

Special Article

THE TREATMENT OF UNRELATED DISORDERS IN PATIENTS WITH CHRONIC MEDICAL DISEASES

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ABSTRACT

Background Patients can have several illnesses concurrently, yet some of these diseases may be neglected if one problem consumes attention. We conducted a population-based analysis in Ontario, Canada — where universal health insurance is provided — to determine whether unrelated disorders are less likely to be treated in patients with chronic diseases.

Methods We studied the 1,344,145 residents of Ontario in 1995 who were 65 or older and eligible to receive prescription medications free of charge as part of the Ontario Drug Benefit program. Patients with diabetes mellitus were identified by prescriptions for insulin, pulmonary emphysema by prescriptions for ipratropium bromide, and psychotic syndromes by prescriptions for haloperidol. For each chronic disease, we selected an unrelated treatment: estrogen-replacement therapy for patients with diabetes mellitus, lipid-lowering medications for those with pulmonary emphysema, and medical treatment of arthritis for those with psychotic syndromes.

Results The 30,669 patients with diabetes mellitus were less likely to receive estrogen-replacement therapy than the other subjects in the study (2.4 percent vs. 5.9 percent, $P < 0.001$). The disease was associated with a 60 percent reduction in the odds of estrogen treatment (odds ratio, 0.40; 95 percent confidence interval, 0.37 to 0.43). Findings were similar for the 56,779 patients with pulmonary emphysema, who were less likely to receive lipid-lowering medications (odds ratio, 0.69; 95 percent confidence interval, 0.67 to 0.72; $P < 0.001$), and the 17,336 patients with psychotic syndromes, who were less likely to receive medical treatments for arthritis (odds ratio, 0.59; 95 percent confidence interval, 0.57 to 0.62; $P < 0.001$).

Conclusions In patients 65 or older who have chronic medical diseases and who receive prescription medications free of charge, unrelated disorders are undertreated. Clinicians caring for patients with chronic diseases should remain alert to other disorders and minimize the number of missed opportunities for treating them. (N Engl J Med 1998;338:1516-20.)

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MOTHER Nature has no mercy. As a consequence, the presence of one disease usually provides no immunity against others. Given the laws of probability, the coincidental occurrence of two unrelated diseases in one patient must happen often in a large population. However, the laws of probability are not intuitively obvious.^{1,2} One common error in particular is the misconception that bad luck tends to be followed by good luck (a pattern of reasoning termed the gambler's fallacy).³⁻⁶ In medicine, this misconception might create a belief that unusual coincidences are extremely unlikely in every individual patient. Such a belief can be reinforced by Occam's razor, a scientific canon that urges thoughtful investigators to use the simplest explanation possible to explain all the facts observed.⁷

Research in nonmedical situations has found that reasoning may be inconsistent even when one is confronted by two clearly separate problems. For example, a \$200 cost seems less expensive when placed in the context of a \$20,000 expenditure than when considered in isolation.^{8,9} Such decreased cost-consciousness helps explain why consumers sometimes make imprudent choices, such as purchasing an overpriced radio when buying a reasonably priced automobile.¹⁰ More generally, secondary problems may receive unduly little attention when they occur at the same time as another, larger problem. As a consequence, people may underestimate the importance of multiple concurrent diseases even if they understand the laws of probability.

Medical training encourages clinicians to consider a broad differential diagnosis when treating the individual patient. One classic dictum states: "Even psychiatric patients can have surgical diseases." However, we postulate that fundamental mistakes in reasoning are not eliminated by formal medical train-

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ing. Clinicians, that is, are neither especially vulnerable to nor especially protected from the errors that occur in nonmedical situations. Our specific hypothesis is that patients are less likely to receive treatment for selected disorders if they have a chronic medical disease. To address this question, we analyzed medical treatments in a setting in which there is universal access to care and no financial charges for patients.

METHODS

Setting and Patients

We selected residents of Ontario, Canada, in 1995 who received prescription medications free of charge as part of the Ontario Drug Benefit program. This group included all residents 65 years of age or older, regardless of whether they were receiving home care benefits, were residents of long-term care facilities, or were living independently in the community. Ontario was chosen because it is the largest Canadian province (with about one third of the country's population), and 1995 was chosen because it was the most recent year for which comprehensive data were available. In 1995, Ontario had a population of 11,008,400, with 25,624 licensed physicians, 6201 licensed dentists, and \$3.5 billion in Ontario Drug Benefit expenditures.¹¹

Chronic Medical Diseases

We selected three chronic systemic medical diseases that were complicated to manage and identifiable through medication prescriptions. Patients with diabetes mellitus were identified by any prescription for insulin, patients with pulmonary emphysema were identified by any prescription for ipratropium bromide, and patients with psychotic syndromes were identified by any prescription for haloperidol. In each analysis, every patient was counted once as having or not having received the medication. These criteria rendered the identification procedure prone to false negative results (some patients with emphysema do not receive ipratropium bromide) and false positive results (some patients without emphysema receive ipratropium bromide). These two misclassification errors tend to decrease the power of statistical comparisons and can bias the analysis toward a finding of no differences even when such differences might exist.

