



Cost-Effectiveness of Interventions for Musculoskeletal Conditions

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BURDEN OF MUSCULOSKELETAL DISEASE

Musculoskeletal conditions are the most common cause of chronic disability around the world. The importance of musculoskeletal conditions as a cause of mortality and morbidity has been recognized by the designation of 2000–10 as the Bone and Joint Decade (Hazes and Woolf 2000) by the United Nations, World Health Organization (WHO), and more than 60 countries around the world. WHO (2003, 2004) has highlighted the burden of musculoskeletal conditions. Estimates of the global burden of these conditions have increased 25 percent over the past decade (WHO 2000). Conditions considered under this rubric include osteoarthritis (OA); inflammatory arthritis (rheumatoid arthritis and the seronegative spondyloarthropathies); back pain; musculoskeletal injuries, including sports injuries; crystal arthritis (gout and calcium pyrophosphate disease), and metabolic bone disease, principally osteoporosis (OP).

Back pain is extremely common in both industrial and developing countries, with up to 50 percent of workers suffering an episode each year. Back pain causes 0.8 million disability-adjusted life years (DALYs) each year and is a major cause of absence from work and of correspondingly high economic losses. Nearly 40 percent of back pain is due to occupational risk factors, and many of these factors can be prevented with the cooperation of labor, management, industrial engineers, ergonomists, and health workers.

OA is increasing among the world's aging populations and is the sixth leading cause of years lost because of disability globally. It accounts for nearly 3 percent of the total global years lost to disability, and 10 percent of men and 18 percent of women

over the age of 60 have OA. Table 51.1 provides an estimate of the contribution of musculoskeletal conditions to the global burden of disease, including a disaggregation by gender and between the developed and developing world. The proportions presented in the second and third panels are the most noteworthy data in table 51.1. First, the second panel shows that musculoskeletal conditions account for approximately 1.7 and 2.4 percent of the burden of disease experienced by males and females, respectively, or, across both genders, approximately 2 percent of the global burden of disease. The disaggregation by developing and developed regions, however, shows that while musculoskeletal conditions account for around 3.4 percent of the total burden of disease in the developed world, they account for 1.7 percent in the developing world. The data also show that, of the set of musculoskeletal conditions, OA accounts for the largest burden, approximately 52 percent of the total in developing regions and 61 percent in developed regions.

Table 51.2 provides a further disaggregation of the estimated burden of musculoskeletal conditions by developing region and mortality stratum. Note that the burden of disease caused by musculoskeletal conditions varies considerably by region: in Africa, mortality stratum D, musculoskeletal conditions account for less than 1 percent of the burden from all causes, while in the Western Pacific, mortality stratum B, they account for more than 3 percent of the total burden of disease. Similarly, the relative importance of rheumatoid arthritis (RA) and OA varies considerably by region. In the African regions, where the prevalence of RA is low, only 12 percent of the burden created by musculoskeletal diseases is due to RA; in the Americas, however, that proportion is approximately 24 to 27 percent.

Table 51.1 Estimated Burden of Musculoskeletal Diseases, by Gender and by Developed or Developing Regions, 2001

	Total	Males	Females	Developing regions (both genders)	Developed regions (both genders)
Numbers of DALYs (thousands)					
Rheumatoid arthritis	4,757	1,353	3,404	3,238	1,520
Osteoarthritis	16,372	6,621	9,750	11,049	5,323
Other musculoskeletal diseases	8,699	5,033	3,638	6,789	1,880
All musculoskeletal diseases	29,798	13,007	16,792	21,076	8,723
Percentage of total DALYs					
Rheumatoid arthritis	0.32	0.18	0.49	0.27	0.59
Osteoarthritis	1.12	0.86	1.39	0.91	2.05
Other musculoskeletal diseases	0.59	0.65	0.52	0.56	0.73
All musculoskeletal diseases	2.03	1.69	2.40	1.74	3.37
Percentage of musculoskeletal DALYs					
Rheumatoid arthritis	15.96	10.40	20.27	15.36	17.42
Osteoarthritis	54.94	50.91	58.07	52.43	61.02
Other musculoskeletal diseases	29.10	38.69	21.66	32.21	21.56

Source: Calculated from WHO (2004).

Note: Totals may not sum due to rounding.

Table 51.2 Estimated Burden of Musculoskeletal Conditions by Region and Mortality Stratum, Selected WHO Regions, 2001

Condition	Africa		Americas		Southeast Asia		Eastern Mediterranean		Western Pacific
	D	E	B	D	B	D	B	D	B
Numbers DALYs (thousands)									
Rheumatoid arthritis	127	141	532	83	117	855	99	218	1,065
Osteoarthritis	625	687	969	117	931	2,474	227	577	4,442
Other musculoskeletal diseases	285	316	677	107	516	1,756	159	408	2,590
All musculoskeletal diseases	1,037	1,144	2,178	307	1,564	5,085	485	1,203	8,097
Percentage of total DALYs									
Rheumatoid arthritis	0.09	0.07	0.66	0.47	0.19	0.24	0.43	0.19	0.44
Osteoarthritis	0.42	0.33	1.19	0.67	1.52	0.69	0.99	0.51	1.84
Other musculoskeletal diseases	0.19	0.15	0.83	0.60	0.84	0.49	0.69	0.36	1.06
All musculoskeletal diseases	0.70	0.55	2.68	1.74	2.55	1.42	2.11	1.06	3.34
Percentage of musculoskeletal DALYs									
Rheumatoid arthritis	12.28	12.29	24.45	27.23	7.50	16.82	20.38	18.11	13.19
Osteoarthritis	60.27	60.10	44.49	38.50	59.51	48.66	46.90	47.97	54.99
Other musculoskeletal diseases	27.44	27.61	31.06	34.27	32.99	34.53	32.71	33.92	31.82

Source: Calculated from WHO (2004).

Notes: The letters in the column heads refer to mortality strata. B = low child and low adult mortality, D = high child and high adult mortality, E = high child and very high adult mortality.

RA has a prevalence of 0.7 to 0.1 percent worldwide and results in significant work disability and long-term treatment costs. In addition, OP is increasing with the aging of populations: one in three people over the age of 50 suffers a fracture

because of OP. Back pain, OA, trauma, and RA account for 32,948,765 DALYs, or 2.15 percent of the global total for 2000.

A recent review of the prevalence of rheumatic disorders in Sub-Saharan Africa suggests that the frequency of RA is

increasing in East, Central, and South Africa but is rare in West Africa (McGill and Oyoo 2002). Gout is also prevalent throughout the continent, and the HIV epidemic has spawned a variety of associated spondyloarthropathies among the aging population. Countries such as Thailand are also recognizing an increasing burden of disease caused by arthritis and trauma (Jitapunkul and others 2003).

NATURE, CAUSES, AND EPIDEMIOLOGY OF MUSCULOSKELETAL CONDITIONS

Osteoarthritis is the most common condition affecting human joints and causes significant disability. The principal clinical features are pain, which varies in severity and character, and stiffness. Disability occurs as a result of pain, weakness, joint instability, and reduced range of motion.

The following are the major forms of inflammatory arthritis:

- rheumatoid arthritis
- seronegative spondyloarthropathies
 - ankylosing spondylitis
 - reactive arthritis
 - enteropathic arthritis
 - psoriatic arthritis
- juvenile chronic arthritis
 - systemic
 - pauciarticular
 - polyarticular
- arthritis associated with systemic connective tissue diseases
 - systemic lupus erythematosus
 - progressive systemic sclerosis
 - vasculitis
 - polydermatomyositis
- crystal arthritis
 - gout
 - calcium pyrophosphate deposition disease

RA has a prevalence of between 1 and 3 percent in most countries for which figures are available, but it may be slightly less common in tropical countries. The exact etiology of RA is unknown, but the evidence suggests an immune reaction, and it presents as an inflammation affecting joints and other tissues. Its clinical features can be divided into three groups: constitutional, articular, and extra-articular. Constitutional features involve tiredness, fatigue, weight loss, and fever, and articular features involve principally the synovial joints, producing pain and eventual deformity and disability.

