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journal homepage: www.elsevier.com/locate/cuthreA Revised Estimate of the Burden of Illness of Gout[☆]Albert Wertheimer, PhD, MBA^{1,*}, Robert Morlock, PhD², Michael A. Becker, MD³¹ Department of Pharmacy Practice, Temple University, Philadelphia, Pennsylvania² Ardea Biosciences, San Diego, California³ Department of Medicine, University of Chicago, Chicago, Illinois

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ABSTRACT

Background: Gout is a chronic, inflammatory arthritis characterized by painful and debilitating acute/episodic flares. Until recently, gout has been regarded as a minor medical problem, in part because the associated economic burden has not been appreciated. Previous literature on this subject focused on the costs associated with acute episodes of gout rather than on the long-term medical and economic implications of this chronic disorder.

Objective: Our aim was to estimate the current impact of gout in the United States with respect to disability and economic costs.

Methods: The following data sources were used: published data on the incremental economic burden of gout; statistics from the US Census Bureau and the US Bureau of Labor Statistics; and recent epidemiological and clinical literature concerning the course, treatment, and outcomes of the disease. Disability is expressed as days of lost productivity. Charges for gout-related treatments were used as direct cost inputs.

Results: Gout affects an estimated 8 million Americans, among whom those working have an average of almost 5 more absence days annually than workers without gout. On average, the incremental annual cost of care for a gout patient is estimated at > \$3000 compared with a nongouty individual. Even though comorbidities common in gout patients account for a portion of this increased economic burden, the total annual cost attributable to gout patients in the United States is likely in the tens of billions of dollars and comparable to those of other major chronic disorders, such as migraine and Parkinson's disease.

Conclusions: The economic burden of gout is most readily assessable in patients whose acute arthritic flares result in emergency department visits, bedridden days, and episodic loss of productivity. Chronic progression of the disease can also result in long-term impairment of function and health-related quality of life, but the contribution of chronic gout to the economic burden is more difficult to quantitate because gout is frequently associated with serious cardiovascular, metabolic, and renal comorbidities. Recent demonstration that successful gout management can reverse functional deficits in many chronic gout patients, however, supports the views that chronic gout contributes substantially to the medical and thus economic costs of these patients and that early and aggressive efforts to improve gout outcomes are likely to reduce the associated economic burden.

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Introduction

Gout does not readily come to mind when one mentions the most costly and feared diseases. People correctly think about cardiovascular diseases, cancer, asthma, and depression, among

others. The traditional recognition of gout as a disease of the wealthy and influential¹ has likely constrained public concern with this disorder, which, because of limited therapeutic options, has until recently also been regarded by the medical community as “unexciting.”

Recent years have, however, witnessed a re-emergence of interest in gout and its management and costs as topics important to the medical care system. Reasons for renewed interest in gout include increases in the incidence and prevalence of gout, which is now estimated to affect >8 million Americans; recognition of suboptimal long-term gout patient outcomes due, in part, to an inadequate range of therapeutic options and poor use of even these; acquisition of new knowledge about mechanisms underlying expression of the disease; and novel therapeutic initiatives

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for controlling both painful acute episodes of gouty arthritis and the potentially chronic progressive and disabling features of gout.²

These changes in the gout arena, although portending more effective therapy than has previously been available, necessarily come with costs in research, education, pharmaceutical/biological development, and delivery that deserve consideration. Assessments of the era of gout pharmacotherapy limited to generic nonsteroidal anti-inflammatory drugs, unbranded (and unapproved but nevertheless marketed) colchicine, and allopurinol have shown gaps in the effectiveness and safety delivered. The new initiatives have underscored the needs for educating providers in the optimal use of the available agents and for expediting development of new therapeutic agents. In the past 3 years, the US Food and Drug Administration has reviewed for marketing approval at least 4 new gout agents, 2 of which have been approved (febuxostat and pegloticase), thus surpassing its activity in gout for the past 45 years.