Specific Unrelated Treatments

For each chronic medical disease we selected an unrelated treatment that satisfied the following criteria. First, the treatment was not directly related to either the pathogenesis or the management of the chronic disease. Second, the treatment was not indirectly related to the chronic disease through a shared underlying predisposing factor. Third, the treatment was relatively straightforward but perhaps less important than therapy for the chronic disease. Fourth, the treatment was not trivial and would require follow-up. The specific treatments identified were estrogen-replacement therapy for the patients with diabetes mellitus, lipid-lowering medications for the patients with pulmonary emphysema, and medical arthritis treatment for the patients with psychotic syndromes. These three pairings were selected in advance, and the subsequent comparisons were prespecified.

We used a relatively exhaustive approach to identify the unrelated treatments in the study patients. Estrogen-replacement therapy could be oral or transdermal and included conjugated estrogens, esterified estrogens, 17 β -estradiol, and combinations including ethinyl estradiol. Lipid-lowering medications included cholestyramine, colestipol, clofibrate, bezafibrate, fenofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, and fluvastatin. Medical treatment for arthritis included auranofin, aurothioglucose,

gold sodium thiomalate, diclofenac, etodolac, fenoprofen, floctafenine, flurbiprofen, hydroxychloroquine, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.

Supplementary Analyses

We conducted two additional analyses to test for the lack of a difference where we expected no difference. To do so, we focused on unrelated treatments that were distinctive. In the first, we selected patients who had a history of breast cancer (identified by prescriptions for tamoxifen) and tested for glaucoma treatment. Glaucoma treatment included ophthalmic preparations of betaxolol, carbachol, dipivefrin, echothiophate, levobunolol, pilocarpine, and timolol. Our hypothesis was that ophthalmologic disorders might be sufficiently distinct to be treated despite the previous cancer. In the second, we selected patients with hypothyroidism (identified by prescriptions for thyroxine) and tested for antibiotic treatment. Antibiotic treatment included any oral or parenteral antibiotic formulation. Our hypothesis was that acute infections might be sufficiently distinct to be treated despite the coexisting metabolic disorder. Both these pairings were selected in advance, and the subsequent comparisons were prespecified.

Confidentiality and Identification of Medications

This study was approved by the ethics committee of the Sunnybrook Health Science Centre and was conducted with use of protocols from the Institute for Clinical Evaluative Sciences in Ontario for safeguarding confidentiality. Patients were identified by unique numbers encrypted in a manner that allowed linkages among data sets yet preserved anonymity. Medications were coded by Drug Identification Number and identified from claims filed electronically by pharmacies. To avoid errors due to incorrectly entered codes, we created an in-house master conversion program that allowed programmers to obtain all relevant codes by selecting the medication by its generic name. Analyses were performed on a Sparc 1000 UNIX system computer using SAS software (version 6.11) that required about five hours of mainframe time for a single comparison.

Statistical Analysis

All comparisons were two-tailed, were expressed as odds ratios, and involved the full data base. Calculations of sample size estimated that each analysis would have sufficient power to identify an absolute difference of about 1 percent or more in the proportion of patients receiving treatment. We used the chi-square test to compare the proportions of patients with and patients without the chronic medical disease who were receiving the designated unrelated treatment. In multivariate comparisons we used logistic regression to adjust for imbalances in age and sex (with the exception of the evaluation of estrogen-replacement therapy, which excluded all the men).¹² As a check for reliability, we replicated all the 1995 comparisons with data from 1990, using separate Ontario Drug Benefit data from 1990 that were obtained, coded, and analyzed by the same methods used in the main analyses.

RESULTS

The study included 1,344,145 patients (56 percent were women, and the mean age was 74 years). Overall, 1,226,064 of them (91 percent) received at least one prescription medication (58 percent of these patients were women, and the mean age was 74). Collectively, 30,335,555 separate prescriptions were filled during 1995, representing work by 25,849 physicians and dentists. If each prescription was for one month of treatment and each medication was prescribed for a full year, these data suggest

that the average patient received about two medications in 1995 ($30,335,555 \div 1,344,145 \div 12$). As in other population-based studies of drug use, the most common prescriptions were for acetaminophen with codeine, ranitidine, digoxin, and furosemide.^{13,14}

Overall, 30,669 patients had diabetes mellitus (55 percent were women, and the mean age was 74). These patients were less likely to receive estrogen-replacement therapy than other patients (2.4 percent vs. 5.9 percent, $P < 0.001$). In other words, diabetes mellitus was associated with a 60 percent reduction in the odds of receiving estrogen treatment (Table 1). The observed relative reduction persisted after adjustment for age and after the analysis was restricted to women (99.5 percent of the patients who received a prescription for estrogen were women). Moreover, the relative reduction was found for both oral and transdermal preparations. Analyses of patients in 1990 revealed a similar relative reduction in the probability of treatment.