The seronegative spondyloarthropathies are primarily inflammatory arthropathies and share several common features, including familial aggregation, asymmetric joint involvement,

and mucocutaneous lesions. These conditions may follow gastrointestinal or sexually acquired infections and can be associated with HIV. Gout and other forms of crystal arthritis tend to present as an inflammatory response to the presence of uric acid (gout) or various calcium crystals (chondrocalcinosis).

Much of the pain that produces complaints and reduced function does not emanate from a frank arthropathy, but from the soft tissues in or around a joint. When these pains are confined to a particular area of the body's surface, they can be referred to as regional pain syndromes and may or may not be related to injury or overuse. If these pains are more widespread and are associated with specific tender points, the condition is known as fibromyalgia. Fibromyalgia is well recognized in the industrial world and has also been noted in China and Malaysia and among Tamil Indians.

The major causes of infectious arthritis can be viral, bacterial, fungal, or helminthic. Each can present as either a polyarticular presentation or a monoarthritis. Many of the helminthic infections present with more generalized aches and pains and involvement of muscle tissues as well as joints. All the conditions have specific diagnostic features and treatments.

OP is characterized by low bone mass and deterioration in the microarchitecture of the bone, which leads to fracture after low or moderate trauma. The condition is defined by diagnostic criteria based on bone mineral density as follows: a bone mineral density of more than -2.5 standard deviations below the average bone mineral density of young adult women.

The clinical features of OP are primarily due to its major outcome: fracture. The most important fractures occur in the distal radius, vertebrae, or hip, often following minor trauma. Vertebral fractures lead to loss of height, kyphosis, and back pain. The incidence of fracture varies with country and with type of fracture. Hip fractures are low in African countries but high and increasingly reported in Australasia, Europe, and North America. Fracture risk increases with age and is beginning to have a significant impact on quality of life, mortality, and health care costs in many countries.

Rickets is caused by a mineralization defect of newly formed bone in the growing skeleton. This defect leads to an increase in the amount of nonmineralized bone tissue (osteoid) and a thinning of the growth plates. This condition produces bone pain, bone deformation, swelling of the joints, and growth retardation. Rickets is primarily caused by a lack of exposure to sunshine because of climate, pollution, or overuse of clothing or sunscreens. Rickets is relatively rare in industrial countries, but it does occur as a consequence of dietary deficiency or excess clothing.

Osteomalacia is the adult equivalent of rickets. It is similarly characterized by an increase in osteoid tissue and causes bone pain and fractures. It occurs primarily in the elderly in Europe and North America because of a lack of exposure to sunshine that is not compensated for by adequate vitamin D intake.

Osteomalacia may also occur in countries with abundant sunshine where clothing prevents sun exposure. Osteomalacia is commonly reported among migrants to Western Europe from India and the Middle East.

Back pain accounts for the majority of musculoskeletal disease presentations to health professionals, and its lifetime prevalence exceeds 80 percent in most industrial countries. *Spinal disorder* refers to a wide range of specific and nonspecific musculoskeletal disorders affecting the spinal column. These conditions include congenital lesions such as scoliosis, infective problems such as osteomyelitis and neoplastic disorder (myeloma or secondary cancers), and trauma and referred back pain.

The majority of individuals with acute back pain will improve significantly over a six-week period, although in many cases the pain may recur. Early diagnosis and treatment, particularly of pain, by means of a modified exercise program will reduce long-term morbidity and disability.

Musculoskeletal injuries are extremely common, whether in the workplace or associated with sporting activities or with daily living. Motor vehicle trauma, household accidents, and occupational accidents occur frequently and are a major cause of damage to the musculoskeletal system.

Table 51.3 shows the major genetic and environmental risk factors for musculoskeletal diseases. Lack of exercise and obesity are major contributors to soft tissue disorders, OA, and back pain. Infectious forms of musculoskeletal disease depend on the environment and on the types of organisms that are prevalent.

Table 51.3 Risk Factors for Musculoskeletal Disease

Condition	Genetic	Environmental
Rheumatoid arthritis	HLA DR	
Seronegative spondyloarthropathy	HLA B ₂₇	
Osteoarthritis	Severe osteochondropathies	Obesity Lack of exercise
Soft tissue		Occupation Environment
Crystal arthritis	Congenital (Lesch Nyhan)	Obesity Nutrition
Infectious		Environment
Osteoporosis		Lack of exercise Nutrition
Metabolic bone disease		Environment Nutrition
Back pain		Obesity Occupation Lack of exercise
Trauma		Environment

PREVENTIVE STRATEGIES

Obesity brought about by increases in sedentary lifestyles and changes in eating patterns is becoming a major problem worldwide. Weight reduction has been demonstrated to reduce pain and disability from OA of the knee and other forms of lower limb arthropathy. In OA of the knee, weight reduction will not only reduce pain and improve mobility, but it can put off the time when surgical replacement of the weight-bearing joint is necessary. Obesity can also be associated with back pain, and weight reduction is an important factor in reducing the recurrence of episodes of back pain and in reducing long-term disability and chronic pain.

Smoking and excessive alcohol use are also associated with OP. Adequate calcium intake (1,000 to 1,500 milligrams per day) has been shown to maintain bone density and reduce the risk of axial (vertebral) fractures. Smoking also increases the risk of developing RA.

Weight reduction and diet are also important considerations in the management of gout. Appropriate nutrition and exercise underpin many of the preventive and treatment strategies for musculoskeletal disease.

TREATMENTS

A range of treatment approaches is available to address the multiple aspects of musculoskeletal disorders.

Symptomatic Treatments

Symptomatic treatments for musculoskeletal disease principally involve pain reduction. Nonpharmacological treatments such as massage, heat, and ice, and physiotherapeutic techniques such as ultrasound may be useful in the short term. Pure analgesic agents such as acetaminophen should be tried initially; if no response occurs, compound analgesics or opioid derivatives, including codeine, may be useful. The side effects of the latter compounds are significant, particularly in the elderly, with constipation and disorientation being the most common. Table 51.4 shows the principal modalities of pain relief for arthritis and soft tissue rheumatism. In many countries, complementary medicines (traditional medicines) are also used extensively, particularly for the management of pain. These compounds remain unproven, and clinical studies to explore their worth should be encouraged.

Recent years have seen the introduction of a number of specific antiosteoarthritic agents, including glucosamine, chondroitin sulfate, soybean extract, and injectable hyaluronic acid derivatives. Clinical trials have demonstrated that glucosamine and chondroitin sulfate are beneficial in terms of pain reduction in patients with OA, but the effects are relatively small.

Table 51.4 Treatment for Arthritis

Category	Analgesics	Specific antiosteoarthritis agents	Nonsteroidal anti-inflammatory drugs	Disease-modifying antirheumatic drugs
Pharmacological treatments	Acetaminophen Compound analgesics Codeine Opioid derivatives	Glucosamine Avocado extract Soybean Chondroitin sulfate Diacerein Hyaluronic acid (injectable)	Nonspecific NSAIDs Selective COX-1 sparing agents	Chloroquine Hydroxychloroquine Sulfasalazine Gold D-penicillamine Methotrexate Azathioprine Cyclophosphamide Leflunomide Cyclosporine A Corticosteroids Minocycline Biologics: Antitumor necrosis factor Anti-interleukin-1 receptor antagonist
Nonpharmacological treatments	Massage Heat Ice Ultrasound	n.a.	n.a.	n.a.

Source: Authors.
n.a. = not applicable

Many cases of OA and soft-tissue rheumatism and most cases of the inflammatory forms of arthritis will require an anti-inflammatory drug as well as or instead of a pure analgesic. The nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay for treating arthritic conditions for nearly a century. More recently, concern about the adverse gastrointestinal side effects of NSAIDs led to the development of COX-1 (cyclooxygenase-1) sparing agents. These agents have similar effects on pain relief but a reduced incidence of gastrointestinal side effects, although they may produce adverse events in the renal and cardiovascular systems, such as hypertension, decreased renal function, and increased stroke and heart attacks.