If the world of health care was a rational one, resources devoted to individual diseases would be related to their respective burdens of illness. That is not the case. As we are aware, for example, patients and their families can advocate successfully for research and investment in diseases of their specific interest. We read about campaigns to fight breast cancer or to conquer HIV/AIDS and hear public service messages about diet and exercise to prevent diabetes and heart disease, but we do not hear about gout walks, gout parades, gout day, or gout associations. Clearly, the burden of gout is less visible than that of many other medical problems. This may be because most patients affected by gout are 50 years or older, more often (but not universally) male, and afflicted at great frequency with 1 or more of the serious comorbid diseases discussed in the following. Additionally, the natural history of gout usually follows a slow course, characterized initially by acute intermittently disabling flares or attacks, which, in the absence of appropriate uric acid management, evolve to a high risk for progression to chronic pain and physical impairment and increasing economic burden. Many gout patients are thus trying to live with their gradually diminishing health-related quality of life and functional status and, in this setting of multiple illnesses, gout (like cataracts or benign prostate enlargement) is often viewed as a bothersome condition, warranting little attention in its early stages because it seems unlikely to compromise the battle for survival.

Gout is a painful and disabling inflammatory arthritis accompanied by hyperuricemia, defined as a serum uric acid (urate) level exceeding urate solubility in body fluids. Serum urate levels exceeding 6.8 mg/dL (400 μ mol/L) impart a risk for urate crystal formation and deposition in tissues, which can incite the acute inflammatory responses that characterize acute gouty arthritic attacks and chronic inflammation that support silent but massive deposition of urate crystals in a fibrous tissue background that characterizes the gouty tophus. Many individuals experiencing a first acute gout attack (40%–60%) experience a second attack within 1 year³ and increasingly frequent, prolonged, and more severe attacks occur over the years in the majority of gout patients. Tophaceous lesions develop in many untreated gout patients that can cause a chronic erosive and deforming arthritis (gouty arthropathy) and similar damage to bones, tendons, bursas, skin, and even solid organs. Recurrent gout attacks, chronic arthropathy, and tophi are, in many instances, directly responsible for chronic pain, functional impairment for work and activities of daily living, and compromised health-related quality of life. The role of gout in these severe outcomes is demonstrated by substantial improvement and/or reversal in these symptoms and signs when long-term reduction and maintenance of subsaturating serum urate levels are achieved with urate-lowering therapy.^{4,5}

The incidence and prevalence of gout have increased significantly in recent decades, especially among older patients of both sexes. Gout is now estimated to affect >8 million Americans.^{6,7}

It is important to appreciate that gout has the potential to progress, over years, from a disease of episodic acute flares to one of chronic disability (with or without persistent flares). It is also critical to recognize the distinction between medications aimed at reducing the pain and disability of acute attacks (anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs, colchicine, and corticosteroids) and those used to reverse hyperuricemia (urate-lowering agents, such as allopurinol, febuxostat, pegloticase, and uricosuric drugs). Anti-inflammatory agents do not lower urate levels, and currently available urate-lowering agents do not have anti-inflammatory properties; nevertheless, appropriate use of these 2 classes of medication (alone or in combination) is paramount in achieving the management aims of prompt alleviation of painful gout flares, prevention of flare recurrences, and prevention or reversal of disease progression. Success in achieving these aims is associated with improved quality of life and physical function.^{4,5}

It is a reasonable, although, to date, unproved, hypothesis that successful long-term management should reduce the financial burden of gout, which, as discussed in the following, is substantially greater than has been documented. That is, prevention and reversal of the symptoms and signs of gout, aims increasingly attainable in an era of renewed interest and an expanding therapeutic armamentarium, very likely will mitigate the high costs associated with poorly controlled and progressive gout.

A potential impediment to an accurate estimate of the overall financial burden of gout is the well-established association of both hyperuricemia and gout with a number of important comorbid diseases, including hypertension, cardiovascular disease, metabolic syndrome, and chronic kidney impairment. In fact, hyperuricemia and gout are established risk factors (although not necessarily causal risk factors) for these disorders, each of which carries a high disease burden for patient's physical and societal financial well-being. In this setting, it is often difficult to attribute with certainty the costs of health care in the individual to one of several coexisting diseases. It is significant, then, that in a recent study⁴ of patients with severe and advanced gout refractory to standard oral urate-lowering therapy, maintenance of serum urate levels well within the subsaturating range during treatment with a urate-lowering biological agent demonstrated significantly improved outcomes with regard to pain, physical function, and health-related quality of life, symptoms that might a priori have been attributed to their multiple associated diseases.

