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ORIGINAL RESEARCH

Costs of moderate to severe chronic pain in primary care patients – a study of the ACCORD Program

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Background: The economic burden of chronic noncancer pain (CNCP) remains insufficiently documented in primary care.

Purpose: To evaluate the annual direct health care costs and productivity costs associated with moderate to severe CNCP in primary care patients taking into account their pain disability.

Materials and methods: Patients reporting noncancer pain for at least 6 months, at a pain intensity of 4 or more on a 0 (no pain) to 10 (worst possible pain) intensity scale, and at a frequency of at least 2 days a week, were recruited from community pharmacies. Patients' characteristics, health care utilization, and productivity losses (absenteeism and presenteeism) were documented using administrative databases, pharmacies' renewal charts, telephone, and self-administered questionnaires. Patients were stratified by tertile of pain disability measured by the Brief Pain Inventory questionnaire.

Results: Patients (number =483) were, on average, 59 years old, mainly women (67.5%), and suffered from CNCP for a mean of 12 years at an average pain intensity of 6.5±1.9. The annual direct health care costs and productivity costs averaged CAD $9,565 (±$13,993) and CAD $7,072 (±$11,716), respectively. The use of complementary health care services accounted for almost 50% of the direct health care costs. The mean adjusted total direct health care costs (considering pain-related hospitalizations only) and productivity costs increased with more pain disability: low disability, CAD $12,118; moderate, CAD $18,278; and severe, CAD $19,216; P=0.001.

Conclusion: The economic burden of CNCP is substantial and increases with the level of pain disability, which suggests the need for and potential benefits of improving CNCP management through specific and adapted treatment plans targeting the impact of pain on daily functioning.

Keywords: noncancer chronic pain, primary care, cohort study, direct health care costs, productivity costs, Brief Pain Inventory

Introduction

Chronic noncancer pain (CNCP) is defined by the International Association for the Study of Pain as a pain persisting beyond the normal healing time for a specific illness or injury.[1] It is estimated that more than 25% of the Canadian population is affected by CNCP,[2,3] a prevalence that tends to increase in our aging society.[4] Based on four European studies published between 1991 and 2002, Ospina and Harstall[5] estimated the prevalence of chronic pain to be 35.5%. Affected individuals report lower quality of life,[6] experience interferences in their daily activities[4,7,8] and are at higher risk of suffering from depression and anxiety disorders,[4,8] sleep problems,[7] and additional comorbid conditions.[9]

CNCP is associated with substantial direct health care costs. In Quebec (Canada), the annual direct health care costs associated with rheumatoid arthritis, fibromyalgia, and painful neuropathic disorders are estimated to average CAD $10,287 (±$12,728 [2002 values]; $12,257 [2011 values]),[10] CAD $4,065 (±$6,798 [2007 values]; $4,339 [2011 values]),[11] and CAD $4,163 (±$7,536 [2002 values]; $4,960 [2011 values])[12] per patient, respectively. Individuals with CNCP make more physician visits (mean of 12.9 visits per year versus 3.8 visits per year) and have longer hospital stays (mean of 3.9 days versus 0.7 days) than individuals without it.[13]

Chronic pain also causes substantial productivity losses arising from work absences (absenteeism) and reduced productivity at work (presenteeism).[8] A Canadian survey revealed that individuals with CNCP missed an average of 9.3 (95% confidence interval [CI]: 4.7–13.7) workdays annually due to their pain, a number rising to 16.0 (95% CI: 5.1–26.9) among individuals with severe pain.[2] In Australia, the productivity costs associated with CNCP are estimated to amount to AU $5.1 billion annually.[14]

Pain-related direct health care costs and productivity costs yield considerable global societal costs. Total CNCP expenditures represent more than 3% of Finland's gross national product[15] and US $2.1 million per employer annually (1998 values) in the United States.[16] More severe pain disability seems to be associated with higher societal costs. Patients with arthritis and rheumatism reporting more disability incurred higher direct health care[17,18] and productivity costs.[19,20] In the United States, when these costs are considered, the total annual cost of pain was greater than the annual costs of treating heart disease, cancer, and diabetes respectively.[21]

Although the vast majority of CNCP patients are followed-up in primary care,[8] most studies have evaluated the economic burden of CNCP in patients recruited in specialized clinics.[18,22–24] The objective of this project was, therefore, to describe the direct health care and productivity costs associated with CNCP among primary care patients. Patients with various diagnoses were considered and the costs were described as a function of their pain disability.

Materials and methods

Study design

As part of the ACCORD Program (Application Concertée des COnnaissances et Ressources en Douleur), a knowledge translation research program in the field of CNCP, a cohort study was conducted (one submitted paper is accepted for publication).[25,26] In this cohort study, individuals with CNCP having an active analgesic prescription from a primary care physician were recruited from May 2009–January 2010 in community pharmacies. Patients completed a structured telephone interview and a self-administered questionnaire. Governmental administrative databases, the Régie de l'assurance maladie du Québec (RAMQ; Quebec health insurance board; QC, Canada) and the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO – a hospitalization database), as well as community pharmacies' renewal charts were used to document health care use and costs in the year preceding the recruitment. Ethical approvals were obtained from the Comité scientifique et d'éthique de la recherche of the Centre de santé et de services sociaux de Laval (Laval, QC, Canada) and from the Commission d'accès à l'information (QC, Canada). Each patient signed an informed consent form and received a financial compensation of $25 for completing the questionnaires. Pharmacists received a financial compensation of $50 for every consenting patient.