Rheumatoid Arthritis

The medical community now appreciates the importance of early diagnosis and treatment of RA. All patients with RA should be started on a specific antirheumatic drug on diagnosis. These drugs have been shown to be efficacious in randomized controlled trials (Gabriel, Coyle, and Moreland 2001), but each has a quite different spectrum of adverse side effects. Even with the new biologic agents, few patients with RA actually go into complete remission, and disease activity continues despite a reduction in endpoints, such as the number of painful and swollen joints, function impairment, and pain. Most patients with RA now receive combinations of antirheumatic drugs, the

most common being methotrexate, hydroxychloroquine, and sulfasalazine. Corticosteroids are also used intermittently in many cases. Patients with RA also need to receive information about exercise programs and education on activities of daily living so that they can make informed choices in relation to their therapies.

Osteoporosis

A number of therapies are available for OP, including calcitonin, calcium, bisphosphonates, hormone replacement therapy (HRT), and selective estrogen receptor modifiers. Clinical trial data support the use of HRT, bisphosphonates, selective estrogen receptor modifiers, calcitonin, vitamin D and calcium supplementation, and calcitriol in reducing fracture rates in high-risk patients. Calcium and vitamin D supplementation are recommended to reduce hip fractures among the elderly living in assisted living accommodations and nursing homes. The recommended daily requirement for calcium varies significantly between countries—for example, from 1,000 milligrams per day in the United States to less than 500 milligrams per day in India. Recommended levels of vitamin D supplementation range from 500 to 1,000 international units per day, particularly for at-risk aging females. In addition to these pharmacological interventions, attention to risk factors for falling is also important.

Surgical treatments vary, from the use of external splints for fractures, to interventions such as arthroscopy, internal fixation for complicated fractures, and insertion of prosthetic devices, most commonly total hip and knee replacements. Biomaterials are increasingly being used to repair bone or cartilage defects in younger patients, particularly those with sporting or other traumatic injuries.

Rehabilitation treatments include a range of activities, from single discipline interventions such as physiotherapy to multi-disciplinary programs, particularly for complex problems such as back pain.

ECONOMIC ISSUES

An economic discussion of health policies designed to prevent, treat, and manage musculoskeletal conditions in developing countries is inherently difficult for a variety of reasons, but primarily because of the lack of both epidemiological and cost-effectiveness data for most developing countries. Some progress has been made by Symmons, Mathers, and Pflieger (2004a, 2004b), who provide incidence estimates for OA and RA from epidemiological data on prevalence and relative mortality risks, although data from many areas are scant.

Perhaps a more important constraint on economic evaluations in this field is the surprising number of interventions for which trial data on efficacy are inadequate. Another issue, currently the target of a concerted effort to improve practice in the field, is the lack of cross-study comparability of the results of economic evaluations of interventions for OA, RA, and OP. One of the most important variables is the choice of comparator used to assess the cost-effectiveness of interventions.

The Outcome Measures in Rheumatology Clinical Trials Economics Working Group, which was established in 1996, has made some progress toward redressing this problem. In principle, the relevant comparator is generally the next-best alternative or alternatives to the intervention of interest. The choice of comparator is especially important for cost-effectiveness analysis, because cost-effectiveness is a relative, not an absolute, concept; whether a particular intervention is considered efficient depends on the efficiency of other interventions and on budget constraints. This issue is a fundamental one, because a great many health sector innovations involve new ways of producing desirable effects with existing technology. The relevant consideration in such cases is the additional benefits that the innovation is expected to confer and the relative cost of achieving those benefits. In such circumstances, the computation of incremental cost-effectiveness ratios (ICERs) on the basis of a no-treatment alternative is of limited use, unless that scenario is genuinely under consideration. Unfortunately, the no-treatment (or, more accurately, the placebo treatment) option is precisely the comparator that much of the literature has used.

Another characteristic of economic evaluations in this field is that they have been performed almost entirely for developed countries. In the sections that follow, we discuss the steps we have taken in an attempt to minimize the adverse consequences of reliance on the literature for developed countries. Nevertheless, the pragmatic approach that we have adopted is subject to some important limitations and caveats.

Cost-effectiveness is a relative concept, in the sense that cost-effectiveness ratios (CERs) are useful only for comparing alternative ways of achieving a desired outcome—for instance, improving the quality and length of life. Assertions that an intervention is, in its own right, cost-effective are usually based on the notion that a particular CER represents a cutoff between those interventions that are efficient and those that are not. Thresholds of this kind involve an assumption about the value of life—for example, that a quality-adjusted life year (QALY) is worth US\$30,000. Nevertheless, the literature routinely uses cost-effectiveness rules that are based on thresholds without the theoretically necessary explicit consideration of implicit budget constraints.

We have tried to avoid using a threshold type of approach in relation to the discussion of cost-effectiveness. Instead, we critically reviewed the cost-effectiveness literature in rheumatology to provide an indication of the relative costs and consequences of available interventions. In some cases, an intervention appears to be inefficient because it costs more and produces fewer benefits than a competing alternative or because two interventions produce identical effects but one costs less than the other. Nevertheless, we have provided a summary of our views—for ease of reference—as table 51.5. This table summarizes our thoughts on the weight of the current effectiveness and cost-effectiveness evidence and the likelihood that developing countries might realistically consider each intervention. For the reasons given above, though, we have articulated the evidence in more detail in the text.

Cross-country differences in the epidemiology of conditions of interest, the age structure of populations, and the access to health care, along with differences in relative prices, are liable to affect the cost-effectiveness of any given intervention. Some of the substantive gaps between the developed and developing worlds may compound the problem. For example, if the price of labor relative to that of capital is consistently lower in the developing countries, capital-intensive interventions may be relatively less attractive than they are in the developed countries, especially if labor-intensive alternatives exist.

To improve comparability across the literature, we adjusted reported CERs by converting them to 2001 U.S. dollar prices (therefore, those we report generally differ from those the original authors cite). Generally, we adjusted outcomes to U.S. dollars for studies outside the United States that reported CERs in local currencies using the official exchange rate in effect at that time, but wherever such studies reported only U.S. dollar

Table 51.5 Summary of the Economic Evaluation of Interventions for Musculoskeletal Conditions

Conditions and treatment options	Considered cost-effective in developed countries? ^a	Generally recommended for developing countries? ^b	References	Additional comments
<i>Osteoporosis</i>				
Primary prevention				
Physical activity	No	Yes (for low-cost interventions)	Katzmarzyk Gledhill, and Shephard 2000; Geelhoed, Harris, and Prince 1994; Patrick and others 2001	Based on consensus
Calcium plus vitamin D	Yes	Yes	Willis 2002	
HRT	Yes	—	Geelhoed, Harris, and Prince 1994; Armstrong and others 2001; Kanis and others 2002	
Raloxifene	No	No	Armstrong and others 2001; Kanis and others 2002	Based on evidence
Secondary prevention				
Screening	No	No	Norlund 1996	
Calcium and calcium plus vitamin D	Yes	Yes	Kanis and others 2002	
HRT	Yes	Yes	Fleurence, Torgerson, and Reid 2002; Kanis and others 2002	Differences in life expectancy and incidence of OP will affect age at which recommended
Raloxifene	No	No	Kanis and others 2002	
Calcitonin, alendronate, and biphosphonates	No	No	Coyle and others 2001; Kanis and others 2002	
Fluoride	No	No	Kanis and others 2002	
Alfacalcidol	No	No	Kanis and others 2002	More randomized clinic trials needed
<i>Osteoarthritis</i>				
Primary prevention	No evidence	Yes		Based on consensus
Secondary prevention				
Education program	No	Further research needed	Lord and others 1999	
Exercise program	No evidence	Low-cost programs may be useful	Patrick and others 2001	
Nonselective NSAIDs	No for nabumetone		McCabe and others 1998	
Gastroprotective agents	Yes, but several qualifiers		Van Dieten and others 2000; Gabriel, Campion, and O'Fallon 1994	
Synovial fluid replacement	Yes	No	Torrance and others 2002	Different comparators, relative price
Tertiary interventions				
Total hip arthroplasty	Yes	—	Chang, Pellissier, and Hazen 1996	
Knee replacement	Yes	—	Segal and others 2004	
<i>Rheumatoid arthritis</i>				
Inpatient or outpatient	No evidence	—		
Telephone help line	Yes	Yes	Nordstrom and others 1996; Hughes and others 2002	With good communications and low levels of access to medical care

