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Initiation of Acetylcholinesterase Inhibitors and Complications of Chronic Airways Disorders in Elderly Patients

Evan L. Thacker[1,2] and *Sebastian Schneeweiss*[1,2]

1 Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA
2 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA

Abstract

Background and objective: Acetylcholinesterase inhibitors (AChEIs), commonly prescribed in Alzheimer's disease, may trigger complications of chronic airways disorders. The aim of this study was to determine whether initiation of therapy with AChEIs contributes to complications of chronic airways disorders in an elderly population.

Methods: Sequence-symmetry analysis was used to assess two cohorts of patients, both with a history of chronic airways disorders. Both cohorts comprised Medicare beneficiaries who received drug coverage through the Pennsylvania Pharmaceutical Assistance Contract for the Elderly, between 1997 and 2002. One cohort of 922 patients initiated treatment with an AChEI; the other cohort of 2819 patients initiated treatment with a β-adrenoceptor antagonist (β-blocker), a comparator drug also contraindicated in chronic airways disorders. The occurrence of the following four outcomes in claims data was assessed: (i) emergency room visits for complications of chronic airways disorders; (ii) hospitalisations for complications of chronic airways disorders; (iii) physician visits for complications of chronic airways disorders; and (iv) dispensing of an antibacterial and an oral corticosteroid on the same day. Rate ratios (RRs) were adjusted for age, sex, race, nursing home residence, cognitive status, severity of chronic airways disorders, comorbid illnesses and all other patient characteristics that can be assumed to remain constant over the study period.

Results: Initiators of AChEIs had no detectable increased rate of complications of chronic airways disorders. Adjusted RRs of the four outcomes ranged from 1.00 (95% CI 0.61, 1.62; p = 0.99) for physician visits to 1.64 (95% CI 0.55, 4.89; p = 0.37) for emergency room visits, none reaching statistical significance. In contrast, β-blocker initiators had significantly increased rates of all four outcomes after treatment, with adjusted RRs ranging from 1.97 (95% CI 1.18, 3.29; p = 0.009) for emergency room visits to 2.76 (95% CI 1.71, 4.45; p < 0.0001) for dispensing of an antibacterial and oral corticosteroid on the same day.

Conclusion: These results suggest that, in current clinical practice, physicians can prescribe AChEIs safely to elderly patients with chronic airways disorders, while β-blocker prescribing continues to result in adverse health outcomes.

Background

Effective clinical management of multiple chronic conditions is a common challenge in caring for elderly patients. In particular, appropriate pharmacological treatment of patients with numerous illnesses requires astute decision making when drug treatment for one condition may trigger complications in another condition. In this study, we examine the concurrence of Alzheimer's disease (AD) and chronic airways disorders such as chronic bronchitis, emphysema and asthma, which are relative contraindications for the widely prescribed treatments for AD of mild-to-moderate severity – the acetylcholinesterase inhibitors (AChEIs) donepezil, rivastigmine and galantamine.

According to recent research, chronic airways disorders are not uncommon in elderly patients with AD. A survey of a population-based dementia registry found that 5% of AD patients have chronic pulmonary disease.[1] In nursing homes, approximately 8% of AD patients have chronic obstructive pulmonary disease (COPD) or asthma, according to 1999 National Nursing Home Survey data.[2] Recent results from a cross-sectional study indicate that, among patients diagnosed with AD of mild-to-moderate severity, 12–15% have respiratory problems.[3] Because of incomplete reporting and under-diagnosis of comorbid illnesses in AD patients,[1] the concurrence of AD and chronic airways disorders may be even higher than these estimates suggest. With 4.5 million Americans diagnosed with AD[4] and >7 million Americans aged >65 years with COPD or asthma,[5,6] concomitant AD and chronic airways disorders potentially affect a substantial segment of the elderly population in the US.