Study population

The study was conducted in the Réseau universitaire intégré de santé de l'Université de Montréal (Montreal, QC, Canada), which encompasses six areas in the province of Quebec (Canada): Mauricie et Centre du Québec; Laval; Montréal; Laurentides; Lanaudière; and Montérégie, representing more than 40% of the population in this province. Based on the Quebec Health Ministry's atlas, 513 community pharmacies were identified in this territory.[27] Among those, a random sampling stratified by region and weighted by the number of pharmacies located within each region was done. To recruit 60 pharmacies, selected pharmacies were sequentially contacted until the target numbers of pharmacies were reached in each region. To recruit 600 patients, each pharmacy had to identify between 10 and 15 consecutive and potentially eligible patients. During the course of the study, additional pharmacies were invited to participate, so as to compensate for those that did not recruit the expected number of patients.

To be eligible, patients had to: 1) be ≥18 years of age; 2) report suffering from noncancer pain for at least 6 months and for a minimum of 2 days per week; 3) rate their average pain in the past 7 days as ≥4 on a 0–10 intensity scale (0= no pain; 10= worst possible pain);[28] 4) have an active analgesic prescription from a primary care physician; and 5) speak and read French or English. Patients reporting migraine as the only source of pain and those unable to provide informed consent were not eligible. The Canadian Pain Society and

the World Health Organization define chronic pain as a pain lasting 6 months or more.[29,30] This definition is currently used in research.[31] In order to ensure that patients' pain had some impact on various aspects of their daily functioning, only those who reported pain at least 2 days a week were selected.

Direct health care and productivity costs

Direct health care costs

Direct health care costs, expressed in Canadian dollars, were estimated for each participant based on the health care resources used in the year preceding the recruitment.

All outpatient physician visits, as well as tests and interventions (related and unrelated to CNCP), were documented from the RAMQ database. In this database, a service code is assigned to each of these components, along with the specialty of the professional consulted, the date, the site, and the amount reimbursed by the RAMQ, which was used to estimate the cost of the services. A pain specialist (DL) reviewed all tests and interventions provided to cohort patients in order to identify those related to CNCP.

All visits to emergency rooms (ER) were considered. Costs of these visits were documented from the RAMQ database and they included the costs of the visit, tests and interventions, and physician consultations. For each ER visit, a unitary cost of CAD $270.54 (2011 values) was considered. This cost corresponds to the average provincial cost per ER according the Quebec Health Ministry (Direction de l'allocation des ressources, unpublished data) and accounts for expenses incurred by the health care institution itself, including overheads and consumables. The costs of physician consultation(s), test(s), and intervention(s) provided during the ER stay were those paid by the RAMQ during the year preceding the recruitment (May 2008–January 2009).

All hospitalizations and those related, or possibly related, to CNCP were considered. Hospitalizations were documented from the MED-ÉCHO database, where information regarding the admission date, the primary and secondary diagnoses, the length of stay, and the site are recorded. The hospitalization costs included those of the hospital stay, physician visits, tests, and interventions. The cost of hospital stay represents a per diem cost of CAD $948.73 (2011 values) according the Quebec Health Ministry (Direction de l'allocation des ressources, unpublished data), including overheads and consumables. This cost is the mean provincial cost per day of hospitalization, and it accounts for expenses related to the costs of nursing care, laboratory tests, medications, laundry, food, administration, and maintenance. Physician visit and test/intervention costs provided during hospitalizations were documented from the RAMQ database and corresponded to those reimbursed by the RAMQ from 2008–2009. The primary and secondary diagnostic codes associated with the hospitalizations were reviewed by a pain specialist (DL) (see Table S1) to identify those related or possibly related to CNCP.

The use of nonpharmacological health care services was documented during the telephone interview by asking patients, "Now, I will read a list of different types of therapy that can be used to relieve pain. Please stop me each time I name a therapy you have used in the past." Overall, 23 therapies were enumerated: relaxation/breathing techniques; meditation; hypnosis; visualization; individual distraction; individual psychotherapy; group psychotherapy; self-help support group; physiotherapy; occupational therapy; hydrotherapy/hot bath/aqua therapy; electrostimulation; intramuscular stimulation; ultrasounds; biofeedback; acupuncture; massotherapy; chiropractic; osteopathy; therapeutic touch; reflexology; Reiki; and magnet therapy. When patients identified a therapy that they had employed, the interviewer then asked them, "Have you used it in the past 6 months?" and if yes, "How frequently did you use it in the past 6 months? Every day, a few times every week, a few times every month, or a few times every year?" Those frequencies were translated into actual numbers of annual visits; every day =260 (annual number of weekdays); a few times every week =104; a few times every month =24; and a few times every year =2. The costs of each visit corresponded to the mean cost per visit in the Montreal area (QC, Canada) as a function of the type of professional consulted, and it varied between CAD $45 and CAD $90 (2007 values).[32]

