I would like to kill myself," 3 = "I would kill myself if I had the chance." For analytic purposes, responses 1 through 3 were considered indicative of SI.

Asthma control questionnaire

The Asthma Control Questionnaire (ACQ; 29) is a self-report questionnaire designed to evaluate a patient's level of control of their asthma according to specific international (GINA) criteria.²¹ The ACQ measures asthma symptoms (shortness of breath, wheezing, daytime and nighttime dyspnea), activity limitations, and bronchodilator use in the past week. An additional question concerning spirometry results (% of predicted FEV₁) is completed by the research assistant following the patients pulmonary function testing. The ACQ comprises 7 items on a 7-point scale (0 = good control, 6 = poor control). The ACQ has demonstrated strong measurement properties, with intra-group correlation coefficients of 0.90–0.95, good construct validity and good cross-sectional and longitudinal validity.^{28–30}

Pulmonary function testing

According to standard procedure, spirometry has been used to assess pulmonary function as part of the patients asthma clinic visit. At least 4 h before all tests, rescue medication was withheld, and predicted values of FEV₁ and FVC were calculated from reference values for patients less than³¹ and greater³² than 70 years respectively, yielding % predicted FEV₁ and % predicted FEV₁/FVC.

Statistical analyses

Imputation of missing data

Multiple imputation is the method of choice for studies with missing values that affect less than 60% of the sample.³³ The imputation method used assumed that the data were missing at random, and included all covariates that were included in the final logistic analyses. Using PROC MI in SAS v9.1 (SAS Institute, Cary, NC, USA), we produced five independent replicated datasets. Each imputed dataset comprised 664 patients, which was the final sample size used for analyses in this study. For the main analyses, estimation for model coefficients was produced using PROC MIANALYZE, which averages all estimates and adjusts standard errors according to Rubin's rule.³⁴ Details of the amount of missing data per variable are presented in Table 1.

Baseline analyses

Group differences in sociodemographic, medical/asthma history, and medication use between patients with and without SI were examined using General Linear Models (GLM's). For these analyses, the original non-imputed dataset was used.

Main analyses

Two logistic regression model analyses were carried out to examine the specific effects of each type of medication: theophylline and LABA use, on SI. Both models adjusted for age, sex, years of education, mood disorders (including major/minor depression and/or dysthymia), smoking status, and asthma severity, determined a priori based on previously documented impacts on suicidal behavior.^{3,6–13}

Results

Sociodemographic and asthma characteristics

Thirty nine percent of participants were male ($n = 259$) and the mean age $\pm$ SD of the sample = 49 ± 14 years. A total of 76 patients (11.5%) reported having SI according to responses on the BDI-II.

Sociodemographic characteristics presented as a function of SI (yes, no) are presented in Table 1. Patients reporting SI were significantly more likely to live alone than patients not reporting SI. There were no other significant group differences in sociodemographic characteristics.

Asthma characteristics presented as a function of SI are also presented in Table 1. Patients reporting SI were significantly more likely to have higher scores on the ACQ (indicating worse asthma control) but had better pulmonary function (higher FEV₁ % predicted). This discrepancy may be explained by the fact that disease control is better measured by assessing bronchodilator reversibility of FEV₁ rather than baseline (resting) levels of FEV₁, the former of which was not assessed in the present study. Also, they were significantly more likely to be current smokers and have a heavier smoking history (greater number of pack-

Table 1 Sociodemographic, clinical, asthma and asthma medications characteristics as a function of suicidal ideation.