Whereas exacerbations of chronic airways disorders are usually precipitated by bacterial or viral infections,[7] complications of chronic airways disorders may arise in conjunction with comorbid conditions, including adverse reactions to medications prescribed for other conditions.[8-10] AChEIs used to treat AD of mild-to-moderate severity may have bronchoconstricting effects in some patients,[11,12] potentially leading to complications in those with chronic airways disorders. The hypothesised potential for respiratory adverse effects has resulted in specific warnings in AChEI prescribing information.[13-15] However, the extent to which AChEI treatment contributes to complications of chronic airways disorders in routine care is unknown. Clinical trials and postmarketing studies of AChEIs for AD and other dementias have yielded little information on this issue, because patients with clinically relevant COPD or asthma were typically excluded,[16-24] or were included in insufficient numbers to investigate respiratory adverse effects.[25-27] The aim of the present study was to quantify the outcomes of AChEI therapy in elderly patients with chronic airways disorders in routine care.

Methods

We assembled a cohort of patients who began treatment with AChEIs despite having evidence of chronic airways disorders, and used administrative claims data to assess the occurrence of complications of these conditions before and after AChEI initiation. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital and is part of an ongoing data use agreement with the Center for Medicare and Medicaid Services.

Patients

We obtained patient information such as age, sex and diagnosis codes from Medicare administrative datasets, including the denominator, outpatient, inpatient, and skilled nursing facility files; and drug dispensing information, including national drug codes, dosage forms, dispensing dates and days supplied, from administrative data of the Pennsylvania

Table I. Drugs used to identify patients with at least one dispensing of a drug used for maintenance treatment of chronic airways disorders

Drug class	Drug
Anticholinergics	Ipratropium bromide, tiotropium bromide
Short-acting β-agonists	Adrenaline (epinephrine), isoetharine, isoprenaline, levosalbutamol, orciprenaline (metaproterenol), pirbuterol, salbutamol (albuterol), terbutaline
Long-acting β-agonists	Formoterol, salmeterol
Inhaled corticosteroids	Beclometasone, budesonide, dexamethasone, flunisolide, fluticasone propionate, triamcinolone
Leukotriene antagonists	Montelukast, zafirlukast, zileuton
Xanthines	Aminophylline, choline theophyllinate, diprophylline (dyphylline), theophylline

Pharmaceutical Assistance Contract for the Elderly (PACE). Eligibility for drug coverage through PACE requires that patients be not enrolled in other drug-benefit plans; therefore, the PACE data contain comprehensive prescription drug dispensing records for each patient. To protect patient privacy, datasets were combined using scrambled social security numbers.

We identified all patients who received their first dispensing of one of three commonly-used AChEIs between 1 January 1997 and 30 November 2002. The three AChEIs were donepezil (Aricept®,[1] Eisai Co., Ltd., Teaneck, NJ, USA), rivastigmine (Exelon®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), and galantamine (Reminyl®, Janssen Pharmaceutica Products, L.P., Titusville, NJ, USA; renamed Razadyne® since April 2005, Ortho-McNeil Neurologics, Inc., Titusville, NJ, USA).

The date of AChEI dispensing was the index date for each patient. From among the AChEI initiators, we selected all patients with a history of chronic airways disorders, on the basis of two criteria: (i) at least one dispensing, 7–12 months before their index date, of a drug used for maintenance treatment of chronic airways disorders (see table I); and (ii) at least one emergency room visit, hospitalisation, or physician visit, 7–12 months before their index date, with an International Classification of Disease, 9th Edition (ICD-9) code for chronic bronchitis, emphysema, asthma, bronchiectasis or other chronic airways obstruction (see table II).

Drug Exposure

Drug exposure was defined as receiving a first dispensing of an AChEI. Time periods after the index date, including the index date, were 'treated' time periods, and time periods preceding the index date were 'untreated' time periods with regard to an AChEI.