Prescribed analgesics dispensed 1 year prior to the recruitment were documented from the RAMQ database or from pharmacies' dispensing charts; the latter allowed for the documentation of pharmacologic treatments of individuals not insured by the RAMQ for their medications. For each analgesic prescription (new and renewals), the following information was recorded: date of dispensation; common drug denomination; form; dosage; and quantity. Analgesics included acetaminophen, nonsteroidal antiinflammatory drugs, antidepressants, anticonvulsants, muscle relaxants, opioids, antiretroviral therapy, disease-modifying antirheumatic drugs, and antirheumatic biologic agents. Only antidepressants and anticonvulsants recommended for pain treatment were taken into account (see Table S2),[33,34] and they were documented for patients not reporting depression or epilepsy. Antiretrovirals were those recommended to treat

zona-related pain[35] (valacyclovir, famciclovir, acyclovir). Prescribed medications to prevent or control the gastrointestinal adverse effects that are frequently reported with analgesics were also documented (laxatives, antacids, gastroprotectants, and antiemetics). The costs of each medication corresponded to those reimbursed by the RAMQ (List of Medications 2011)[36] based on the form and the dosage of each product. The pharmacist's fee for each medication dispensed was also considered. For patients insured by the RAMQ, we used the actual dispensing fee paid by the RAMQ. For patients not insured by the RAMQ, a fee of CAD $7.87, which corresponds to the mean dispensing fee paid by the RAMQ in 2011, was assumed.

To document over-the-counter medications used to treat pain and adverse effects associated with analgesics, patients were asked during the telephone interview: "In the past 6 months, have you taken over-the-counter medications or natural products for pain and for drug-related side effects such as constipation, heartburn, and nausea or vomiting?" The frequency of use was described in terms of every day, a few times every week, a few times every month, and a few times every year, and was later translated into annual numbers of daily recommended doses: every day =365; a few times every week =104; a few times every month =24; and a few times every year =2. Unitary costs were estimated using the McKesson database[37] (McKesson distributes medications to more than 6,000 community pharmacies in Canada). Daily dosages represented the minimum recommended daily doses of each specific product in the Vigilance Santé Program[38] – a computerized program that is frequently used in community pharmacies.

Productivity costs

Productivity costs, described in terms of absenteeism and presenteeism, were solely considered for individuals who were currently employed at the time of the interview (full- or part-time job), and for those who were on temporary or permanent disability; they were not considered for unemployed individuals, nor for those who were retired. This information was assessed during the telephone interview, as participants had to choose one of the enumerated choices, which included full- and part-time work and permanent and temporary disabilities.

Absenteeism was documented during the telephone interview using the following question: "In the past 6 months, how many days of work did you miss because of your pain or medical appointment, or treatment for you pain?" To evaluate the annual costs of absenteeism, the reported number of days absent from work due to pain in the past 6 months was multiplied by 2. For individuals with a full- or part-time job, productivity costs were calculated by multiplying the annual number of workdays missed by the mean Canadian hourly wage (CAD $23.06 [2011 values])[39] and the mean number of hours worked daily (7.24 hours).[40] For individuals on temporary or permanent disability, productivity costs were calculated by multiplying the annual number of workdays missed by the minimum wage as estimated in 2011:[41] CAD $9.65/hour; 8 hours/day. For individuals on temporary disability, the annual number of workdays missed represented the reported number of days absent from work due to pain in the past 6 months, multiplied by 2, and for individuals on permanent disability, it corresponded to 260 (annual number of weekdays absent).

As for absenteeism, presenteeism was only estimated for individuals with a full- or part-time job and for those on permanent or temporary disability. Based on the method described by Hu et al,[42] presenteeism was evaluated during the telephone interview using the following question: "In the past 6 months, what percentage of your productivity at work did you lose, on average, because of your pain? Please answer using a scale from 0% to 100% where 0% means 'no loss in productivity' and 100% means the 'loss of all productivity'." Presenteeism was estimated by multiplying the time lost due to pain (the number of workdays with pain by the percent of productivity lost on those days), by the number of hours worked per day (7.24 hours)[40] and by the hourly wage (CAD $23.06 [2011 values]).[39]

Pain disability

The impact of pain on daily functioning was assessed in the telephone interview using the interference items of the modified Brief Pain Inventory (BPI). The BPI is a widely used instrument in pain research and its psychometric qualities are well documented.[43,44] It includes ten interference items. For each one, patients are asked to rate, on a 0–10 scale (0= does not interfere, 10= interferes completely), the extent to which pain interferes with various aspects of their daily living including general activity, walking ability, mood, normal work, relations with other people, sleep, enjoyment of life, self-care, recreational activities, and social activities. A global BPI score is derived by taking the average rating on the ten items.[43]