Overall, 56,779 patients had pulmonary emphysema (46 percent were women, and the mean age was 76). These patients were less likely to receive lipid-lowering medications than the other patients (6.3 percent vs. 8.7 percent, $P < 0.001$). In other words, emphysema was associated with a 31 percent reduction in the odds of receiving lipid-lowering treatment. The relative reduction persisted after adjustments for age and sex, was found for both statin and non-statin agents, and was also present in 1990.

Similarly, 17,336 patients had psychotic syndromes (64 percent were women, and the mean age was 80). These patients were less likely to receive medical treatment for arthritis than the other patients (18 percent vs. 27 percent, $P < 0.001$). In other words, there was a 41 percent reduction in the odds of treatment. The relative reduction persisted after adjustment for age and sex, was found for both nonsteroidal antiinflammatory agents and disease-modifying antirheumatic drugs, and was also present in 1990.

The relative neglect of unrelated disorders was not a universal finding. The 11,094 patients who had breast cancer were just as likely to receive glaucoma treatment as the other patients (5.1 percent vs. 4.8 percent, $P > 0.20$). The 140,460 patients who had hypothyroidism were slightly more likely to receive treatment for acute infections than the other patients (56 percent vs. 54 percent, $P < 0.001$). Apparently, these unrelated diseases were distinct enough that patients received treatment regardless of the occurrence of the corresponding chronic disease.

We selected disease and treatment pairs that were intended to be unrelated. Different pairings yielded different results and one positive association (Table 2). Patients with diabetes mellitus were more likely to receive lipid-lowering therapy than other patients, as would be anticipated because hyperglycemia is as-

TABLE 1. SUMMARY OF THE MAIN ANALYSES.

CHRONIC DISEASE AND UNRELATED TREATMENT	RELATIVE REDUCTION IN TREATMENT (95% CI)*
	percent
Diabetes mellitus and estrogen-replacement therapy	
Basic analysis	60 (57–63)
Multivariate analysis†	60 (57–63)
Stratified analysis	
Oral preparations	60 (57–63)
Transdermal preparations	55 (40–66)
1990 analysis	61 (55–66)
Pulmonary emphysema and lipid-lowering medications	
Basic analysis	31 (28–33)
Multivariate analysis‡	23 (20–26)
Stratified analysis	
Statin agents	32 (30–35)
Non-statin agents	21 (16–26)
1990 analysis	35 (29–40)
Psychotic syndromes and medical arthritis treatment	
Basic analysis	41 (38–43)
Multivariate analysis‡	38 (35–40)
Stratified analysis§	
NSAIDs	41 (39–43)
DMARDs	55 (40–66)
1990 analysis	40 (37–42)

*The relative reductions in treatment are based on odds-ratio calculations. $P < 0.001$ for all reductions. CI denotes confidence interval.

†The analysis was adjusted for age and was restricted to women.

‡The analysis was adjusted for both age and sex.

§NSAIDs denotes nonsteroidal antiinflammatory agents, and DMARDs disease-modifying antirheumatic drugs.

sociated with dyslipidemia. However, the observed relative increase of 38 percent was smaller than the relative increase of roughly 100 percent expected on the basis of some surveillance studies in epidemiology.^{15–17} Pulmonary emphysema was associated with a 29 percent relative reduction in estrogen treatment even though smoking is a risk factor for emphysema, heart disease, and osteoporosis.¹⁸ Patients with pulmonary emphysema had only a 7 percent relative reduction in medical treatment for arthritis, possibly because symptoms of lung disease are distinct from symptoms of arthritis. Patients with psychotic syndromes were consistently unlikely to receive any of the three unrelated treatments.