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Table 51.5 Continued

Conditions and treatment options	Considered cost-effective in developed countries? ^a	Generally recommended for developing countries? ^b	References	Additional comments
<i>Disease-modifying antirheumatic drugs</i>				
Auranofin	Not effective	No	Thompson and others 1988	
Cyclosporine, azathioprine, D-penicillamine	Equal efficacy; cyclosporine should be used after cheaper, more effective drugs	No	Anis and others 1996	Cost, monitoring, and adverse events
Combination therapy	Yes, in some studies	Possibly	Verhoeven and others 1998	
Biologics	No data	No	—	Need trials in developing countries, but current costs are prohibitive
Corticosteroids	Yes	Possibly	Bae and others 2003	Side effects
<i>Low back pain</i>				
Back schools	No evidence	No	Van Tulder 2003	
Massage	Little evidence	Yes, if low cost	Furlan and others 2002	
Early interventions	Yes	Yes	Gatchel and others 2003	Depends on labor market conditions
<i>Ankylosing spondylitis</i>				
Spa exercise	Yes, but ICERs were sensitive to indirect costs	No	Van Tubergen and others 2002	Does not provide compelling evidence
Biologics	No	No	—	Unattractive because of their high price

Source: Authors.

n.a. = not available.

a. Based on a cost-effectiveness threshold value of approximately US\$30,000 or other favorable quantitative data on costs and benefits.

b. Based on authors' judgment of generally favorable/unfavorable cost-effectiveness evidence. See text for precise cost-effectiveness (for example, cost per QALY) data.

equivalents, we took these as given. Finally, we used the U.S. Bureau of Labor Statistics consumer price index data for 2004 to inflate (deflate) the U.S. dollar CERs to 2001 prices. Thus, unless otherwise stated, all price data are expressed in 2001 U.S. dollars.

For clarity, we have classified cost-effectiveness results by condition and also according to whether the intervention constitutes a primary, secondary, or tertiary intervention. The exception is RA, for which the management protocols are less amenable to this type of abstraction. For RA, we found that categorizing the evidence according to a taxonomy that is problem or intervention based was more useful.

Primary Interventions

This section reviews the evidence on the cost-effectiveness of interventions designed to prevent the onset of OP. The works surveyed analyzed interventions in healthy people, primarily

perimenopausal and postmenopausal women, with no established history of OP.

Physical Activity. The prophylactic effects of physical activity are generally well appreciated, and a large proportion of preventable disease is sometimes attributed to sedentary lifestyles. Katzmarzyk, Gledhill, and Shephard (2000) estimate the relative risks for those who are inactive compared with those who are physically active for a range of conditions, including OP. Their results for Canada suggest mean OP relative risk factors of 1.56 to 1.90 for sedentary versus active women, depending on race, and indicate that the population-attributable fraction of OP caused by inactivity was approximately 27 percent and accounted for more than 16 percent of the direct economic costs of physical inactivity.

The effectiveness and cost-effectiveness of programs intended to encourage lifestyle changes are generally not well established. Geelhoed, Harris, and Prince (1994) consider the

effect of an intervention in Australia involving exercise and calcium supplements for healthy postmenopausal women to prevent osteoporotic fractures. They find that the cost of the intervention was US\$96,119 per QALY; however, note that the authors assumed no toxic effect of the lifestyle regimen on diseases other than OP.

Calcium Plus Vitamin D. Willis (2002) analyzes the cost-effectiveness of administering calcium plus vitamin D₃ to healthy postmenopausal women in Sweden and demonstrates that this intervention is a cost-saving one for 50-, 60-, and 70-year-old women with a maternal family history of hip fracture and for 60- and 70-year-old women with either a history of fragility fractures or a smoking habit. In developing regions, calcium plus vitamin D therapy may be a cost-effective or cost-saving intervention if targeted at older, asymptomatic women with maternal histories of hip and other fragility fractures—especially those who smoke. A targeted strategy of this kind is likely to be the most cost-effective in regions where environmental uptake of these elements is limited for dietary or other reasons.

Hormone Replacement Therapy. Geelhoed, Harris, and Prince's (1994) cost-effectiveness analysis of interventions in a hypothetical cohort of 100,000 healthy postmenopausal women includes several HRT strategies: (a) estrogen from age 50 for life, (b) estrogen from age 50 for 15 years, and (c) estrogen from age 65 for life. Compared with a no-therapy alternative, the cost per QALY was US\$8,609 for strategy c, US\$13,268 for strategy a, and US\$30,183 for strategy b.

Armstrong and others (2001) compare HRT with a no-therapy scenario in healthy postmenopausal women and examine how the risks of breast cancer and coronary heart disease (CHD) might influence the cost-effectiveness of the interventions over 5- and 10-year periods, as well as a lifetime intervention of approximately 31 years. They report a relatively low cost per QALY of US\$2,238 to US\$2,850 for women at a 10 to 15 percent risk of breast cancer. The cost-effectiveness of HRT fell as the risk of breast cancer increased.

Both the base cases in these studies assume that HRT reduces hip fracture rates, and Armstrong and others (2001) also assume reductions in CHD. These constitute important assumptions because, as Kanis and others (2002) point out, data from randomized clinical trials (RCTs) support the hypothesis of no effect of HRT on either appendicular fractures or CHD. Thus, the ICERs reported by both the studies may either understate or overstate the true cost per QALY produced by using HRT as a primary prevention.

Raloxifene. Armstrong and others' (2001) study also includes a cost-effectiveness analysis of raloxifene use (compared with HRT and no intervention) in healthy postmenopausal women. Their results indicate that, by comparison with raloxifene, HRT

is a dominant long-term therapy for U.S. women at average risk (in this case, a 10 percent lifetime risk) of breast cancer: the 5- and 10-year period ICERs were US\$37,620 and US\$33,472 per QALY, respectively. For women at a 30 percent or higher risk of breast cancer, the ICER for raloxifene versus HRT was less than US\$4,160, and decreased with risk.

Kanis and others (2002) argue that existing evidence on raloxifene suggests that it has no significant effect on either appendicular fractures or CHD. On the basis of the existing cost-effectiveness evidence, the use of raloxifene as a prophylactic intervention for OP in the developing regions has little to recommend it.

Secondary Interventions

The following studies were concerned with interventions in people with some indication of OP, either from a bone mineral density assessment or a fracture. Some of the general studies include Jönsson and others' (1999) study based on Swedish epidemiological data. The authors consider two different levels of intervention costs, those associated with HRT and those associated with HRT plus bisphosphonates, and find that the higher-cost intervention (HRT plus bisphosphonates therapy) was dominant for the 80-year-old group modeled. In the context of developing countries, note both the relatively higher incidence of osteoporotic fractures among 80-year-olds and the relatively larger size of this demographic group in Sweden.

Screening. Norlund (1996) conducted a cost-benefit analysis of fracture prevention in osteoporotic women age 50 to 54 in Sweden, assuming 70 percent participation in the screening program and an offer of HRT with 30 percent acceptance. The study provides evidence of a negative net benefit, indicating that the costs of a population screening program of this kind exceed its benefits. Thus, population-based bone mineral density screening programs aimed at perimenopausal or postmenopausal women are likely to be a poor use of health resources in the developing world.

