The Health Care Costs of Diabetic Peripheral Neuropathy in the U.S.

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OBJECTIVE — Peripheral neuropathy is common among people with diabetes and can result in foot ulceration and amputation. The aim of this study was to quantify the annual medical costs of peripheral neuropathy and its complications among people with type 1 and type 2 diabetes in the U.S.

RESEARCH DESIGN AND METHODS — A cost-of-illness model was used to estimate the numbers of diabetic individuals in the U.S. who have diabetic peripheral neuropathy (DPN) and/or neuropathic foot ulcers (both those with no deep infection and those accompanied by cellulitis or osteomyelitis) at a given point in time, and/or a toe, foot, or leg amputation during a year. Prevalence and incidence rates were estimated from published studies and applied to the general U.S. population. All costs were estimated in 2001 U.S. dollars. In a sensitivity analysis, we varied the rates of complications to assess the robustness of the cost estimates.

RESULTS — The annual costs of DPN and its complications in the U.S. were $0.8 billion (type 1 diabetes), $10.1 billion (type 2 diabetes), and $10.9 billion (total). After allowing for uncertainty in the point estimates of complication rates, the range of costs were between $0.3 and $1.0 billion (type 1 diabetes), $4.3b and $12.7 billion (type 2 diabetes), and $4.6 and $13.7 billion (type 1 and type 2 diabetes).

CONCLUSIONS — The total annual cost of DPN and its complications in the U.S. was estimated to be between $4.6 and $13.7 billion. Up to 27% of the direct medical cost of diabetes may be attributed to DPN.

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Diabetic peripheral neuropathy (DPN) is a particularly debilitating complication of diabetes and accounts for significant morbidity by predisposing the foot to ulceration and lower extremity amputation. It is estimated that between 12 and 50% of people with diabetes have some degree of DPN (1), which may be asymptomatic or symptomatic. Symptoms may be disabling and are manifested as "positive" symptoms, including numbness, prickling, pain (e.g., burning, lancinating, aching), or allodynia. A predominant feature of DPN is sensory loss, which may lead to foot ulceration due to even minor trauma.

Approximately 15% of people with diabetes develop at least one foot ulcer during their lifetime (2–8), and while vascular disease leading to ischemia is certainly a factor in the pathogenesis, 60–70% of diabetic foot ulcers are primarily neuropathic in origin (3). Deep foot ulcers may be accompanied by cellulitis or osteomyelitis, and a severely infected or nonhealing foot ulcer may lead to an amputation of the toe, foot, or leg.

In the U.S., the annual total direct medical and treatment cost of diabetes was estimated to be $44 billion in 1997, representing 5.8% of total personal health care expenditure in the U.S. during that year (9). The management of DPN and its complications is likely to form a large proportion of this total expenditure, because treatment is often resource intensive and long term.

The aim of this cost of illness study was to quantify the annual health care costs associated with the management of symptomatic DPN, foot ulcers, and lower-limb amputations in the U.S.

RESEARCH DESIGN AND METHODS

— A prevalence-based model was constructed to estimate the annual cost of illness and included chronic health states associated with DPN. This model was augmented with an incidence-based model and included acute events associated with the chronic health states (Fig. 1). Prevalence and incidence rates were estimated from published studies and applied to the general U.S. population.

We estimated direct treatment costs of DPN and its complications from the perspective of all health care payers. This perspective includes the total value of health care resource use regardless of who bears the cost (e.g., government, insurers, patients). Mean costs were estimated for 2001, and all results are reported in 2001 U.S. dollars ($).

Health states of clinical and economic significance and transitions between health states were informed by the epidemiology of DPN. We defined a clinically significant health state as a chronic condition or acute event that is medically recognized as being a complication of DPN. We defined an economically significant health state, in which costs are incurred in excess of those expected for a person with diabetes but without evidence of DPN.

Patients with diagnosed type 1 or type 2 diabetes may have symptomatic DPN (causing numbness or pain detected by

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Abbreviations: DPN, diabetic peripheral neuropathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