Study Outcomes

Using Medicare and PACE claims data, we defined a set of four outcomes representing complications of chronic airways disorders. Complications of chronic airways disorders may mimic disease exacerbations, which have been defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication".[28] Thus, we defined three outcomes as healthcare encounters with 4- or 5-digit ICD-9 codes specifying 'exacerbation' of chronic airways disorders (see table II), including (i) emergency room

Table II. International Classification of Diseases 9th Edition codes for chronic airways disorders

Code	Description
491	Chronic bronchitis
491.21[a]	Obstructive chronic bronchitis, with (acute) exacerbation
492	Emphysema
493	Asthma
493.02[a]	Extrinsic asthma, with (acute) exacerbation
493.12	Intrinsic asthma, with (acute) exacerbation
493.22[a]	Chronic obstructive asthma, with (acute) exacerbation
493.92[a]	Asthma, unspecified, with (acute) exacerbation
494	Bronchiectasis
494.1[a]	Bronchiectasis with acute exacerbation
496	Chronic airway obstruction, not elsewhere classified

a Specific codes used for exacerbation of chronic airways disorders.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

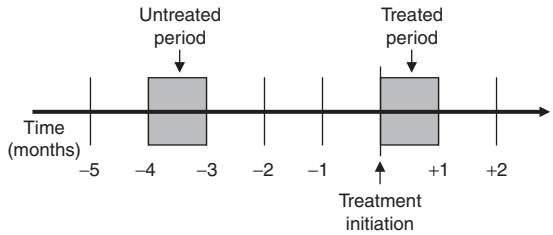

Fig. 1. Study timeline showing treated and untreated periods.

visits, (ii) hospitalisations, and (iii) physician visits. The fourth outcome was the dispensing of both an antibacterial and an oral corticosteroid on the same day, which is a marker for sudden worsening of chronic airways disorders.[29]

Statistical Analysis

We used sequence-symmetry analysis, a special type of crossover design in which, for each patient, a period of drug treatment is contrasted with a period of no drug treatment, and outcomes of interest are ascertained for both periods.[30,31] The design has been used in claims databases to estimate the rate ratios (RRs) of adverse outcomes immediately after drug initiation, implicitly adjusting for all measured and unmeasured non-time-varying confounders, because patients are compared with themselves before and after the index date.[32-36]

Under the null hypothesis – where the treatment has no effect on the outcome – and under the assumption of no time trends in the prescribing of the agent of interest during the study period and no other time-dependent confounding, the rate of the outcome (complications of chronic airways disorders) after treatment will be no different from the rate before treatment, i.e. outcomes will be distributed symmetrically around the index date of treatment initiation.

For each patient, the 1-month interval after AChEI initiation was assigned the treated period, and the 1-month interval 4 months before the index date was the untreated period (figure 1). For each patient, we ascertained the four outcomes during the treated and untreated periods. Type A patients experienced complications only in the treated period, not in the untreated period. Type B patients experienced complications only in the untreated period, not in the treated period. The RR of each outcome for AChEI initiators versus non-initiators was estimated as the ratio of type A patients to type B patients.[31] Through sequence symmetry, these analyses are automatically adjusted for age in years, sex, race, nursing-home residence, cognitive status, underlying severity of chronic airways disorders, comorbid illnesses and all other patient characteristics that can be assumed to remain constant over a short study period. We used conditional logistic regression models[37] to adjust for two confounders unaccounted for by the sequence-symmetry analysis: healthcare utilisation for complications of chronic airways disorders immediately preceding the treated and untreated periods and flu season.

Comparison Cohort: β-Adrenoceptor Antagonist Initiators

To provide a reference scenario to the AChEI cohort for the assessment of medication-related complications of chronic airways disorders, we assembled a cohort of patients with chronic airways disorders who began treatment with non-ophthalmic β-adrenoceptor antagonists (β-blockers), which have been associated with bronchoconstrictive adverse effects in elderly patients with chronic obstructive airway diseases.[38-40] Methods for identifying the β-blocker cohort, defining drug exposure, measuring study outcomes, and performing statistical analysis were the same as in the AChEI cohort.

Results

During the time period under study, the rate at which patients with evidence of chronic airways disorders received a first dispensing of an AChEI was 21 per 1000 person-years and the rate at which they received a first dispensing of a β-blocker was 158 per 1000 person-years.