With this background, including the number of affected persons, the costs and capabilities of treatment regimens, the limited number of studies looking at the burden of gout and the difficulties of making precise attributions of cost, it remains appropriate to take a fresh look at the economic burden of gout, starting with what is known to date.

Methods

A literature search was conducted using PubMed, Embase, and Cochrane Reviews to identify articles pertaining to gout disease burden and associated costs of chronic gout. Records were reviewed manually to identify the most relevant studies pertaining to the objective of this article. In addition, bibliographies of retrieved articles were screened to identify additional sources of information. Estimates from the US Census Bureau and the US Bureau of Labor Statistics were used to quantify disability expressed as days of lost productivity. Charges for gout-related treatments were used as direct cost inputs.

Results

The most cited work looking at the burden of gout estimated annual gout-related treatment costs for patients newly diagnosed

with acute gout at ~\$27 million.⁸ This estimate was from data for 2002, before the availability of newer treatments and revised recommendations for the use of traditional therapies and only included incident cases of gout in men who experienced their first flare. In addition, with evidence that the incidence rate of primary gout has recently increased 2-fold over 2 decades,^{6,7} it seems likely that the costs associated with even this small subset of gout patients (reported in 2003) would be substantially greater by 2013. In a 2008 study, Wu et al⁹ controlled for confounding comorbid conditions and found that gout patients cost \$3038 more annually than patients without gout, and Khanna et al¹⁰ recently reported that the cost of medical care is as high as \$25,000 annually for each individual with severe gout (≥ 6 attacks per year) and \$18,000 per year per person with 3 acute attacks annually. In contrast, individuals without gout in this study were reported to average total health care costs of ~\$5000 per year.¹⁰

In 2002, gout was reported to account for an estimated 3.9 million annual ambulatory care visits (69% to primary care physicians and < 5% to rheumatologists).¹¹ A recent study looking at data from 2006 to 2008 found that gout-related visits accounted for 0.7% of all emergency department visits, with an annual cost in 2008 of \$166 million.¹² Data collected from 2001 to 2004 in an employed population showed that annual health care costs to employers were \$3165 higher for an employee with gout than for one without (\$6870 vs \$3705).¹² Costs were higher for medical claims, sick leave, prescription drugs, short-term disability, and workers' compensation benefits.¹³ In addition, and as described in the following, employees with gout have more absence days annually for all categories of health-related work absence than those without gout.¹⁴

Using the recently reported estimate of >8 million gout patients in the United States,⁷ the gout patient overall annual medical care costs reported by Wu et al,⁹ and the \$3165 difference between the cost of care for those patients with and without gout in 2006,¹³ the overall aggregate annual costs for the medical care of gout patients may have exceeded \$20 billion in 2006; it is clear that overall aggregate annual costs for the medical care of gout patients exceeded \$20 billion. To achieve accuracy in estimating the costs directly attributable to gout, it is, of course, necessary to adjust the annual costs for gout patient care to exclude costs incurred by comorbid diseases highly prevalent among gout patients. There is, however, no information available to determine with reliability the magnitude of this adjustment. Nevertheless, even if, conservatively, only 20% of the economic burden of gout patient care is directly associated with gout, a \$4 billion direct cost of gout-related patient care is clearly not a minor problem.

In addition, indirect costs of gout add to the burden of this disease. Lynch et al¹³ found an increasing relationship between number of gout attacks and short-term disability and absence days. Brook et al¹⁴ and Kleinman et al¹⁵ report that employed gout patients on average have almost 5 more work absence days annually than employees without gout. The US labor force consisted of 155 million persons in July 2012.¹⁶ If gout is present in 2% of workers (3.1 million persons) and each misses 5 days annually as a result of the disease, the yearly loss of wages/productivity amounts to \$833 per worker (based on 2010 data¹⁷) or an aggregate loss of \$2.6 billion. Thus, a combined provisional estimate of annual direct and indirect costs of gout patient care totals >\$6 billion. In fact, the actual disease burden is even greater when the cost and health risks of over-the-counter analgesic and anti-inflammatory drugs, the missed wages of spouses, and the need for caregivers or transport providers are added.