Patients' characteristics

Sociodemographic and pain characteristics were documented with the self-administered questionnaire and

telephone interview. The characteristics of pain included its duration (time since onset) and frequency in the past week. The circumstances surrounding the onset of the pain and its location(s) were also recorded. Pain diagnoses were based on patients' self-reports using the following question during the telephone interview: "I will read a list of diagnoses that can be at the origin of your pain. Please stop me each time I read a diagnosis corresponding to your condition." The list included ten diagnoses, and patients had the opportunity to report diagnoses not included in the list. Diagnoses were then grouped into eight main categories: 1) back pain; 2) neck pain; 3) fibromyalgia; 4) neuropathic pain; 5) visceral pain; 6) inflammatory arthritic pain (for example, rheumatoid arthritis); 7) degenerative arthritic pain (for example, osteoarthritis); and 8) tendinitis, bursitis, capsulitis, and epicondylitis. The impact of pain on sleep was investigated using the Chronic Pain Sleep Inventory,[45] while depression and anxiety levels were measured using the Hospital Anxiety and Depression Scale.[46] Depression and anxiety scores were rated as "absent" (scores ≤7), "uncertain" (scores between 8–10), or "probable" (scores ≥11). The presence of comorbid conditions was assessed through the Charlson Comorbidity Index, an instrument that takes into account the number and seriousness of comorbid diseases.[47]

Data analyses

Annual costs were described on the basis of a societal perspective, in terms of direct health care and productivity costs. They were adjusted to 2011 Canadian dollar values based on the consumer price index (Statistics Canada, Ottawa, ON, Canada).[48] Taking into account the resources used in the year preceding the recruitment, the costs of hospitalizations, the ER visits, the outpatient physician, and other health care professional visits, pharmacotherapy (prescribed and over-the-counter medications that were used to treat pain and adverse effects associated with analgesic medications), as well as the costs associated with productivity loss due to absenteeism and presenteeism, were computed for each patient. Thereafter, the total direct health care costs and the costs associated with productivity loss were computed. The mean (± standard deviation) of these costs was computed for the entire cohort, as well as by three subcohorts defined by the tertile of the global BPI scores labeled as mild, moderate, and severe disability. The statistical significance of the between subcohort differences was estimated using a univariate linear regression model and chi-square statistics for continuous (for example, annual health care resource use and health care costs) and categorical variables, respectively.

Multivariate linear regression models were also developed to predict the costs as a function of the BPI tertile after adjusting for the following confounders: age;[12,17] sex;[12] duration of pain;[17,49] and the Charlson comorbidity score.[22,23,50,51] All variables associated with at least a 10% change in the cost estimate in the univariate analyses were included in the final multivariate model. Given the lack of precision in the identification of hospitalizations related to CNCP, all-cause hospitalizations were considered in this analysis. In a secondary analysis, only pain-related hospitalizations were reported. For each BPI tertile, the mean cost and its 95% CI were calculated. Gamma transformations of costs were employed in all cases.[52] Statistical analyses were carried out using SPSS Statistics Base 19.0 for Windows® (IBM Corporation, Armonk, NY, USA) and SAS® Software (version 9.1; SAS Institute Inc., Cary, NC, USA).

Results

Between May and October 2009, a total of 296 community pharmacies were invited to participate; 84 pharmacies were recruited and 70 completed the study and recruited patients (Figure 1). Between May 2009 and January 2010, pharmacists referred 609 potentially eligible patients, of whom 38 were ineligible and 85 refused to participate. Data from the community pharmacies' renewal charts and from the RAMQ and the MED-ÉCHO databases were available for all participants (number [n] =486). Telephone interviews and self-administered questionnaires were completed by 485 and 483 individuals, respectively. Based on the BPI tertile scores, three subcohorts were created and included 483 individuals: mild disability, BPI scores between 0.0–4.30 (n=165); moderate disability, scores between 4.31–6.40 (n=160); and severe disability, scores between 6.41–10.0 (n=158).

As reported in Table 1, participants were middle aged (mean age: 59±13 years), mainly women (67.5%), Caucasian (96.3%), and French-speaking (90.5%). The majority reported having an elementary school diploma or less (27.3%) or a high-school diploma (35.2%) as their highest level of education. Differences were observed between the subcohorts of patients defined by BPI tertile scores; those reporting more severe pain disability were younger, reported lower familial income, and were more likely to be on permanent or temporary disability.

Clinical and psychological characteristics

As reported in Table 2, on average, individuals suffered from pain for 12 years (±11 years). The proportion of patients reporting a pain duration of 4 years or more tended to be