Calcium and Calcium Plus Vitamin D. Citing trial evidence, Kanis and others (2002) assume that calcium supplements alone reduce only vertebral fracture risks in women with established OP. Assuming a compliance rate of 70 percent, the authors find that the intervention's cost per QALY for 50-, 60-, 70-, and 80-year-old cohorts were approximately US\$64,995, US\$31,548, US\$10,271, and US\$10,527, respectively. They also examine the cost-effectiveness of calcium plus vitamin D on the basis of trial evidence that this combination also reduces appendicular fractures. Assuming a 70 percent compliance rate, they find that calcium plus vitamin D was cost saving in 80-year-olds and either cost saving or a low-cost intervention (mean cost per QALY of US\$584) in 70-year-olds. For 50- and

60-year-olds, the mean costs per QALY were US\$29,357 and US\$13,730, respectively. Thus, in developing regions, calcium plus vitamin D therapy may be an attractive investment for elderly women with established OP.

Hormone Replacement Therapy. Fleurence, Torgerson, and Reid (2002) demonstrate an ICER of US\$12,800 to US\$19,700 for HRT for their Scottish sample. Kanis and others (2002) show that while HRT was generally a dominant therapy for 80-year-olds, with a cost per QALY of US\$4,527, it was an expensive therapy for 50-year-olds at a cost per QALY of US\$42,940. These results suggest that HRT is likely to be an attractive intervention for established OP for some age groups in the developing regions. Differences in life expectancy and the underlying incidence of OP will, however, have a considerable bearing on the age at which HRT interventions may be considered desirable in each region.

Raloxifene. Kanis and others (2002) find that the cost per QALY associated with raloxifene was approximately US\$835,622 in 50-year-olds, and although this cost generally fell with age, it remains an expensive intervention. Raloxifene therapy is not an attractive investment for the developing regions.

Calcitonin and Bisphosphonates. The cost-effectiveness evidence on nasal calcitonin is unambiguous. It is a particularly expensive intervention and represents an unattractive investment of health care resources even in wealthy developed countries. The most favorable cost-effectiveness results for nasal calcitonin come from a study by Coyle and others (2001), who find that both calcitonin and alendronate reduced wrist, hip, and vertebral fractures in postmenopausal women but that etidronate had no such effect on hip and wrist fractures. The ICERs for nasal calcitonin for 65-year-old women for five years of therapy were US\$34,166 per QALY compared with no therapy and US\$23,952 per QALY compared with etidronate. The results of this study were sensitive to the underlying fracture rate.

Kanis and others (2002, iv) also conclude that calcitonin is “not cost-effective at any age largely because of its costs.” Indeed, their estimates of costs per QALY for 70- and 80-year-old women, the groups for which the intervention is most cost-effective, equate to approximately US\$245,373 and US\$181,109, respectively. By contrast, both alendronate and etidronate were dominating interventions for 80-year-olds. At current prices, calcitonin therapy is not an attractive investment for the developing regions.

Fluoride. Kanis and others (2002) find that fluoride was generally a dominant intervention in women with established OP, because it appears to decrease the risk of vertebral fracture but to increase the risk of hip fracture, although the latter result is

statistically insignificant. When they assume that fluoride has a neutral effect on hip fractures, the authors find that the cost per QALY was in the acceptable range for interventions in the United Kingdom—that is, less than US\$46,684. Fluoride is unlikely to be a desirable intervention for preventing OP in developing countries.

Alfacalcidol. Kanis and others (2002) report wide confidence intervals on the cost per QALY of an alfacalcidol intervention. This result is largely due to substantial variation in the apparent vertebral, hip, and humeral fracture risk available from RCTs. Thus, alfacalcidol does not appear to be a good investment for developing economies; however, additional RCTs are required to reduce the uncertainty regarding the cost-effectiveness of this intervention.

COST-EFFECTIVENESS OF INTERVENTIONS FOR OA

Primary Interventions

Despite clear evidence of an association of OA with obesity and of a reduction in symptoms and progression of the disease with weight reduction, no formal studies of the cost-effectiveness of this intervention are available.

Secondary Interventions

Patient education programs, exercise programs, medications, and synovial fluid replacement have demonstrated varying levels of cost-effectiveness.

Education Programs. Lord and others (1999) evaluated the cost-effectiveness of a nurse-led education program for patients with OA of the knee in the United Kingdom, using usual care as the comparator. They found that the costs for the intervention group were greater than for the control group, but that the outcomes for the two groups were not statistically different.

The cost-effectiveness of education programs for OA patients in the developing countries is unknown. Education programs will be subject to diminishing returns, and their marginal effectiveness may depend directly on the basic level of education of those targeted. Though the scant evidence presented here suggests that education programs may not be cost-effective, further research on their effectiveness and cost-effectiveness in developing countries is required.

Exercise Programs. Patrick and others (2001) analyzed the cost-effectiveness of an aquatic exercise program for the management of OA and compare it with usual care. The study involved a 20-week randomized trial of aquatic classes for 249

adults age 55 to 75 with a confirmed diagnosis of OA. The results were generally unfavorable. In many cases (24 percent of the bootstrapped estimates), the exercise program was dominated by usual care, and the 95 percent confidence interval ranged from dominated to US\$498,700 per QALY gained.

Evidence of the cost-effectiveness of exercise programs for established OA is currently meager. Nevertheless, as part of a diversified portfolio, low-cost exercise programs may still play a useful role in the aging populations of developing regions and confer some benefit on those with established OA, particularly if they are associated with weight reduction.

Nonselective NSAIDs. In a U.K. study, McCabe and others (1998) consider the cost-effectiveness of the use of five different NSAIDs (nabumetone, diclofenac, ibuprofen, piroxicam, and naproxen) in RA and OA. Taking the least and most expensive of the five NSAIDs—namely, ibuprofen and nabumetone, which were also at the high- and low-risk ends of the spectrum in terms of adverse gastrointestinal events—the authors conclude that nabumetone is not a cost-saving prescription.

Gastroprotective Agents. The most common side effects of NSAIDs are gastrointestinal; therefore, evaluating therapies to reduce these events is important. Van Dieten and others (2000) review the literature on the cost-effectiveness of misoprostol in reducing adverse gastrointestinal events in OA and RA patients who take NSAIDs. Unfortunately, the reviewed studies evidently reported CERs based on such nongeneralizable measures as cost per patient ratios. Nevertheless, van Dieten and others (2000) argue that strong evidence exists that gastroprotection is cost-effective for OA and RA patients taking NSAID therapy. This finding appears to be true in relation to several of the reviewed studies, which produced estimates of cost savings derived from prophylaxis. However, van Dieten and others' (2000) study is at variance with that of Gabriel, Campion, and O'Fallon (1994), who conclude that misoprostol was generally dominant in that it provided no greater quality-of-life improvement and cost more.

Synovial Fluid Replacement. In a Canadian study, Torrance and others (2002) analyzed the cost-effectiveness of synovial fluid replacement in a randomized, one-year, multicenter trial of 255 patients with OA of the knee. Patients were randomized to appropriate care with hylan G-F 20 or to appropriate care without hylan G-F 20. The mean QALY gain in the intervention group was 0.071, and the resulting ICER was US\$5,233 per QALY (with similar results from sensitivity analyses). However, the relevant incremental comparators in developing regions are likely to be quite different from those used by the foregoing study. Also, the relative price of this product is likely to be higher. Thus, we cannot find strong grounds for recommending that developing regions adopt this intervention.

Tertiary Interventions

Total joint replacement for arthritis is one of the most commonly performed and cost-effective operations in developed countries. In developing countries, however, the availability of this intervention is constrained by the availability of surgeons able to perform the operation. If the surgical expertise is available, the cost-effectiveness of total joint replacement is likely to be as good as in Australia, Europe, and North America.