<i>n</i> (%) or <i>M</i> ± <i>SD</i>	Suicidal ideation		<i>F</i>	<i>p</i>	Missing data% (<i>n</i>)
	Yes 76 (11.5)	No 588 (88.5)			
<i>Sociodemographics</i>					
Age (yr)	48 ± 13.5	50 ± 14.3	0.83	0.362	—
Sex (male)	25 (33)	235 (40)	1.41	0.235	—
Ethnicity (Caucasian)	71 (93)	547 (93)	0.01	0.939	—
Lives alone	46 (60)	176 (30)	28.19	<0.0001	2 (10)
Years of education	12.9 ± 4.45	13.1 ± 3.47	0.26	0.610	2 (11)
Employed	39 (51)	365 (62)	3.70	0.055	2 (10)
<i>Clinical and asthma characteristics</i>					
Asthma Control Questionnaire (ACQ) ^a	1.8 ± 1.0	1.4 ± 1.0	8.91	0.003	—
Duration of asthma (years)	18.7 ± 17.8	19.4 ± 15.4	0.13	0.718	2 (13)
FEV ₁ , % predicted ^b	85 ± 20	79 ± 23	4.50	0.034	8 (53)
FEV ₁ /FVC, % predicted ^b	74 ± 10	72 ± 13	1.51	0.220	12 (56)
Atopy	54 (71)	417 (71)	0.00	0.952	1 (7)
Pack-years ^c	12.9 ± 19.4	8.3 ± 14.7	5.66	0.018	15 (97)
Current smoker	12 (16)	41 (07)	6.78	0.009	—
Mood disorders	37 (49)	76 (13)	65.03	<0.0001	—
Benzodiazepines use	16 (21)	65 (11)	6.28 ^e	0.012	—
<i>Asthma medications</i>					
Use of short-acting bronchodilator (# puffs/week) ^d	10 ± 20.9	8.0 ± 14.1	1.92	0.166	1 (7)
Short-acting b2 adrenergic, anticholinergic	75 (99)	570 (97)	0.42	0.516	1 (3)
Long-acting bronchodilators (LABA's) (alone or combined)	49 (64)	388 (66)	0.17	0.682	1 (3)
Inhaled corticosteroids (ICS) (alone or combined)	70 (92)	553 (94)	0.31	0.578	1 (3)
Oral corticosteroids	9 (12)	47 (8)	1.44	0.2305	1 (4)
Anti-leukotrienes	11 (8)	12 (71)	0.08	0.779	1 (3)
Theophylline	11 (8)	5 (29)	3.18	0.075	1 (3)
Anti-rhinitics	19 (14)	17 (100)	0.12	0.730	1 (3)

^a Higher score = worse control.^b FEV₁ = Forced expiratory volume in 1 s; FVC = Forced vital capacity.^c Pack-years = average number of packs (20 cigarettes) smoked per day multiplied by the number of years smoked.^d Value is *M* ± *SD*.^e Chi-square value.

years) than patients not reporting SI. Finally, patients reporting having SI were significantly more likely to have mood disorders (including major/minor depression and/or dysthymia) than patients not reporting having SI. There were no other significant group differences in asthma characteristics.

Asthma medications presented as a function of SI are presented in Table 1. There were no significant differences in rates of medication use among patients with versus without SI.

Multivariate association between asthma medications and suicidal ideation

Results of multivariate logistic regression model analyses examining the association between asthma medication use (theophylline, LABA) and SI are presented in Tables 2 and 3. Though no significant association between LABA use and SI was found (OR = 1.02, 95% CI = 0.56–1.84), theophylline use was found to be significantly associated with an

increased risk of SI (OR = 2.67, 95% CI = 1.07–6.65) after covariate adjustment.

Sensitivity analysis: assessing the impact of cohabitation, asthma control, and benzodiazepine use

Though cohabitation status (i.e., living alone) has been linked to SI in previous studies, this link has been inconsistent^{6,13,35} which is why it was not included as a covariate a priori. However, the exceptionally high rate of living alone (60%) in the SI group relative to the no-SI group (30%) was unexpected, so we ran an extra set of analyses including cohabitation as an additional covariate. Although the risk of SI was still more than two-fold greater among patients taking theophylline, adjustment for cohabitation rendered the association between theophylline use and SI no longer statistically significant (see Table 2). In addition, both asthma control levels and benzodiazepine use were

Table 2 Multivariate logistic regression analysis examining the effects of theophylline on suicidal ideation.