Discussion

For reasons given earlier, a precise figure for the economic burden of gout remains elusive; nevertheless, our minimum

estimate for annual costs exceeding \$6 billion is substantially greater than previously appreciated. The high and increasing prevalence of gout and considerable clinical impact (both direct and related to urate crystal deposition and indirect in the form of association with important comorbidities) have raised both professional and public attention to the disease and made it a significant health concern. The nature of the link of gout and hyperuricemia to important and costly other cardiovascular, metabolic, and renal diseases remains to be clarified and is an important contemporary public health concern.^{18–20}

Our provisional estimate of the economic burden of gout is based on the limited published data on the subject over several decades, publicly available health care and health economics data, and recent epidemiological and clinical evidence pertaining to disease course and prevalence, comorbid associations, and contemporary therapeutic recommendations. Key questions to be resolved are the extent to which successful control of the hyperuricemia of gout can relieve symptoms and signs of the disease and what impact such treatment may have on the course of the morbidities with which gout is associated. Answers to these questions should shed light on the important and currently uncertain issue of how much of the disabilities and costs associated with care of gout patients are directly attributable to or causally related to gout rather than to associated morbid processes. Until such questions are addressed, it is unlikely that accurate and satisfying estimates of the burden of gout illness will be achieved. Thus, we make a rather conservative estimate of the burden of gout in the hope of amplifying interest in this disease that has received little attention until the past decade.

Although we believe the provisional estimate of gout economic burden presented in this study is a reasonable and very conservative approximation and more closely describes the current situation than previously appreciated, there are some limitations to this work. We used secondary data sources incorporating several time periods. In addition, gout patients still in the work force may be underproductive or some may have left the work force altogether; as a result, the total cost of gout may be significantly higher, given the reduced productivity. As pointed out at length, distribution of costs for gout patient care to gout as opposed to comorbid diseases is not evidence based; we regard our choice to ascribe only 20% of the cost of gout patient care to gout as quite conservative; if, in fact, the proportion of costs for direct gout care is greater, then we have underestimated the financial burden of gout. Finally, we did not include costs associated with nonwork activities, the significant impact on quality of life, or the impact of rare but costly life-threatening events such as severe cutaneous reactions associated with allopurinol use.²¹

Conclusions

Patients with gout have significant direct and indirect costs associated with their disease. Urate crystal burden associated with gout results in both increasing levels of disability and attacks that significantly impair health-related quality of life and physical function. Strategies for improving patient outcomes while decreasing the economic burden of gout to managed care, employers, and insurers are desirable.

Identifiable areas where an improvement can be made to reduce costs are as follows:

- Prescribing optimal treatments for the management of acute attacks, preventive treatment for recurrent attacks, and initiating treatment for reversal of hyperuricemia in gout patients at an earlier stage of the disease than is typically done today.

- Increasing awareness of adherence with treatment because noncompliance is one of the causes of progression to chronic gout and therefore higher costs.
- Updating the efficacious use of long-available treatment strategies, such as with allopurinol, is good. However, the development of novel, highly selective therapies for controlling hyperuricemia and alleviating gouty inflammation are indicated for specific patient populations. These new therapies will be especially helpful for patients with extensive or advanced comorbidities, which often limit efficient use of traditional gout treatment.
- It is a reasonable goal to raise awareness in primary care physicians, who see most gout patients, about the newest therapies and guidelines and to increase their skills in enhancing drug-regimen compliance in their patient populations. In this way, progression of gout to more severe and costly stages might be prevented or avoided.

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All authors made substantial contributions to the conception and design of the study and the acquisition, analysis, or interpretation of data. All contributed to the intellectual content of this manuscript at each stage of preparation, and all authors have read and approved the final version.

Conflicts of Interest

The authors have indicated they have no conflicts of interest regarding the content of this article.

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