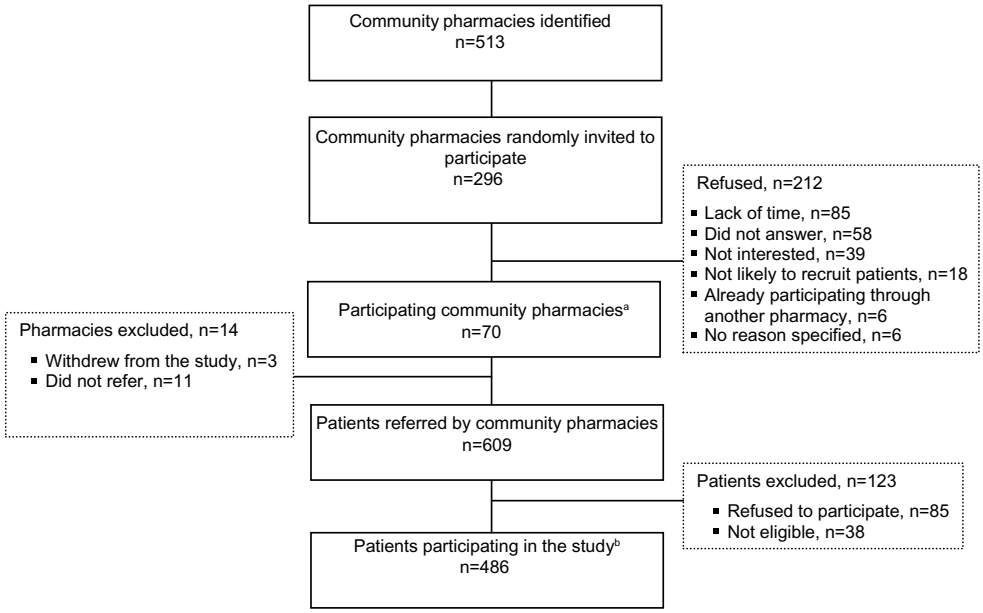

Figure 1 Recruitment of pharmacies and patients.
Notes: [a]Pharmacy distribution per region (n of recruited pharmacies/total n per region): Mauricie et Centre du Québec, 6/60 (10.0%); Montréal, 18/134 (13.4%); Laval, 13/70 (18.6%); Lanaudière, 8/77 (10.4%); Laurentides, 14/95 (14.7%); Montérégie, 11/77 (14.3%); [b]patient distribution per region (n of recruited patients per region/total n of patients): Mauricie et Centre du Québec, 44/486 (9.1%); Montréal, 92/486 (18.9%); Laval, 67/486 (13.8%); Lanaudière, 91/486 (18.7%); Laurentides, 117/486 (24.1%); Montérégie, 75/186 (15.4%).
Abbreviation: n, number.

higher among those with more severe pain disability. In terms of pain frequency, the majority (75.2%) were suffering continuously. Patients reported a mean pain intensity score of 6.5 (±1.9) in the past week. Based on the Hospital Anxiety and Depression Scale[46], 24.0% and 40.0% of participants probably suffered from depression and anxiety, respectively. The mean number of reported pain diagnoses per individual was 2.5 (±1.3), the most frequent being chronic back pain (64.0%) and degenerative osteopathies such as osteoarthritis and arthrosis (60.7%). Patients classified in the severe disability category reported more frequent and more intense pain than those in the mild and moderate categories. They were also more likely to feel depressed and anxious, experience more pain-related sleep problems, and suffer from multiple pain syndromes.

Health care resource utilization and productivity losses

Individuals were hospitalized for an average of 1.9 (9.9) days annually, where 1.1 (8.3) days were possibly related to CNCP (Table 3). Overall, 19.7% of the cohort of patients were hospitalized (all causes considered) and 8.9% of the cohort of patients were hospitalized for a cause that was possibly related to pain (data not reported in table). During this 1-year period, participants visited the ER 0.9 times (±1.6) on average and saw primary care physicians and specialists for an average of 4.8 (±4.9) times and 2.1 (±3.1) times, respectively. Patients reporting more pain disability were more likely to have visited the ER or be seen by primary care physicians and specialists. The majority of participants (56.1%) reported at least one visit to a health care professional other than a physician (data not reported in table), with an annual number of visits per patient averaging 74.6 (±135.5). Physiotherapists and massage therapists were the most frequently seen with an average of 40.3 (±90.1) visits per patient and 13.5 (±48.8) visits per patient, respectively. In terms of pain medication, individuals took an average of 3.9 (±2.0) and 1.5 (±1.6) different prescribed and over-the-counter medications to treat pain and/or the adverse effects of pain treatments, respectively. The number of prescribed medications was the highest among patients classified in the severe pain disability subgroup. Patients with more pain disability were more likely to have opioid analgesics dispensed in the year prior to recruitment: mild, 49%; moderate, 68%; and severe, 80%; P=0.0001. Among those on opioids, 19 patients were dispensed a high oral morphine-equivalent dose (>200 mg per day). These patients were equally distributed across the pain disability subgroups (data not reported in table).

Work productivity data revealed that individuals lost an equivalent of 69.4 (±111.3) workdays annually due to pain or its treatment; the number of days lost due to absenteeism and presenteeism averaged 57.3 (±106.3) days and 12.1 (±36.0)