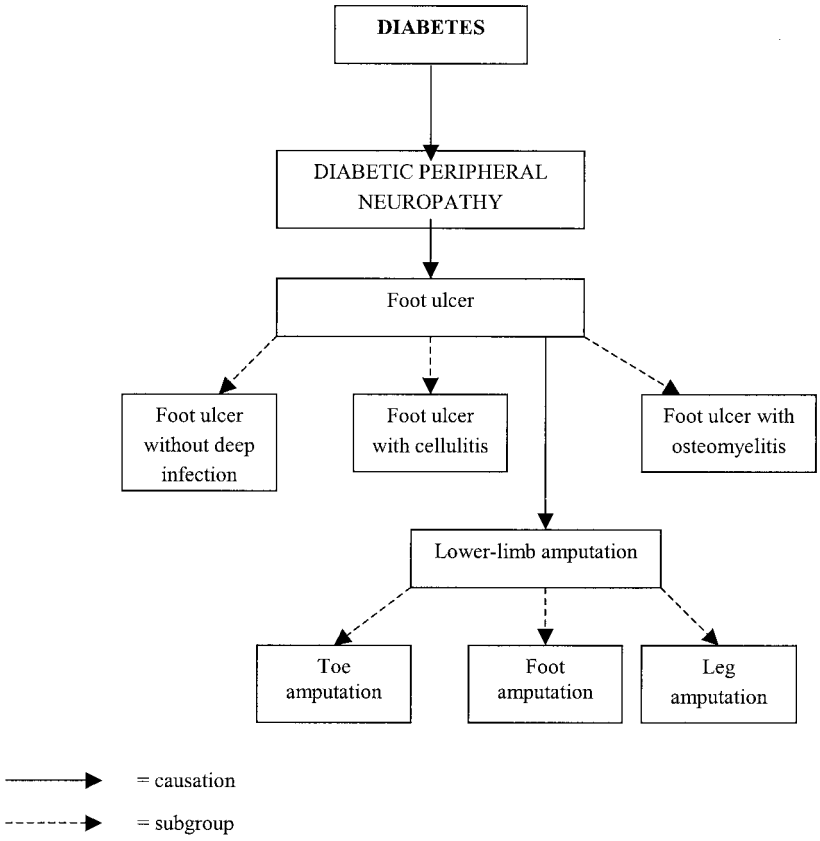

Figure 1—*Health states and transitions in the cost-of-illness model.*

the patient) or asymptomatic DPN (detected only by a diagnostic instrument). Patients with symptomatic DPN may have a foot ulcer, which may be accompanied by cellulitis or osteomyelitis. Patients with foot ulcers may require a lower-limb amputation (i.e., toe, foot, leg) during the year due to severe infection (i.e., osteomyelitis). People with undiagnosed diabetes were not included in the analysis since it is expected that complications only occur in diagnosed patients; the latest time that patients are diagnosed with diabetes is the time at which they are diagnosed with the complication.

Rates

We estimated that there are 11.1 million people in the U.S. with diabetes, a national prevalence of ~4.0% (10). The proportions of people with diabetes having type 1 (7.5%) and type 2 (92.5%) variants were estimated as the midpoints of the reported ranges (10).

Prevalence and incidence rates of complications were derived from the literature and local and national clinical databases. Foot ulcers may develop from DPN and/or ischemia, and we adjusted the prevalence of foot ulceration to include only foot ulcers that are primarily neuropathic in origin (65% of foot ulcers) (Table 1) (3).

National prevalence and incidence rates were estimated for the health states. Where data were available, rates were estimated separately for people with type 1 and type 2 diabetes. DPN and foot ulceration are longer-term conditions, and the rates of these complications are national prevalence rates. Lower-limb amputations are acute events, and the rates of these complications are national incidence rates.

The total annual costs of treating DPN and foot ulcers are estimated assuming that prevalence rates remain constant throughout a given year. Constant prevalence does not require that the same patients remain in that health state throughout the year; instead, it requires that there are the same numbers of patients in that health state at any point in time.

The products of the numbers of people with type 1 and type 2 diabetes and the national rates of complications were used to estimate the total numbers of people with diabetes who have DPN and a foot ulcer at a given point in time or who underwent an amputation during a year.

Costs

DPN and foot ulceration incur ongoing weekly costs. Mean weekly costs were the products of the mean weekly quantities of resources used and their respective unit costs. Amputations generally incur one-off costs, which were calculated as the products of the total quantities of re-

Table 1—*Rates of DPN and its complications in the U.S.*

Health state	Population	Estimated rate	References
		Prevalence	
DPN	People with diabetes	59.40% (t1) 49.00% (t2)	(13)
Neuropathic foot ulcer	People with diabetes	6.2% (t1)* 6.8% (t2)*	(3, 17)
Not infected	People with diabetes and a foot ulcer	87.4%†	(18)
With cellulitis		9.0%†	
With osteomyelitis		3.6%†	
		Incidence	
Lower-limb amputation	People with diabetes	0.6%	(3, 19)
Toe		39.0%	
Foot	Lower-limb amputations	12.0%	(20)
Leg		47.0%	

*Estimated prevalence rates of foot ulceration = 9.5% (type 1 diabetes) and 10.5% (type 2 diabetes); estimated proportion of foot ulcers being neuropathic = 65%. †Proportions of patient weeks spent in each state of ulceration. t1, type 1 diabetes; t2, type 2 diabetes.