The AChEI cohort comprised 922 patients who received a first dispensing of an AChEI, despite having evidence of chronic airways disorders, in the 7–12 months before the index date. Donepezil was by far the most common AChEI prescribed (n = 799; 86.7%). The β-blocker cohort comprised 2819 initi-

Table III. Characteristics of the acetylcholinesterase inhibitor (AChEI) and β-adrenoceptor antagonist (β-blocker) cohorts

Variable	AChEI cohort [n (%)]	β-Blocker cohort [n (%)]
All patients	922 (100)	2819 (100)
Mean age ± SD (years)	82 ± 6	78 ± 7
Females	718 (77.9)	2026 (71.9)
White race	878 (95.2)	2645 (93.8)
Nursing-home residence	8 (0.9)	28 (1.0)
Type of AChEI		
donepezil	799 (86.7)	
rivastigmine	88 (9.5)	
galantamine	35 (3.8)	
Type of β-blocker		
cardioselective		2328 (82.6)
nonselective		218 (7.7)
with α-adrenoceptor antagonist		273 (9.7)

SD = standard deviation.

ators of β-blockers who had evidence of chronic airways disorders. Both cohorts comprised mostly White females with an average age of approximately 80 years, very few of whom resided in nursing homes (table III). Results from the two cohorts are listed in table IV.

Emergency Room Visits

Patients in the AChEI cohort showed no statistically significant increase in emergency room visits for complications of chronic airways disorders after initiating treatment with AChEIs compared with before initiation (RR = 1.64; 95% CI 0.55, 4.89; p = 0.37). In contrast, patients initiating β-blockers were significantly more likely to be admitted to the emergency room for complications of chronic airways disorders after initiating a β-blocker (RR = 1.97; 95% CI 1.18, 3.29; p = 0.009).

Hospitalisations

Patients had no increased rate of hospitalisation for complications of chronic airways disorders after initiating AChEIs (RR = 1.17; 95% CI 0.54, 2.52; p = 0.69). In contrast, patients were significantly more likely to be hospitalised for complications of chronic airways disorders after initiating β-blocker therapy (RR = 2.14; 95% CI 1.43, 3.20; p = 0.0002).

Physician Visits

Patients who began treatment with AChEIs were equally likely to visit a physician for complications of chronic airways disorders before and after AChEI initiation (RR = 1.00; 95% CI 0.61, 1.62; p = 0.99). Patients in the β-blocker cohort were significantly more likely to visit a physician for complications of chronic airways disorders after β-blocker initiation (RR = 1.99; 95% CI 1.50, 2.64; p < 0.0001).

Joint Dispensing of Antibacterials and Oral Corticosteroids

Patients in the AChEI cohort were no more likely to receive pharmacological treatment for complications of chronic airways disorders, in the form of joint dispensing of an antibacterial and an oral corticosteroid, after initiating AChEIs than before initiating AChEIs (RR = 1.19; 95% CI 0.52, 2.74; p = 0.68). On the other hand, patients in the β-blocker cohort were nearly three times more likely to receive the antibacterial plus corticosteroid regimen after initiating β-blocker therapy (RR = 2.76; 95% CI 1.71, 4.45; p < 0.0001).

Discussion

The results of this sequence-symmetry study controlling for measured and most unmeasured confounders showed that the hypothesised respiratory

adverse effects of AChEIs in patients with chronic airways disorders are not occurring to any consequential extent in the routine care of Medicare patients aged ≥65 years. The lack of association was consistent across four separate claims-based outcome measures, all representing complications of chronic airways disorders, including emergency room visits, hospitalisations, physician visits and pharmacological treatment. In contrast, for the same outcome measures, initiating a β-blocker despite a history of chronic airways disorders was associated with a 2- to 3-fold increased rate of complications in the month after treatment initiation.

Comparison of the AChEI cohort with the β-blocker cohort greatly aided the interpretation of our results. The potential for β-blocker therapy to complicate chronic airways disorders is well documented in previous publications.[38-40] The increased rate of complications of chronic airways disorders we observed for β-blocker initiators probably results from bronchoconstriction and is in agreement with these previous reports, thus validating our study methodology. Our reliance on administrative data to measure our study outcomes may have led to some outcome misclassification, which would have been nondifferential with regard to AChEI or β-blocker treatment, resulting in underestimation of the RRs. If such a bias occurred in our study, it was not strong enough to obscure the increased rates of complications of chronic airways disorders we observed in the β-blocker cohort. Thus, we could reasonably expect that, if AChEIs had produced respiratory adverse effects to the same extent as β-blockers in our study, we would have seen similar increases in outcome rates in both cohorts. Instead, the associations in AChEI initiators were much closer to the null than for the β-blocker initiators for all four outcomes, and none of the AChEI associations were statistically significant at $\alpha = 0.05$.