Total Hip Arthroplasty. Chang, Pellissier, and Hazen (1996) assess the cost-effectiveness of total hip arthroplasty in various age groups compared with nonsurgical management. Their analyses suggest that, in 60-year-old white women, total hip arthroplasty is dominant compared with nonsurgical management. For 85-year-old men, the cost per QALY is US\$6,893. Generally, their results suggest that, when total hip arthroplasty is used as a treatment for OA of the hip with significant functional limitation, it is cost-effective.

Knee Replacement. Segal and others (2004) review a number of interventions for OA and suggest a cost per QALY of US\$5,407 for knee replacement in Australia.

COST-EFFECTIVENESS OF INTERVENTIONS FOR RA

The result of a decade of vigorous debate about the appropriate treatment strategies for RA appears to be a consensus that patients with moderate or severe RA should be treated early and aggressively, if possible, by combining several disease-modifying antirheumatic drugs (DMARDs) (Maetzel and others 2002).

The complex medical management of RA can involve the use of a large number of agents, including NSAIDs, low-dose corticosteroids, and a long list of DMARDs. The economic literature for interventions in RA has, for good reason, tended to focus on the cost-effectiveness of the alternatives that arise when a particular management strategy fails. In that sense, the intervention-based taxonomy used in earlier sections of this chapter is a less helpful way to characterize some of the contributions to this field. Thus, the subsections used in this part of the chapter reflect at times a problem-based taxonomy and at other times an intervention-based classification.

Treatment Modalities

One of the challenges common to the developing world is that specialized medical expertise is often scarce. Thus, the consideration of a variety of treatment modalities is worthwhile,

especially those that involve labor substitution between specialist and nonspecialist categories. Unfortunately, relatively few studies of this kind, let alone large randomized studies, are available for RA.

In a nonrandomized study of 26 patients in Finland, Nordstrom and others (1996) compare the costs of treating RA patients either as inpatients or as outpatients. Even though the authors find that the cost of treating patients as outpatients was approximately one-sixth the cost of inpatient treatment, the small sample size and possible bias associated with the non-randomized design mean that the study's results cannot be generalized.

An interesting and possibly cost-effective strategy for managing RA involves the use of a telephone help line staffed by specialist nurses. Hughes and others (2002) examine the costs and benefits of such an intervention in the United Kingdom and conclude that it was cost saving. Their work was based on a sample of 87 RA patients who used the telephone help line in a given month. A large proportion of respondents indicated that they used the help line in place of a visit to a general practitioner, and on this basis, the authors computed that the service produced a net saving.

The existing evidence on the effectiveness and cost-effectiveness of a telephone help line for RA patients is based on a relatively small sample. Nevertheless, this type of intervention may be useful in developing regions with good communications but low levels of access to medical care. This type of intervention may be particularly worthy of consideration when direct access to a medical practitioner is associated with large travel costs.

Disease-Modifying Antirheumatic Drugs

DMARDs include cyclosporine, azathioprine, D-penicillamine, sulfasalazine, etanercept, hydroxychloroquine, methotrexate, leflunomide, and gold compounds. Gabriel, Coyle, and Moreland (2001) provide a comprehensive review of the effectiveness and cost-effectiveness of DMARDs, including a comprehensive literature search in which they retrieved 30 articles from 500 identified for possible relevance. Only six of those papers included economic evaluations, and of those six, only three included measures of both benefits and costs. Only one of the articles used a nonclinical outcome measure (QALYs). Thus, the cost-effectiveness evidence for the use of DMARDs to treat patients with RA is generally scant.

The three full economic evaluations of DMARDs that Gabriel, Coyle, and Moreland identified were studies of auranofin (oral gold) (Thompson and others 1988), cyclosporine (Anis and others 1996), and combined therapy (Verhoeven and others 1998).

Auranofin. Thompson and others (1988) compare the cost-effectiveness of auranofin with that of a placebo using data

from a six-month RCT of 311 patients with RA. The authors report that the cost of auranofin was approximately US\$692 greater than for the placebo treatment, but the lack of efficacy of auranofin means that it is now rarely used in RA treatment.

Cyclosporine, Azathioprine, and D-penicillamine. In a Canadian study, Anis and others (1996) conduct a cost-effectiveness analysis of cyclosporine use in patients with RA based on the results of a meta-analysis of five RCTs. Their comparators included a placebo control, azathioprine, and D-penicillamine and analyses based on societal costs or third-party payer costs, but the ICERs were expressed as the cost per patient per year improved, so the results are difficult to interpret in the context of a general priority-setting exercise for health expenditures. For the purposes of this chapter, perhaps the study's most useful result was that it found no statistically significant differences between cyclosporine, azathioprine, and D-penicillamine.

Given that the existing evidence on cyclosporine, azathioprine, and D-penicillamine indicates similar levels of efficacy, cyclosporine should be used only after less expensive and more effective therapies for the management of RA, including azathioprine and D-penicillamine.

Combination Therapy. Verhoeven and others (1998) analyze the use of combination therapy using data from the Combinatietherapie Bij Reumatoide Artritis, or COBRA study, conducted in Europe between 1993 and 1995. The study was a 56-week trial that involved treating an intervention group with sulfasalazine, methotrexate, and prednisolone versus sulfasalazine alone as a control. Even though the authors conclude that combined therapy is cost-effective, they qualify the results by stating that the study was probably underpowered. Despite the lack of good cost-effective data, the standard approach to RA treatment is to use combination therapy with DMARDs and to maintain corticosteroids at 7.5 milligrams per day or less if possible.

Biologics. A number of trials have shown that the biologic agents (tumor necrosis factor inhibitors and others) are the most effective agents available for reducing inflammation in RA. Their cost (US\$10,000 to US\$15,000 per patient per year); mode of administration (intramuscular, subcutaneous, or by intravenous infusion); and potential side effects (particularly the reactivation of tuberculosis) preclude their use in developing countries. Until trials are carried out in developing environments and are combined with robust cost-effectiveness data, we cannot recommend their use.

Corticosteroids. Bae and others (2003) analyze the cost-effectiveness of low-dose corticosteroids for the long-term treatment of RA. They compare the results of corticosteroid

treatment with treatment using any DMARDs plus a corticosteroid and with treatment using DMARDs and NSAIDs. Their modeling includes a consideration of the rates of relevant side effects of the treatments. They also look at NSAID-use scenarios that included Proton Pump Inhibitor prophylaxis and the use of COX-2-specific inhibitors rather than nonspecific NSAIDs.

The results generally showed that corticosteroids dominate nonselective NSAIDs in terms of their cost-effectiveness. The exceptions were when the adverse events rate for corticosteroids was assumed to be 1.5 times that of the base case and when the comparators' adverse events rates were assumed to be 0.5 to 1.0 times the base case rate. In the latter case, the cost per QALY was US\$114,168, and in the former, NSAIDs were dominant. The comparison of COX-2-specific inhibitors with corticosteroids produced a higher-cost and higher-utility outcome: the resulting incremental cost per QALY was US\$132,880.

The authors also produced useful age-specific estimates of the cost-effectiveness of the two alternative treatment approaches. Their ICERs show that corticosteroids dominate for the management of 50- and 60-year-olds with RA. For 40-, 30-, and 20-year-olds, the ICERs were US\$11,258, US\$30,938, and US\$46,981, respectively.

The evidence suggests that a management strategy of DMARDs plus low-dose corticosteroids is a less costly and more effective strategy than DMARDs plus NSAIDs in older age groups, largely because of the higher risks of adverse gastrointestinal events in those groups. For developing countries, a relevant question to consider is the extent to which life expectancy and risk factors for adverse gastrointestinal events will differ from the age groups Bae and others (2003) studied. Corticosteroid-induced OP is also a long-term risk, but for women with RA starting corticosteroid therapy, watchful waiting is recommended as preferable to screening, as long as the steroid dose remains below 7 milligrams per day.