Table 2—*Costs of DPN and its complications in the U.S.*

Health state	Estimated cost ($)	References
	Mean weekly cost	
Painful symptomatic DPN	$5.90*	(12)
Foot ulcer		
Not infected	$178.97†	(12)
With cellulitis	$472.73†	(12)
With osteomyelitis	$876.52†	(11, 12)
	Total event cost	
Amputation		
Toe	$22,702.65	(11)
Foot	$42,673.04	(11)
Leg	$51,280.94‡	(11)

Price year: 2001. *Typical weekly cost of a tricyclic antidepressant. †Gauze dressing two times a day. Mean numbers of weekly outpatient clinic attendances: 0.5 (no deep infection), one (with cellulitis), and 1.5 (with osteomyelitis). Proportions of patients receiving nurse home visits: 25% (no deep infection), 50% (with cellulitis), and 75% (with osteomyelitis). Mean numbers of weekly nurse home visits: three (no deep infection) and five (with cellulitis or osteomyelitis). Drugs received: cephalexin (500 mg four times a day; 50% of patients with no deep infection), clindamycin (300 mg three times a day; 50% of patients with no deep infection and all patients with a foot ulcer accompanied by cellulitis or osteomyelitis), and ciprofloxacin (500 mg two times a day; all patients with a foot ulcer accompanied by cellulitis, 400 mg two times a day; all patients with a foot ulcer accompanied by osteomyelitis). ‡Assumed cost of prosthetic leg: $15,000.

sources used and their respective unit costs.

The annual costs of DPN and foot ulceration are 52 times the weekly costs, multiplied by the numbers of patients in the associated health states at a given point in time. The annual costs of amputations were calculated as the products of the costs of amputations and the annual numbers of amputations. The total annual cost of managing DPN and its complications was the sum of these costs.

Management costs are presented in Table 2. Resource use was estimated from hospital episode data and clinical opinion (11). Unit costs were obtained from the Red Book, hospital episodes data, fee schedules, and, where necessary, augmented with clinical opinion (11,12).

We estimated that 14% of patients with DPN would experience mild or severe pain and we assumed that these patients would receive pharmacotherapy (13). It was assumed that patients with asymptomatic or less painful symptomatic DPN (e.g., with symptoms of numbness and tingling) would not consult their general physician and, hence, would not receive targeted therapy.

Patients with a foot ulcer may attend a primary care physician clinic for checkups and wound dressing and may receive regular nurse home visits. Proportions of patients having visits and the frequency of visits were estimated with the assistance of a clinical expert. The frequency of visits varies by factors such as the geographic region, the size of the ulcer, and the length of time that the patient has had the ulcer; we estimated mean frequencies of visits among all patients with each type of foot ulcer. We assumed that 30% of all patients would receive a pair of surgical shoes. It was estimated that 50% of patients with a foot ulcer and cellulitis and 75% of patients with a foot ulcer and osteomyelitis would be referred to secondary care for hospital inpatient treatment. The lengths of stay (cellulitis 5.2 days, osteomyelitis 8.4 days) and bed-day charges for these patients (mean total charge/mean length of stay) were estimated as the means among hospital discharges during 2000 (principal ICD-9-CM diagnosis codes 681.10 [cellulitis, toe nos], 682.6 [cellulitis of leg], 682.7 [cellulitis of foot], and 730.06 [acute osteomyelitis–l/leg]) (11).

For patients undergoing amputations, we included the costs of inpatient stay (11) and prosthetics. We assumed that 40% of foot amputees had their whole foot removed and received a prosthetic foot, and the remainder received surgical shoes following a partial foot amputation. We assumed that all leg amputees received a prosthetic leg.

Sensitivity analysis

The point estimates for parameters that are expected to have a substantial influence on the cost of illness and/or that we were least certain about were varied in a sensitivity analysis. This tests the robustness of the cost-of-illness estimates to changes in prevalence and incidence rates and uncertainty around our baseline estimates.

DPN has no clear medical definition. Therefore, different studies use different criteria in defining DPN; this has led to a wide variation in estimates of prevalence between studies. Our baseline point estimates were partly determined by the definitions used by the source study. We increased and reduced the prevalence rates of DPN by up to 50% in the sensitivity analysis.