Common adverse effects of AChEIs that typically occur shortly after initiation of the drugs are well documented in randomised clinical trials.[13-15] However, at the time the present study was conducted, trials and postmarketing studies of AChEIs had for

Table IV. Association between initiation of acetylcholinesterase inhibitors (AChEIs) or β-adrenoceptor antagonists (β-blockers) and complications of chronic airways disorders

Chronic airways disorder treatment outcome	Outcome when treated/untreated (no. of patients)				Symmetry-adjusted RR[a] (95% CI)	Fully adjusted RR[b] (95% CI)
	no/no	yes/yes	yes/no (*A*[c])	no/yes (*B*[d])		
AChEIs						
Emergency room	903	1	10	8	1.25 (0.49, 3.17)	1.64 (0.55, 4.89)
Hospitalisation	892	1	15	14	1.07 (0.52, 2.22)	1.17 (0.54, 2.52)
Physician visit	839	15	34	34	1.00 (0.62, 1.61)	1.00 (0.61, 1.62)
Drug treatment	891	1	17	13	1.31 (0.64, 2.69)	1.19 (0.52, 2.74)
β-Blockers						
Emergency room	2740	4	50	25	2.00 (1.24, 3.23)	1.97 (1.18, 3.29)
Hospitalisation	2695	6	81	37	2.19 (1.48, 3.23)	2.14 (1.43, 3.20)
Physician visit	2556	30	158	75	2.11 (1.60, 2.77)	1.99 (1.50, 2.64)
Drug treatment	2708	2	82	27	3.04 (1.97, 4.69)	2.76 (1.71, 4.45)

a Symmetry-adjusted RRs are adjusted for age, sex, race, cognitive status, severity of chronic airways disorders, comorbid illnesses and all other factors that are stable within individuals over the study period, through the sequence-symmetry analysis. For each outcome, the symmetry-adjusted RR is calculated as the number of patients with outcome pattern *A* (outcome occurred during the treated period only) divided by the number of patients with outcome pattern *B* (outcome occurred during the untreated period only).

b Fully adjusted RRs are additionally adjusted for flu season and healthcare utilisation for chronic airways disorders immediately preceding the treated and untreated periods.

c Outcome pattern 'A' – outcome occurred during treatment period only.

d Outcome pattern 'B' – outcome occurred during untreated period only.

RR = rate ratio.

the most part excluded patients with COPD or asthma.[16-27] Therefore, adverse effects hypothesised to occur only in patients with chronic airways disorders would have happened too infrequently to be noticed in such studies. Our study was larger than most previous AChEI trials and focused specifically on patients with chronic airways disorders. Thus, it seems likely that respiratory adverse effects of AChEIs would have been observed in our study had they occurred with any appreciable frequency.

The observed lack of association for AChEIs can be explained by two scenarios. Either physicians are aware of the potential adverse effects of AChEIs and selectively prescribe AChEIs to patients who have less severe chronic airways disorders and who are intrinsically at a low risk of complications, or AChEIs used for dementia treatment are truly not associated with respiratory adverse effects. In either case, our failure to find an increase in complications after AChEI initiation in the routine care of elderly patients with chronic airways disorders suggests that AChEI prescribing in such populations has a good safety profile with regard to the potential for complications.

A major strength of our work in comparison with previous studies on AChEIs is that we assembled a sufficiently large cohort of patients with chronic airways disorders to test the specific hypothesis that AChEI initiation leads to disease complications in this group. Our study of >900 initiators of the three commonly-used AChEIs, donepezil, rivastigmine and galantamine, thus fills a gap in our knowledge of the safety of these drugs in routine care.