COST-EFFECTIVENESS OF INTERVENTIONS FOR OTHER MUSCULOSKELETAL CONDITIONS

Low Back Pain

Low back pain is as common in developing countries as it is in the developed world. Health professionals now generally agree that conservative care for acute lower back pain is the initial treatment of choice, unless there is structural evidence of pathology that is amenable to surgical intervention (Gatchel and others 2003). Evidence also indicates that programs that incorporate some physical activity may reduce the costs of both acute and chronic low back pain compared with those that do not involve activity.

For economic evaluations, one of the important complicating factors associated with low back pain is that the

nonmeasurement of indirect costs may introduce substantial bias into estimates of the cost-effectiveness of interventions. This problem is potentially serious because, in some cases, investigators have estimated the indirect costs of low back pain at more than twice those of the direct medical costs (Bolten, Kempel-Waibel, and Pfforinger 1998).

Back Schools. Van Tulder and others (2003) review 15 RCTs of back schools for patients with recurrent and chronic low back pain, but they consider only three of these to be of high quality. They conclude that the evidence is only moderate that back schools have better short-term effects than other treatments for chronic back pain. They also find some evidence that back schools are more effective than placebos or waiting list controls in occupational settings. However, the authors note that little is currently known about the cost-effectiveness of back schools. Thus, evidence is insufficient to provide a recommendation on the probable cost-effectiveness of back schools for low back pain in developing countries; however, early intervention, education, and exercise programs should be encouraged.

Massage. Furlan and others (2002) examine the effectiveness and cost-effectiveness of a variety of massage techniques for nonspecific low back pain by comparing them with (a) sham or placebo massage, (b) other medical treatments, or (c) no treatment. The authors conclude that massage might be beneficial for patients with subacute and chronic nonspecific low back pain, especially when combined with exercises and education. The evidence suggests that acupuncture massage is more effective than classic massage, but this finding needs to be confirmed.

Little is known about the cost-effectiveness of massage for low back pain. On the basis of the existing evidence, in countries or regions in which massage—especially acupunctural massage—is routinely available at low cost, the intervention may be cost-effective. Where acupunctural interventions are considered, the costs of bloodborne disease transmission must also be weighed against the expected benefits of the intervention. This consideration may be important in countries where the prevalence of bloodborne viruses is high, particularly if strict infection control measures are not routinely followed.

Early Interventions. The few studies of early intervention programs to reduce the progression of acute low back pain to chronic pain have tended to report considerable cost savings. Gatchel and others (2003) published a prospective trial of early interventions in individuals with acute low back pain and a high risk of the pain progressing to chronicity. The authors screened approximately 700 patients and designated them as being at either low or high risk. The patients were then assigned to early or nonintervention groups and followed for 12 months. The early intervention was generally conducted over a

three-week period and involved an intensive, multidisciplinary approach that included exercise classes, biofeedback and pain management classes, group education sessions, case manager and occupational therapist sessions, and interdisciplinary team conferences.

The early intervention resulted in statistically significant differences in return-to-work outcomes, number of health care visits, and number of disability days caused by back pain. It also resulted in a variety of pain surrogates. Furthermore, the mean cost savings were approximately US\$9,000 per patient. The direct costs for the intervention group were approximately US\$2,500 higher than those for the intervention group, but this finding was largely the result of the up-front costs of the intervention program itself. The direct costs of health care visits and pharmaceuticals were considerably lower for the intervention group.

The evidence suggests that an intensive, multidisciplinary, early intervention program is cost saving for individuals with acute low back pain who are at high risk of having the pain progress to chronicity; however, the cost savings associated with this intervention are attributable to improved labor market outcomes and earnings for injured individuals. The intervention itself may increase costs in the short term, but it appears to be associated with medium and long-term net benefits. Labor market conditions, including wages, along with the age of low back pain sufferers, may have an important bearing on the viability of this type of intervention in developing countries.

Ankylosing Spondylitis

Although the direct costs associated with ankylosing spondylitis are relatively low, its impact on indirect costs, including pain and suffering, are substantial. To date, little work has been done on the economics of interventions for ankylosing spondylitis. Pharmaceutical interventions are currently typically limited to NSAIDs and DMARDs such as methotrexate and sulfasalazine. Van Tubergen and others (2002), however, analyze the cost-effectiveness of a spa exercise intervention. The intervention period was three weeks, and although the authors argue that the cost-effectiveness of the intervention was favorable, they also note that the ICERs were sensitive to variations in assumptions about indirect costs.

Although a spa exercise program is apparently beneficial and may even be considered cost-effective for ankylosing spondylitis sufferers in developed countries, the current cost-effectiveness evidence does not provide a compelling case for widespread adoption of the intervention in developing regions. Patients, however, should be encouraged to exercise—especially to swim. The cost-effectiveness of tumor necrosis factor-inhibiting drugs is not yet evident for ankylosing spondylitis, but the drugs are currently unattractive investments for developing countries because of their high price.

IMPLEMENTATION OF CONTROL STRATEGIES: LESSONS OF EXPERIENCE

Given the increasing burden of musculoskeletal conditions worldwide, addressing ways of preventing musculoskeletal conditions is an important step. Few examples are available of the implementation of strategies aimed specifically at preventing musculoskeletal conditions, but many recommendations are aimed at modifying determinants that affect other aspects of health in addition to musculoskeletal health. These recommendations include ensuring adequate physical activity to maintain physical fitness; maintaining an ideal body weight; ensuring a balanced diet that meets the recommended daily allowances for calcium and vitamin D; avoiding smoking; balancing the use of alcohol and avoiding alcohol abuse; and putting in place accident prevention programs to reduce musculoskeletal injuries related to road traffic accidents, leisure activities, and workplaces. Various programs involve changes in the behavior of individuals and control of environmental hazards (these programs are considered elsewhere in this volume). Personal behavior changes can be achieved by education but may require resources such as sports facilities. A safe environment will involve all sectors, and successful implementation may require legislation. The benefits of these interventions on musculoskeletal health are not quantified, but in any case they are probably small. Physical activity and an ideal weight will benefit the broadest range of musculoskeletal conditions.

Osteoarthritis

The strategy for managing OA is pain management with simple analgesics or NSAIDs, along with education to facilitate self-management and rehabilitative programs to improve function, activities, and participation. These strategies include general and specific exercise programs, devices such as walking sticks, and environmental modifications. Joint replacement surgery should be considered for end-stage joint damage. Simple analgesics can be accessible over the counter or through health clinics. Education and rehabilitative programs can also be delivered through health clinics. Joint replacement surgery requires resources in terms of physical facilities, financial resources, and expertise. The cost-effectiveness of arthroplasty is greatly affected by complications such as infection or failure of the prosthesis, both of which are related to inadequate resources.

Pain management should be available to those who have disabling symptoms and is dependent on access to drugs and education with respect to the benefits and risks. Access to arthroplasty will be the greatest challenge, given the increasing needs in the developing world brought about by aging populations and increases in other risk factors such as reduced physical activity and increasing obesity.

Rheumatoid Arthritis

The greatest successes in recent years include advances in managing RA and the ability to control disease activity; to prevent tissue damage; and to improve function, activities, and participation. Methotrexate is a readily accessible, effective antirheumatic drug. Monitoring full blood count and liver function is recommended, but the rarity of serious adverse events may necessitate a review of this recommendation if the costs and difficulties of monitoring would deny access to the drug. Symptomatic therapy with NSAIDs and multidisciplinary rehabilitation are also key components of the management of RA. Central to this approach is ensuring early and accurate diagnosis with long-term expert review, which requires public awareness about arthritis and adequate competency and facilities in the community and in health clinics for diagnosis and management. Education and rehabilitation can also be delivered in these settings. Paramedical workers can be trained to undertake much of this work. The problem is to ensure adequate training and experience of health care workers for a condition that affects 0.3 to 0.5 percent of adults in developing countries. Without treatment, the effects of RA can be great, so effective management can yield significant gains. The costs are relatively low, because paramedical workers can deliver much of the care and because the drugs are not new and are widely available.