				Sensitivity analysis								
				Model with cohabitation			Model with asthma control			Model with benzodiazepines use		
Variable	OR ^a	95% CI		OR ^a	95% CI		OR ^a	95% CI		OR ^a	95% CI	
Theophylline	2.67	1.07	6.65	2.34	0.90	6.09	2.54	1.04	6.37	2.71	1.09	6.78
Mood disorder	6.21	3.66	10.54	5.86	3.40	10.08	5.48	3.18	9.45	5.89	3.44	10.10
Asthma severity (GINA category)	0.77	0.47	1.28	0.78	0.47	1.30	0.63	0.34	1.19	0.77	0.47	1.28
Current smoking	1.73	0.79	3.79	1.64	0.73	3.72	1.57	0.71	3.49	1.66	0.75	3.67
Age	1.00	0.98	1.02	1.01	0.99	1.03	1.00	0.98	1.02	1.00	0.98	1.02
Sex (male)	0.84	0.49	1.43	0.94	0.54	1.64	0.82	0.48	1.41	0.86	0.50	1.47
Years of education	0.99	0.92	1.06	0.99	0.92	1.07	0.99	0.92	1.07	0.99	0.92	1.07
Cohabitation				0.33	0.19	0.56						
Asthma control (ACQ scores)							1.32	0.95	1.83			
Benzodiazepines use										1.43	0.45	2.87

^a Covariate adjusted.

found to be different among patients with (score on ACQ = 1.8, 21% taking benzodiazepine) versus without (score on ACQ = 1.4, 11% taking benzodiazepine) SI. Extra analyses including asthma control or benzodiazepine as an additional covariate, showed no effect on the association between theophylline use and SI (see Table 2).

Discussion

The present study assessed the prevalence of suicidal ideation (SI) among adult, tertiary care patients with asthma, and the association between certain asthma medications (i.e., daily use bronchodilators: theophylline and LABA) and SI. Results revealed that 11.5% of adult asthmatics reported having SI in the last two weeks, which is nearly four times greater than the 12-month

prevalence (2.9%) found in a comparable age group (45–64 years) of the general Quebec population.³⁶ It is therefore possible that the observed prevalence of 11.5% would have been even greater if, as in the general Quebec population, it had been measured over a period of 12 months. This finding is consistent with earlier studies demonstrating a high prevalence of suicidal behaviors among asthmatic adults.^{3,6,7,37,38}

We expected both theophylline and LABA use to be associated with a significantly increased risk of SI among adult asthmatics, independent of covariates. Our hypotheses were partially confirmed: although there was no increased risk of SI associated with LABA's, theophylline use increased the likelihood of SI in adult asthmatics nearly three-fold. This was found to be independent of several important covariates including having a comorbid mood disorder, asthma severity, levels of asthma control, age,

Table 3 Multivariate logistic regression analysis examining the effects of LABA's on suicidal ideation.

			Sensitivity analysis									
Variable	OR ^a	95% CI		Model with cohabitation			Model with asthma control			Model with benzodiazepines use		
				OR ^a	95% CI		OR ^a	95% CI		OR ^a	95% CI	
LABA's	1.02	0.56	1.84	1.02	0.55	1.86	1.09	0.59	2.02	1.02	0.56	1.85
Mood disorder	6.02	3.57	10.16	5.73	3.35	9.83	5.29	3.08	9.08	5.73	3.36	9.77
Asthma severity (GINA category)	0.83	0.49	1.40	0.83	0.48	2.21	0.66	0.33	1.29	0.83	0.49	1.40
Current smoking	1.85	0.85	4.02	1.73	0.77	3.87	1.65	0.75	3.65	1.80	0.83	3.92
Age	1.00	0.98	1.02	1.00	0.99	1.03	1.00	0.98	1.02	1.00	0.98	1.02
Sex (male)	0.85	0.50	1.46	0.97	0.56	1.68	1.20	0.49	1.43	0.88	0.51	1.50
Years of education	0.98	0.91	1.06	0.99	0.92	1.06	0.99	0.92	1.07	0.99	0.92	1.06
Cohabitation				0.31	0.18	0.54						
Asthma control (ACQ scores)							1.34	0.96	1.87			
Benzodiazepines use										1.39	0.70	2.79

^a Covariate adjusted.

sex, years of education, smoking status, and benzodiazepine use. To our knowledge, no prior studies have identified an increased risk of SI associated with theophylline use in adult asthmatics. However, our results are consistent with two previously reported case studies: one reporting an association between SI and theophylline use in an adult with COPD,³⁹ and one reporting an association between theophylline use and depression in a patient with asthma.¹⁶ Also consistent with our results, symptoms of agitation, irritability, anxiety, and psychosis have been reported in case studies of adult asthmatics taking theophylline at therapeutic doses.^{18,40–45}