Table 1 Sociodemographic characteristics

	All patients (n=483)	Patients stratified by level of pain disability			*P*-values
		Mild disability[a] (n=165)	Moderate disability[b] (n=160)	Severe disability[c] (n=158)	
Age (years), mean (SD)	59 (13)	61 (13)	58 (12)	57 (11)	0.002
Women, n (%)	326 (67.5)	110 (66.7)	106 (66.3)	110 (69.6)	0.783
Type of insurances, n (%)					0.321
Public (RAMQ)	295 (61.1)	96 (58.2)	95 (59.4)	104 (65.8)	
Private	188 (38.9)	69 (41.8)	65 (40.6)	54 (34.2)	
Ethnicity (Caucasian),[d] n (%)	465 (96.3)	161 (97.6)	154 (96.3)	150 (94.9)[e]	0.457
First language (French),[f] n (%)	437 (90.5)	151 (91.5)	146 (91.3)	140 (88.6)	0.931
Highest level of education completed,[g] n (%)					0.664
None or elementary school	132 (27.3)	48 (29.1)	41 (25.6)	43 (27.2)	
High-school	170 (35.2)	54 (32.7)	61 (38.1)	55 (34.8)	
College-technical school or CEGEP	90 (18.6)	26 (15.8)	30 (18.8)	34 (21.5)	
University	87 (18.0)	36 (21.8)	28 (17.5)	23 (14.6)	
Civil status,[h] n (%)					0.034
Married or common law	263 (54.5)	98 (59.4)	91 (56.9)	74 (46.8)	
Single	64 (13.3)	15 (9.1)	19 (11.9)	30 (19.0)	
Separated/divorced	98 (20.3)	27 (16.4)	33 (20.6)	38 (24.1)	
Widowed	57 (11.8)	25 (15.2)	16 (10.0)	16 (10.1)	
Annual family income,[i] n (%)					0.011
<$20,000	128 (26.5)	33 (20.0)	36 (22.5)	59 (37.3)	
$20,000–$50,000	188 (38.9)	66 (40.0)	66 (41.3)	56 (35.4)	
>$50,000	117 (24.2)	44 (26.7)	42 (26.3)	31 (19.6)	
Current work status,[j,k] n (%)					<0.0001
Full-time job	93 (19.3)	43 (26.1)	33 (20.6)	17 (10.8)	
Part-time job	22 (4.6)	9 (5.5)	9 (5.6)	4 (2.5)	
Temporary disability	19 (3.9)	2 (1.2)	7 (4.4)	10 (6.3)	
Permanent disability	86 (17.8)	16 (9.7)	24 (15.0)	46 (29.1)	

Notes: [a]Patients in the first BPI tertile (scores ranging from 0–4.3); [b]patients in the second BPI tertile (scores ranging from 4.31–6.4); [c]patients in the third BPI tertile (scores ranging from 6.41–10.0); [d]additional categories were reported: Black; Native American; Hispanic; Asian; and other; [e]one patient refused to answer; [f]additional categories were reported: English; Spanish; Italian; Portuguese; German; Arabic; Chinese; Japanese; and Vietnamese; [g]one and three patients refused to answer in the mild and severe disability groups, respectively; [h]one patient refused to answer in the moderate disability group; [i]twenty-two, 16, and 12 patients refused to answer in the mild, moderate, and severe disability groups, respectively; [j]additional categories were reported: homemaker; student; unemployed; laid off; and volunteer; [k]two, seven, and four patients refused to answer in the mild, moderate, and severe disability groups, respectively.

Abbreviations: n, number; SD, standard deviation; RAMQ, Régie de l'assurance maladie du Québec; CEGEP, Collège d'enseignement général et professionnel; BPI, Brief Pain Inventory.

days, respectively. Annual workdays lost were higher in individuals with more severe pain disability.

Unadjusted direct health care and productivity costs

The mean annual total direct health care costs per patient averaged CAD $7,334 (±$9,276), CAD $11,128 (±$19,131), and CAD $10,311 (±$11,501) for patients with mild, moderate, and severe pain disability, respectively (Table 4). Major cost components included nonpharmacologic health care services, which accounted for 47.1% (CAD $4,505/CAD $9,565) of the total direct health care costs, hospitalizations and ER visits (24.6%), prescribed medications (20.5%), and outpatient medical visits (6.3%). For patients with mild, moderate, and severe pain disability, productivity costs per patient averaged CAD $4,523 (±$8,951), CAD $8,254 (±$13,386), and CAD $8,536 (±$12,077), respectively. Absenteeism and presenteeism costs accounted for 71.4% and 28.6% of those costs, respectively. When combining the direct health care costs and productivity costs, the mean annual costs per patient were equal to CAD $11,857 (±$13,685), CAD $19,382 (±$23,228), and CAD $18,847 (±$18,734) for patients with mild, moderate, and severe pain disability, respectively. The costs of hospitalizations, outpatient visits, prescribed medications, and total costs were found to be significantly and positively related to the level of pain disability.

Adjusted direct health care costs and productivity costs

Once they were adjusted for age, sex, pain duration, and Charlson comorbidity scores, the mean annual direct costs