It has been estimated that the prevalence of foot ulceration among people with diabetes in the U.K. is between 5 and 7% (14). Because it is thought that the epidemiology of diabetic foot ulceration is not substantially different between the two countries, we expected that the true U.S. prevalence rates of foot ulceration were no higher than our baseline estimates. Therefore, in the sensitivity analysis, we reduced the prevalence rates of foot ulceration by up to 50% but did not increase the rates. The proportions of foot ulcers accompanied by cellulitis or osteomyelitis were varied between 1 and 10% (i.e., the assumed minimum and maximum prevalence rates).

The literature suggests that the annual national incidence of lower-limb amputation is between 3 and 10 per 1,000 people with diabetes. Although the degree of error in our baseline rate is likely to be small, we expect that the total cost of DPN and its complications will be sensitive to small changes in the amputation rate because the associated procedure costs are high. In the sensitivity analysis, we increased and reduced the incidence rates of amputations by up to 50%, holding constant the proportions of amputations by type.

RESULTS — The estimated numbers of people with diagnosed diabetes in the U.S. were 0.83 million (type 1 diabetes), 10.27 million (type 2 diabetes), and 11.10 million in total (type 1 and type 2 diabetes combined). The total annual costs incurred by all payers in treating people with DPN and associated complications were estimated to be $0.76 billion (type 1 diabetes), $10.15 billion (type 2 diabetes), and $10.91 billion (type 1 and type 2 diabetes combined) (Table 3).

Table 3—*Annual costs of DPN and its complications in the U.S.*

Health state	Type 1 diabetes		Type 2 diabetes		All diabetes	
	Patients	Annual cost ($ millions)	Patients	Annual cost ($ millions)	Patients	Annual cost ($ millions)
Diabetes (type)*	832,500	—	10,267,500	—	11,100,000	—
DPN*	494,505	$21	5,027,995	$216	5,522,500	$237
Foot ulcer						
Not infected*	44,917	$418	612,290	$5,698	657,207	$6,116
With cellulitis*	4,632	$114	63,144	$1,552	67,776	$1,666
With osteomyelitis*	1,858	$85	25,323	$1,154	27,181	$1,239
Amputation						
Toe†	1,266	$29	15,617	$355	16,883	$383
Foot†	390	$17	4,805	$205	5,195	$222
Leg†	1,526	$78	18,820	$965	20,346	$1,043
Total annual cost	—	$761	—	$10,145	—	$10,907

*Number of patients at a given point in time; †number of new cases per year.

We estimated that 85% of the annual cost of illness is attributable to the management of longer-term complications (DPN [2%] and foot ulceration [83%]). The cost of illness is largely driven by the costs of primary and secondary care and antibiotics for patients with foot ulcers. Amputations incur mainly one-off costs, are undergone by relatively few people with diabetes, and comprise only 15% of the total annual cost of illness.

Sensitivity analysis

The total annual cost of DPN and its complications was insensitive to changes in the prevalence of DPN and quite insensitive to changes in the incidence of amputation; for every 10% variation in the incidence of amputation, the total cost varies by 1.5% (Table 4). However, the total annual cost was very sensitive to changes in the overall prevalence of foot ulceration but less sensitive to changes in the proportions of foot ulcers accompanied by cellulitis or osteomyelitis. For every 10% increase (reduction) in the prevalence of foot ulceration, the total annual cost of DPN and its complications increased (decreased) by ~8%.

The total annual cost of DPN and its complications was less sensitive to changes in the baseline proportions of foot ulcers accompanied by infections. When the proportions of foot ulcers accompanied by cellulitis and osteomyelitis were 50% lower than at baseline, the total cost of treating diabetic neuropathy complications was 9% lower. When the proportions of foot ulcers accompanied by cellulitis were adjusted to the assumed maximum (10%) and the proportions of foot ulcers accompanied by osteomyelitis were 50% higher than at baseline, the total annual cost of DPN and its complications was 5% higher.

When all parameters in the sensitivity analysis were set at their lowest rates (best scenario) or highest rates (worst scenario), the total annual cost of DPN and its complications was estimated to be ~57% lower or 26% higher than at baseline for people with type 1 diabetes, type 2 diabetes, and all diabetes combined.

CONCLUSIONS — Approximately 3.9% of people in the U.S. have been diagnosed with diabetes, and we estimated that 50% have some degree of peripheral neuropathy. In the U.S. the total annual cost of treating DPN and its complications was $10.91 billion.

We estimated that people with type 2 diabetes incur a proportional amount of this total cost. People with type 2 diabetes comprise 92.5% of all people with diabetes and account for 93.1% of the total costs of DPN. Although the prevalence of DPN was estimated to be higher among people with type 1 diabetes (59% type 1 diabetes vs. 49% type 2 diabetes), the prevalence of foot ulceration was estimated to be higher among people with type 2 diabetes (9.5% type 1 diabetes vs, 10.5% type 2 diabetes). Whereas painful symptomatic DPN incurs low costs, the management of foot ulcers is substantially more expensive.