The validity and strength of the sequence-symmetry analysis,[30,31] using patients as their own controls, was the elimination of confounding by measured and unmeasured constant patient characteristics such as treatment indication (or contraindication), which is an important threat to validity in traditional pharmacoepidemiology cohort studies based on insurance claims data. Through the matched design and analysis of short-term outcomes, associations were adjusted for age, sex, race, access to health services, cognitive status, severity of underlying chronic airways disorders, comorbid illnesses and all other stable patient characteristics. The successful adjustment for confounders by the sequence-symmetry analysis was demonstrated by observing the association between β-blocker initiation and complications of chronic airways disorders that has previously been described by others.[38-40]

However, even the sequence-symmetry analysis does not automatically control for confounders that do not remain reasonably stable within individual patients during the study period. In this regard, it is important to consider two variables. First, complications of chronic airways disorders may vary seasonally, becoming more common during flu season. Second, recent complications, just before the treated or untreated period, are likely to have an effect on subsequent complications[41] and may also influence AChEI prescribing over the next 1–2 months. Results from our additional adjustments for flu season and recent complications point to the same conclusions as the symmetry-adjusted results: no association in the AChEI cohort and a positive association in the β-blocker cohort.

Any study with a null finding must be scrutinised to determine whether it has obscured a clinically important association by being underpowered. The precision in the AChEI analysis was not as good as in the β-blocker analysis; the 95% CIs in the AChEI cohort are relatively wide for some outcomes. Thus, our findings are potentially compatible with AChEI associations as strong as the β-blocker associations. However, the comparison between the two cohorts shows sufficient contrast to conclude that AChEI initiation did not cause complications of chronic airways disorders to any clinically meaningful extent. The consistency with which the AChEI cohort produced null results, regardless of which outcome measure was used, strengthens our conclusion that AChEIs did not increase the rate of complications in elderly patients with chronic airways disorders.

The validity of the sequence-symmetry analysis with regard to measuring the association between a treatment and an outcome relies heavily on the assumption that the outcome of interest has no effect on subsequent treatment.[42] Three of our four outcomes defined complications of chronic airways

disorders in terms of health services encounters, which can have strong, immediate effects on subsequent drug prescribing. For example, if dementia is first recognised in a patient during a hospitalisation for a chronic airways disorder, the patient is likely to be referred to a specialist for dementia diagnosis and be dispensed with an AChEI shortly after leaving the hospital, despite the warning against AChEI use in patients with chronic airways disorders. The hospitalisation 'causes' the AChEI dispensing 1 or 2 months later. The assumption of independence of outcome and subsequent treatment is violated, and the association measure estimated by the sequence-symmetry analysis may be biased towards the null or even suggest a spurious protective association.

In order to reduce this bias in our study, we slightly modified the original structure of the sequence-symmetry analysis, where the untreated period immediately precedes the index date of drug initiation.[30,31] Instead, we designated the fourth month before the index date as the untreated period for all analyses. Healthcare encounters for complications of chronic airways disorders are unlikely to lead to initiation of AChEI or β-blocker prescribing 4 months later. This modification to the traditional analyses of sequence-symmetry data allowed us to maintain statistical control over confounding by matching patients to themselves, while improving the validity of our results by adhering to the essential assumption of the sequence-symmetry analysis – independence of the outcome and subsequent treatment.

Conclusion

On the basis of the results of this study, we conclude that AChEI initiation did not lead to an increased rate of complications in elderly patients with chronic airways disorders in routine care. In general geriatric clinical practice, AChEIs are frequently prescribed to patients with chronic airways disorders, despite their cholinergic adverse effects and warnings in prescribing information; however, physicians can apparently manage this risk in routine care. We do not interpret these data as a basis for indiscriminately prescribing AChEIs to patients with chronic airways disorders. Nor do our results imply that the warnings relating to COPD and asthma patients in AChEI prescribing information are unnecessary. Rather, we see the data as evidence that, in current clinical practice, physicians are prescribing AChEIs appropriately to patients with chronic airways disorders and no change in practice is warranted.

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Mr Thacker contributed to the study concept and design, analysis and interpretation of data, and preparation of the manuscript. Dr Schneeweiss contributed to the study concept and design, acquisition of data, and analysis and interpretation of data. The authors have no conflicts of interest to declare.

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Correspondence and offprints: Mr *Evan L. Thacker*, Nutrition Department, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115, USA.
E-mail: ethacker@hsph.harvard.edu