Table 2 Clinical and psychosocial characteristics

	All patients (n=483)	Patients stratified by level of pain disability			*P*-values
		Mild disability[a] (n=165)	Moderate disability[b] (n=160)	Severe disability[c] (n=158)	
Duration of pain (years), mean (SD)	12 (11)	11 (11)	11 (11)[d]	13 (12)	0.186
Duration of pain, n (%)[d]					0.003
6–12 months	37 (7.7)	17 (10.3)	12 (7.5)	8 (5.1)	
13–14 months	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	
15–36 months	74 (15.3)	35 (21.2)	23 (14.4)	16 (10.1)	
37–48 months	32 (6.6)	6 (3.6)	12 (7.5)	14 (8.9)	
49 months or more	338 (70.0)	106 (64.2)	112 (70.0)	120 (75.9)	
Frequency of pain in the past 7 days, n (%)					0.000
Always	363 (75.2)	99 (60.0)	125 (78.1)	139 (88.0)	
Occasionally	116 (24.0)	62 (37.6)	35 (21.9)	19 (12.0)	
Never	4 (0.8)	4 (2.4)	0 (0.0)	0 (0.0)	
Average pain intensity in the past 7 days, mean (SD)	6.5 (1.9)	5.5 (1.9)[e]	6.7 (1.6)	7.3 (1.6)	0.000
Pain functional impact score,[f] mean (SD)	5.3 (2.2)	2.8 (1.2)	5.5 (0.6)	7.7 (0.8)	0.000
Depression,[g] n (%)	116 (24.0)	5 (3.0)	38 (23.8)	73 (46.2)[d]	0.000
Anxiety,[g] n (%)	193 (40.0)	34 (20.6)	70 (43.8)	89 (56.3)[d]	0.000
Pain sleep impact score,[h] mean (SD)	5.1 (2.9)	3.3 (2.6)	5.4 (2.7)	6.6 (2.4)	0.000
Comorbidity index,[i] mean (SD)	2.5 (1.9)	2.6 (2.0)	2.3 (1.7)	2.5 (1.9)	0.303
Number of self-reported pain diagnoses per patient, mean (SD)	2.5 (1.3)	2.3 (1.2)	2.4 (1.3)	2.9 (1.5)	0.000
Self-reported pain diagnoses, n (%)[j]					
Chronic back pain	309 (64.0)	90 (54.5)	104 (65.0)	115 (72.8)	0.003
Chronic neck pain	186 (38.5)	52 (31.5)	60 (37.5)	74 (46.8)	0.017
Fibromyalgia	114 (23.6)	33 (20.0)	33 (20.6)	48 (30.4)	0.050
Osteoarthritis, arthrosis, and other degenerative osteopathies	293 (60.7)	102 (61.8)	88 (55.0)	103 (65.2)	0.165
Rheumatoid arthritis and other inflammatory osteopathies	55 (11.4)	17 (10.3)	17 (10.6)	21 (13.3)	0.653
Tendinitis, bursitis, capsulitis, and epicondylitis	101 (20.9)	28 (17.0)	35 (21.9)	38 (24.1)	0.275
Visceral pain	74 (15.3)	16 (9.7)	22 (13.8)	36 (22.8)	0.004
Neuropathic pain	88 (18.2)	38 (23.0)	26 (16.3)	24 (15.2)	0.139

Notes: [a]Patients in the first BPI tertile (scores ranging from 0–4.3); [b]patients in the second BPI tertile (scores ranging from 4.31–6.4); [c]patients in the third BPI tertile (scores ranging from 6.41–10.0); [d]one missing value; [e]two missing values; [f]BPI questionnaire; [g]Hospital Anxiety and Depression Scale; presence of depression and anxiety disorder is probable when score ≥11; [h]Chronic Pain Sleep Inventory questionnaire; [i]Charlson Comorbidity Index; [j]individuals could report more than one diagnosis.
Abbreviations: n, number; SD, standard deviation; BPI, Brief Pain Inventory.

per patient averaged CAD $7,374 (95% CI: $5,819–$8,930), CAD $10,524 (95% CI: $8,383–$12,665), and CAD $9,546 (95% CI: $7,502–$11,590) for patients with mild, moderate, and severe pain disability, respectively (Table 5). Productivity costs were CAD $3,005 (95% CI: $1,587–$4,422), CAD $5,083 (95% CI: $2,647–$7,519), and CAD $5,385 (95% CI: $2,789–$7,981) for each group, with total costs adding up to CAD $12,913 (95% CI: $10,534–$15,292), CAD $17,970 (95% CI: $14,782–$21,159), and CAD $17,292 (95% CI: $14,075–$20,510). A significant positive association was observed between the level of pain disability, as well as the total adjusted direct health care costs (considering pain-related hospitalizations only) and productivity costs: mild disability, CAD $12,118; moderate disability, CAD $18,278; and severe disability, CAD $19,216; P=0.001.

Discussion

This is one of the rare studies providing a comprehensive evaluation of the economic burden of CNCP in a large cohort of patients followed up in primary care. The direct health care costs of CNCP in this cohort of patients represented nearly 60% of the total direct health care and productivity costs. The use of complementary health care services accounted for almost 50% of the direct costs. The total direct health care and productivity costs averaged CAD $16,636 per patient per year and varied according to the level of pain disability – the more disabled the patients were, the higher the costs were. Although high, these numbers represent only a portion of the true costs since they do not include other indirect costs such as patients' travel expenses, paid household help, expenses incurred by family members, and so on.