The fact that the risk of SI associated with theophylline use became non-significant after further adjustment for cohabitation suggests that cohabitation may be important to SI in this population. The impact of cohabitation was examined separately due to the fact that all covariates were chosen *a priori* based on well established associations with the independent or dependent variables. However, previous studies demonstrating a link between cohabitation have been inconsistent, with some showing significant associations between being single or living alone and an increased risk of SI,^{6,13,35} and others not,^{8,10} which made it difficult to assess the pertinence of this variable. Moreover, with the exception of one study,⁶ previous studies were not conducted among patients with asthma or other chronic diseases, which also suggested that cohabitation may not be relevant to an asthma population. Nonetheless, our findings indicate that the majority (60%) of patients with SI lived alone, and suggests that cohabitation may in part mediate the association of SI and theophylline use. Potential mechanisms of this effect are detailed below.

Aside from theophylline and cohabitation, only one other variable was independently associated with SI in this study: mood disorders. The association between mood disorders and SI is not surprising, given that SI is included among the diagnostic criteria for mood disorders⁴⁶ and is highly comorbid with depression.^{6,47} However, it is noteworthy that mood disorders were unable to account for the association between theophylline and SI in this population, suggesting that the results are not simply the result of comorbid depression.

Potential mechanisms: theophylline

Although the present study was not designed to examine the mechanisms potentially linking theophylline use to increased SI, we could speculate on some of the potential pathways. First, theophylline may be related to SI in asthmatics via psychophysiological mechanisms involving the central nervous system (CNS). Theophylline stimulates the CNS, acts as a bronchial smooth muscle relaxant, and increases cerebral blood resistance (which may diminish cerebral blood flow and cerebral oxygen), which may provoke intense feelings of agitation, dyspnea, hyperventilation, and dizziness.^{14,46} In addition, when theophylline is administered at higher doses (>18 mg/L), it can also induce other symptoms including nausea, tachycardia, agitation, trembling, hallucinations, and irritability.^{14,48} Theophylline increases blood levels of catecholamines^{14,49} in a pathophysiological manner similar to panic disorder,^{50,51} which

has been shown to be significantly associated with the presence of SI in patients with asthma.⁵²

Other mechanisms potentially linking theophylline to increased SI include pharmacokinetics (absorption, distribution, metabolism, and elimination of theophylline) and pharmacodynamics (interactions between theophylline and other medications). For theophylline to be effective and to avoid toxic reactions, the recommended plasma concentrations fall within the narrow range of 8–18 mg/L⁴⁸ or 50–100 $\mu\text{mol/L}$.⁴⁹ However, elevated plasma levels of theophylline (>18 mg/L) may be common, especially within a tertiary care population, despite being prescribed at therapeutic doses.⁵³ Although we did not collect data on the circulating levels of theophylline in the patients, it is possible that those with SI might have higher concentrations due to disrupted pharmacokinetics. If this is the case in the current study, due to the design, we would not be able to disentangle the causal direction of this relationship. For pharmacodynamics, interactions with certain antibiotics (e.g., erythromycin, clarithromycin, ciprofloxacin) that are often prescribed to asthmatics,^{54,55} may significantly increase plasma levels of theophylline through competitive inhibition.⁵⁵ Thus, it is possible that combining theophylline with certain antibiotics may give rise to adverse psychological effects such as anxiety or irritability. Unfortunately, we did not collect data on recent antibiotic use in this sample, so we cannot confirm this hypothesis. However, the present study included stable outpatients with no recent (i.e., last 4 weeks) emergency care visits for exacerbations, which reduces the likelihood that patients were taking concomitant antibiotics at the time of their recruitment.

Another interaction effect could be with certain benzodiazepines (diazepam and alprazolam) for which theophylline may have an antagonistic effect.^{56,57} At a cellular level, theophylline inhibits benzodiazepines^{57,58} by binding to the same receptors (blocking adenosine receptors possibly related to GABA-benzodiazepines). In the current study, 21% of patients with SI reported taking benzodiazepines at least occasionally, which is nearly two times greater than those without SI (11%) (see Table 1). However, taking benzodiazepines had no effect on the significant association between theophylline use and SI (see Table 2), which suggests that higher benzodiazepine use is unlikely to account for our findings.