The annual cost of DPN and its complications was very sensitive to the prevalence of foot ulceration, which incurs relatively high long-term costs. Other health states either incur long-term but relatively inexpensive costs (painful symptomatic DPN) or require treatment that is resource intensive but short term (e.g., amputations). Higher and lower rates of these complications did not affect the total costs of illness to any substantial degree.

Our baseline cost of illness ($10.91 billion) is dependent on various assumptions and subject to some uncertainty. However, the total annual cost of DPN and its complications is not expected to be >57% lower or 26% higher than the baseline estimate ($4.64–13.71 billion). Placing this in context, we estimate that up to 27% of the total annual costs of treatment for diabetes and 9% of all health care costs incurred by people with diabetes are attributable to the management of DPN and its complications (9,15,16).

We recognize there are some limitations of our analysis, most of which relate to data availability and quality. Due to a lack of reliable data, we have not included follow-up treatment for patients having undergone an amputation. Potential complications of DPN, such as falls, are less clearly attributable to the illness and were not included in the analysis; this may have underestimated the cost of illness. However, our model includes the major clinically and economically significant health states and their associated costs.

Data were obtained from local and national databases (e.g., for the rates of amputations). The accuracy of our derived estimates is dependent on the accuracy of these datasets. In national hospital

Table 4—*Results of the sensitivity analysis*

	Type 1 diabetes		Type 2 diabetes		All diabetes	
	Patients	Total annual cost ($ million)	Patients	Total annual cost ($ million)	Patients	Total annual cost ($ million)
Baseline estimate*	494,505	$761	5,027,995	$10,145	5,522,500	$10,907
Prevalence of DPN						
Low estimate	247,253	$751	2,513,997	$10,037	2,761,250	$10,788
High estimate*	741,758	$772	7,541,992	$10,253	8,283,750	$11,025
Prevalence of foot ulceration						
Low estimate	25,703	$453	317,009	$6,343	342,713	$6,796
Proportions of foot ulcers accompanied by cellulitis or osteomyelitis						
Low estimate*	514 (c)	$650	7,008 (c)	$8,624	7,522 (c)	$9,273
	514 (o)		7,008 (o)		7,522 (o)	
High estimate*	5,141 (c)	$888	70,076 (c)	$11,876	75,216 (c)	
	5,141 (o)		70,076 (o)	$11,875	75,216 (o)	$12,763
Incidence of lower-limb amputation						
Low estimate†	1,623	$700	20,022	$9,383	21,645	$10,083
High estimate†	4,870	$823	60,065	$10,908	64,935	$11,731
Scenario analysis						
Best scenario	—	$325	—	$4,312	—	$4,637
Worst scenario	—	$961	—	$12,745	—	$13,706

Total annual cost of DPN and all complications. *Number of patients at a given point in time; †number of new cases per year. c, cellulitis; o, osteomyelitis.

episode datasets, some patients' diagnoses and procedures may have been coded incorrectly. The extent of any coding inaccuracies is unknown.

Our estimates of prevalence and incidence are dependent on the quality of studies from which they are derived, and these differ with respect to study populations, settings, analytical methods, and clinical definitions. Selecting the most appropriate studies is problematic and inevitably requires trade-offs in accuracy between study factors (e.g., the appropriateness of the study sample and methods). For this reason, we performed sensitivity analyses on the least certain point estimates.

Treatment costs were based on usual practice with conservative estimates. We assumed that all patients with a foot ulcer received wound dressings, and we did not include the costs of more costly ancillary therapies such as platelet-derived growth factors and cell-based therapies. A relatively small proportion of patients may receive these therapies, and this may have underestimated the cost of illness.

Finally, we have only estimated the direct medical costs of treating DPN and its complications. However, nonmedical direct costs (i.e., travel costs) and productivity losses may be substantial for people with DPN. For example, patients may incur transport costs when attending outpatient appointments for foot ulceration treatment. Patients may require time away from work, either temporarily (e.g., during hospitalization for osteomyelitis) or permanently (e.g., following a major amputation). Friends or relatives of patients may also incur costs if they accompany the patient to treatment sessions or substitute paid employment with caring for the patient.

Regardless of these limitations, we have attempted to quantify the annual health care cost of DPN and its complications among people with diabetes in the U.S. We estimated that health care payers might incur a cost of up to $13.71 billion. Therefore, interventions that could successfully treat DPN to prevent or delay its long-term complications may save substantial health care costs in the U.S.

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