DISCUSSION

Our most important finding is the inverse correlation between the presence of a chronic disease and the likelihood of treatment of an unrelated disorder. In no case did the presence of the chronic disease justify withholding an effective medical treatment. The results are compatible with the theory that one disease provides protection against other diseases, but this theory is unlikely to be correct, given medical pathophysiology and shared underlying predisposing factors.^{19–22} Instead, our findings suggest a

TABLE 2. SUMMARY OF ADDITIONAL ANALYSES.*

CHRONIC DISEASE	PERCENT RECEIVING ESTROGEN-REPLACEMENT THERAPY		PERCENT RECEIVING LIPID-LOWERING MEDICATIONS		PERCENT RECEIVING MEDICAL ARTHRITIS TREATMENT	
	CHRONIC DISEASE PRESENT	CHRONIC DISEASE ABSENT	CHRONIC DISEASE PRESENT	CHRONIC DISEASE ABSENT	CHRONIC DISEASE PRESENT	CHRONIC DISEASE ABSENT
	Diabetes mellitus (n=30,669)	2.4	5.9	11.4	8.5	25
Pulmonary emphysema (n=56,779)	4.2	5.9	6.3	8.7	25	27
Psychotic syndromes (n=17,336)	1.8	5.9	2.1	8.7	18	27

*Each comparison was based on data from all 1,344,145 patients; the first diabetes mellitus comparison (2.4 vs. 5.9), for example, is based on 30,669 patients with diabetes and 1,313,476 patients without diabetes. $P < 0.001$ for all nine comparisons of the probability of treatment.

shortfall in health care — specifically, that unrelated disorders are relatively neglected in patients with chronic medical diseases.

Our work has several limitations, of which three merit emphasis. First, the study was not a randomized trial: it is not possible to assign patients randomly to have or not to have a chronic disease. Subtle confounding could contribute to and possibly justify the observed differences. However, imbalances related to age, sex, insurance status or carrier, ability to pay, or random chance would not explain the findings. Second, optimal rates of secondary treatments are controversial. In theory, our findings could be explained by postulating the overtreatment of patients who do not have chronic diseases. If true, this postulate could represent a potentially more common failure in medical decision making. Finally, the mechanism underlying the results remains a topic for future research — in particular, the question of whether the second disease is not detected in the presence of the first or whether it is detected but not treated.

The observed results might arise from several sources. Patients with chronic diseases may be exhausted and reluctant to accept multiple interventions. Clinicians are often busy and may strive to keep care simple, particularly if they do not have relatively more time for the patients with relatively more complicated conditions. A chronic disease — particularly chronic psychosis — may also limit communication between patient and doctor. Universal insurance coverage could also contribute if the implicit goal of equity is achieved by doing something for all but a lot for none. The results, however, cannot be attributed either to a tendency toward prescribing multiple medications for the elderly or to barriers in access to medical care, both of which work against finding any negative associations.²³⁻²⁵ Similarly, the results cannot be attributed to fraud in

which more than one person uses the same health insurance card.^{26,27}

Unrelated treatments are not always indicated for patients who have chronic diseases. Chronic diseases are sometimes associated with reduced life expectancy, making long-term preventive therapy unrewarding. Adding supplementary medications often increases the risk of unwanted drug interactions and the potential for an adverse event. Prescribing additional medications for an unrelated disorder might also alter a patient's compliance with essential medications and indirectly cause harm. Time constraints, communication problems, the patient's preferences, and the priorities of the specialist involved sometimes make it difficult to address more than one problem effectively in any one patient. Finally, it is often sensible to postpone minor treatments until major problems are resolved.

The unrelated treatments we chose had important implications for each selected chronic disease. Patients with diabetes mellitus are at increased risk for atherosclerosis and may be particularly likely to benefit from estrogen-replacement therapy.^{28,29} The reserve capacity of patients with pulmonary emphysema is seriously compromised, and they may be unable to tolerate even a small cardiovascular event.^{30,31} Patients with psychotic syndromes are often sensitive to discomfort and theoretically might have further worsening of their mental status as a result of joint pain.^{32,33} In all three examples, inadvertent undertreatment may have consequences. Furthermore, these examples are similar to other reported cases of mistakes in the care of patients who have more than one illness.³⁴⁻³⁶

Our findings highlight a role for clinicians who can provide a comprehensive approach to patient care. Contrary to popular opinion, such a comprehensive approach was not fully evident in the mid-1990s under the Canadian system of universal health

insurance. Primary care physicians may be suited to this role if the diversity of their practices makes them responsive to diverse issues. Yet specific training may be required to overcome fundamental pitfalls in reasoning.³⁷ Alternatively, a health care system might look for programs that ensure comprehensive care and avoid focusing solely on the management of well-defined single problems, yet minimize some failures of individual judgment. Although chronic diseases are frequent and unrelated disorders are common, the inevitable coincidences are relatively neglected in clinical practice.

Supported by a career scientist award from the Ontario Ministry of Health (to Dr. Redelmeier), a fellowship award from the Medical Research Council of Canada (to Dr. Booth), and a project grant from the Institute for Clinical Evaluative Sciences in Ontario.

We are indebted to Florence To for programming assistance and to Timothy Evans, C. David Naylor, David Sackett, Carol Schwartz, Steven Shumak, Sharon Straus, Robert Wachter, and J. Ivan Williams for helpful comments on specific points.

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