Potential mechanisms: cohabitation

The significant association between theophylline and SI was rendered non-significant after additional adjustment for cohabitation, suggesting that cohabitation status may be important to SI among asthmatics. Though we did not assess this directly, there are several possible explanations for this finding. Living alone or being unmarried has been shown to increase depression,⁵⁹ alcohol and substance abuse,⁶⁰ anxiety and hopelessness,⁶¹ and suicidal behaviors (SI and actual suicide) among primary care patients and those with completed suicides (the latter determined following autopsy).^{6,13} Moreover, living alone increases the risk of being less compliant to treatment in patients with a chronic disease.⁶² Therefore, living with someone may be a protective factor against SI by having increased access to psychological or social support, by ensuring better

compliance to treatment, and by having help to engage in self-management behavior.^{63–65} Clinically, our findings suggest the importance of providing support for asthma patients who live alone, though this needs to be fully explored in future research.

Study limitations and strengths

The present study has certain limitations that need to be taken into account. Firstly, asking patients to self-report whether they are experiencing any suicidal thoughts is the most direct method of assessing SI. However, patients may choose not to disclose suicidal thoughts. Thus, the prevalence of SI may have been underestimated in the present study. Current medication use was also self-reported in the present study, though this data was systematically verified via chart review. It was also not possible to verify medication adherence in the present study. As such, we cannot verify the extent to which patients prescribed theophylline actually took it, or for how long, or at what doses. Our measure of cohabitation was limited to the number and type of persons the patient lived with, so we cannot comment on the quality of relationships or degree of social support actually received by patients. The cross-sectional nature of the present study also limits the conclusions that may be drawn, so no causal inferences can be drawn. Longitudinal studies are needed to elucidate the temporal relationship between asthma, theophylline use, cohabitation, and SI. Finally, the present study included patients presenting to a tertiary care clinic, and so the results may not be generalizable to asthma patients treated in primary care or in community settings.

Despite these limitations, the present study also has a number of important strengths. First, SI was assessed using a question from a well-validated questionnaire (BDI-II). Second, all self-reported medication use was systematically verified by chart review. Third, this study makes a novel contribution to the existing literature by being the first, to our knowledge, to examine the association between chronic bronchodilator use and SI in a large ($n = 664$) sample of patients with objectively documented physician-diagnosed asthma. Finally, we demonstrated links between theophylline use and SI after examining the effect of multiple risk factors for suicidal behavior including mood disorders (depression), disease severity, asthma control, benzodiazepines use, smoking, age, sex, and level of education. However, the addition of cohabitation status to the model rendered the theophylline-SI link non-significant, suggesting that asthmatics who live alone may be particularly susceptible to SI.

Conclusion

In conclusion, the present study found significant associations between theophylline use and SI in a sample of adult, tertiary-care asthmatics, independent of several covariates including mood disorders, asthma severity and asthma control. However, after further adjustment for cohabitation, this association was no longer statistically significant, suggesting that cohabitation (i.e., living alone) may be a risk factor for SI in asthmatics (or conversely, that living with someone may be protective against SI). These findings

indicate that physicians should be vigilant for patients who may be at increased risk of SI (i.e., those with a suspected or confirmed mood disorder, those requiring potent bronchodilators such as theophylline), particularly in patients who live alone or who are anxious. Also, given the identification of multiple factors potentially influencing the pharmacodynamic and pharmacokinetic properties of theophylline, it may also be necessary to provide close monitoring of plasma concentrations of theophylline in order to evaluate the therapeutic benefits versus potential side effects. Clinically, it may be important for clinicians to provide additional support for patients who live alone and receive only limited support, to screen for SI and anxiety disorder, revise prescriptions, and refer patients for appropriate pharmacotherapy or psychotherapeutic treatment if needed.

Conflict of interest statement

The manuscript has been read and approved by all authors, and is not being considered for publication elsewhere, and there are no conflicts of interest.

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