Several established market economies have set up early arthritis clinics, but running such clinics effectively may be more difficult without a system to encourage and enable early access to specialist care. The management of established RA is usually undertaken by specialists in partnership with primary care. Programs for managing RA are usually self-sustaining and expandable because of the chronic incurable nature of the condition and the general public's gradual recognition of what can be achieved.

Osteoporosis

The prevention of fractures related to OP is based on a "bone-healthy" lifestyle of individuals who have adequate dietary calcium, vitamin D, and weight-bearing exercise and who avoid smoking and excessive alcohol consumption. Implementing such measures requires raising public awareness and educating primary care personnel. In addition, those at high risk of fracture who would benefit from a specific intervention need to be identified by the presence of risk factors, including low bone density. The limitation to this approach is a lack of access to bone densitometry, in which case the decision to treat may have to be made on clinical grounds alone. The occurrence of low-trauma fracture is a good indicator of OP and, in the presence of other clinical risk factors, may be reason enough to treat. In particular, multiple vertebral fractures are virtually diagnostic of OP.

Various local programs aim at identifying and treating those with OP. Their costs relate not only to diagnostic tests but also to treatment. The cost of bisphosphonates is high compared with the income levels in those countries likely to experience the greatest increase in the burden of OP. The speed of benefits of bisphosphonates is good, with clinical trials demonstrating fracture risk reduction within 12 to 18 months. The role of HRT is not clear at present, but because of the likely increased risk of cardiovascular disease and strokes outweighing the benefit of fracture prevention, it is not currently recommended for preventing OP in unselected women. However, the benefit-risk ratio will be favorable in those at increased risk of fracture and low risk of cardiovascular disease, and the costs of HRT are more feasible. Adherence to treatments for OP to prevent fracture is poor because of the silent nature of their effect, and patient education to modify expectations is important. The effectiveness of any fracture prevention program depends on adherence for as long as possible, given the long-term character of the condition.

RESEARCH AND DEVELOPMENT

Another important issue with musculoskeletal disease is the development of a research agenda.

Size and Nature of the Burden of Disease

Uncertainty about the epidemiology of some musculoskeletal conditions is still considerable, especially in developing countries (WHO 2003). Incidence estimates for OA and RA have recently been generated from available epidemiological data on prevalence, relative mortality risks, and so on, though for some regions even these basic epidemiological data are scant (Africa, Asia, and South America for RA and Africa, Eastern Europe, and South America for OA). Additional primary measurement is required to produce a more accurate picture of interregional and intraregional epidemiological variations. This deficiency limits estimates of the overall burdens of the various musculoskeletal conditions and the extent to which they might be reduced.

The studies of the Community-Oriented Program for Control of Rheumatic Disease (COPCORD) (Darmawan and others 1995) are, in part, meeting this need. The Bone and Joint Monitor Project is also undertaking initiatives to standardize data collection and reporting in epidemiological studies to improve the collation and comparison of needed epidemiological data. Global burden-of-disease data concentrate on specific diagnoses, but a far greater burden that has yet to be estimated relates to regional and generalized musculoskeletal problems characterized by pain with disability. More research is necessary in this area.

Evaluation of Existing Interventions

Few reliable economic evaluations of available interventions have been done. One reason is that a surprising number of interventions have inadequate trial data or efficacy measures, and many reasonably well-established interventions need to be tested in trials against appropriate comparators. The heterogeneity of comparators used in different economic evaluations and other methodological differences pose material risks to comparisons of the costs and consequences of different interventions for musculoskeletal conditions, and some standardization is needed.

Many studies have used only clinical outcomes and not life years saved or QALYs as outcome measures. Positive steps are being taken to correct the situation. The Outcome Measures in Rheumatology Clinical Trials Economics Working Group (Gabriel, Tugwell, and Drummond 2002) has made some progress toward redressing this problem in the rheumatology economics literature. Although work is not yet complete, this concerted approach to standardization holds promise for the literature.

Avertable Proportion of the Burden

New data are needed to estimate the burden that could be averted by implementing the proposed strategies. Available data are currently limited and relate predominantly to individual interventions in short-term clinical trials with outcomes that do not enable reliable estimates of the avertable burden. Interventions need to be evaluated, often in combination with outcome measures that enable the burden on individuals and society to be measured meaningfully and in more naturalistic circumstances. Concordance cannot be assumed, in particular for these largely chronic conditions, and it is influenced by many personal and environmental factors. The impact of musculoskeletal conditions is pervasive, underrecognized, and underestimated. Therefore, data are needed not only on what is theoretically avertable, but also on what is being averted and the reasons for any disparities.

Resource Requirements

The implementation of strategies for preventing and controlling musculoskeletal conditions is multisectoral, and the resource consequences of this need to be established. Different models for the delivery of a strategy may have different resource implications. These variations need to be explored to ensure appropriate investment and provision of resources.

Likely Effectiveness of Interventions on Both Health and Nonhealth Benefits

Musculoskeletal conditions are common and have a major impact on individuals and society; however, they are inadequately treated, and the success of simple interventions is not

being achieved because of a lack of prioritization and resources. Strategies for preventing musculoskeletal conditions have a wide range of other health benefits; they need to be jointly promoted, and the additional benefits need to be better recognized. The various determinants of ill health—such as lack of physical activity or obesity—that pose a risk to musculoskeletal health need to be quantified along with their other detrimental effects. The benefits and cost-effectiveness of modifying these determinants of health, with regard to preventing or modifying the outcome of musculoskeletal conditions, need to be quantified and compared with strategies that focus on personal interventions.

Implementation

Improving musculoskeletal health requires implementing strategies for preventing and controlling certain diseases and environmental risk factors. Selected strategies must be in line with local needs, priorities, and resources. Informed decision making at the policy level requires data on the burden and the avertable burden of musculoskeletal conditions, plus the costs for particular populations by strategy. Changes in local demographics that are likely to increase the effect of musculoskeletal conditions also need to be considered before developing plans for implementation.

CONCLUSIONS: PROMISES AND PITFALLS

Musculoskeletal diseases are the most common cause of chronic disability worldwide and will become increasingly important as aging populations require relief from chronic pain and disability. One of the characteristics of musculoskeletal diseases is that they are not fatal and do not have the high profile of other conditions, such as cancer and heart disease. However, they are preventable in many cases, and simple interventions, such as maintaining ideal body weight and participating in an exercise program, may have a significant effect on long-term morbidity. However, the field of musculoskeletal disease is thwarted by a significant lack of epidemiological and outcome data across a broad spectrum of geography, condition, and treatments.

The designation of 2000–10 as the Bone and Joint Decade by the United Nations, WHO, and 60 countries will certainly help raise the profile of these diseases in local communities. All nations have a significant opportunity to embrace the decade, to ensure that their populations understand the importance of these diseases, and to encourage the training of a range of health professionals to deal with this burgeoning epidemic.

Improving knowledge among health workers at all levels about musculoskeletal conditions is important for early diagnosis and intervention, as is the provision of access to specialist services, such as orthopedic surgery. Simple programs that

emphasize the importance of obesity and lack of exercise as predictors of poor musculoskeletal outcomes are low cost, but their implementation and their influence on health outcomes need to be assessed in properly conducted studies. Medications—particularly analgesic and anti-inflammatory drugs for arthritis and pain and vitamin D and calcium supplementation to prevent OP—need to be widely available.

Exciting advances in the treatment of inflammatory forms of arthritis with biologics need to be evaluated from an economic perspective, particularly in developing nations, where the risk of exacerbating underlying infections such as tuberculosis is much higher than in developed countries. Currently, biologic agents are not cost-effective in developing countries, but they may be in the future. Access to hip and knee replacements, probably the most cost-effective surgical intervention available, is important but depends on the availability of a qualified staff.

Musculoskeletal diseases will continue to present a challenge to the health systems of both developing and developed countries, but as we solve some of the issues related to communicable diseases, the hope is that more resources will become available for tackling the burgeoning epidemic of noncommunicable disease, including musculoskeletal conditions.

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