Table 3 Annual health care resource utilization and productivity losses per patient

Mean (SD)	All patients (n=483)	Patients stratified by level of pain disability			*P*-value
		Mild disability[a] (n=165)	Moderate disability[b] (n=160)	Severe disability[c] (n=158)	
Health care resources utilization per patient					
Number of hospitalization days					
All causes	1.9 (9.9)	1.1 (5.8)	3.2 (15.1)	1.5 (5.5)	0.146
Pain-related as possible cause	1.1 (8.3)	0.7 (5.6)	1.8 (12.6)	0.8 (4.2)	0.468
Number of physician visits					
Primary care	0.4 (2.7)	0.2 (1.3)	0.4 (2.3)	0.6 (3.9)	0.423
Specialists	1.1 (4.4)	0.8 (3.8)	1.4 (5.5)	1.1 (3.7)	0.449
Number of emergency room visits	0.9 (1.6)	0.6 (1.3)	0.9 (1.8)	1.1 (1.7)	0.046
Number of physician visits at emergency					
Primary care	0.2 (1.3)	0.2 (1.3)	0.2 (1.3)	0.3 (1.2)	0.645
Specialists	0.9 (3.3)	0.4 (1.9)	1.2 (4.0)	1.1 (3.7)	0.085
Number of outpatient physician visits					
Primary care	4.8 (4.9)	4.4 (3.9)	4.1 (4.1)	6.0 (6.3)	0.001
Specialists	2.1 (3.1)	1.9 (2.7)	1.8 (2.7)	2.8 (3.8)	0.008
Number of outpatient tests and interventions					
All	10.7 (7.5)	10.0 (6.9)	10.6 (8.1)	11.6 (7.3)	0.136
Pain-related	1.4 (1.8)	1.2 (1.6)	1.5 (1.9)	1.4 (1.8)	0.322
Number of complementary health care provider visits					
Psychotherapists	2.7 (13.4)	1.7 (9.5)	2.9 (14.7)	3.5 (15.4)	0.451
Physiotherapists	40.3 (90.1)	31.3 (75.5)	45.3 (98.0)	44.6 (95.6)	0.291
Massage therapists	13.5 (48.8)	9.0 (34.3)	15.1 (49.6)	16.5 (59.6)	0.336
Occupational therapists	5.4 (30.7)	4.4 (30.6)	6.4 (29.4)	5.4 (32.3)	0.848
Acupuncturists	4.3 (21.3)	4.7 (19.9)	4.2 (18.6)	4.0 (25.1)	0.946
Osteopaths	4.2 (18.0)	6.4 (22.8)	3.6 (16.8)	2.7 (12.8)	0.159
Chiropractors	4.2 (18.9)	6.3 (23.8)	2.3 (12.4)	3.9 (18.5)	0.157
Total	74.6 (135.5)	63.9 (110.8)	79.7 (142.7)	80.7 (150.8)	0.454
Number of prescribed pain-related medications[d]	3.9 (2.0)	3.4 (1.9)	4.1 (2.0)	4.2 (2.0)	0.000
Number of over-the-counter pain-related medications[d]	1.5 (1.6)	1.5 (1.6)	1.5 (1.7)	1.5 (1.6)	0.897
Annual productivity losses per patient					
Number of absenteeism days[e]	57.3 (106.3)	32.9 (83.4)	54.9 (104.7)	85.3 (122.0)	0.000
Number of presenteeism days[f]	12.1 (36.0)	8.7 (24.1)	19.0 (46.7)	8.7 (33.0)	0.012
Total number of workdays lost	69.4 (111.3)	41.6 (86.3)	73.9 (114.5)	94.0 (124.7)	0.000

Notes: [a]Patients in the first BPI tertile (scores ranging from 0–4.3); [b]patients in the second BPI tertile (scores ranging from 4.31–6.4); [c]patients in the third BPI tertile (scores ranging from 6.41–10.0); [d]including analgesic and medication to treat side effects of analgesics; [e]individuals with full- or part-time jobs, as well as those on temporary or permanent disability were included. A null value was computed for all other individuals; [f]only individuals answering yes to the question "Do you currently have a paid job?" and those having a full- or part-time job were included. A null value was computed for all other individuals.
Abbreviations: SD, standard deviation; n, number; BPI, Brief Pain Inventory.

Complementary health care services (for example, physiotherapy, massage therapy, occupational therapy) are known to be extensively used by individuals with CNCP,[7,53] including those with chronic low back pain.[54] Not considering these costs may, therefore, lead to an important underestimation of the direct health care costs of CNCP and may explain discrepancies among studies. For example, Lachaine et al[12] estimated that the annual direct health care costs associated with neuropathic painful disorders in Quebec (Canada) averaged CAD $4,065 per patient (±$6,798 [2007 values]; $4,339 [2011 values]). In another study on the costs associated with fibromyalgia in Quebec,[11] the direct health care costs added up to CAD $4,163 (±$7,536 [2002 values]; $4,960 [2011 values]). Differences with our results might be explained by the fact that complementary health care services were not considered in these studies.

In patients with chronic pain, higher than normal absenteeism rates,[2] as well as significant interference with work performance,[8] have been reported. In our study, the mean annual cost associated with productivity losses represented about 40% of the total direct health care and productivity costs. This proportion is consistent with earlier observations made in individuals suffering from fibromyalgia syndrome[55] and chronic low back pain[54] where the proportion of costs associated with productivity

Table 4 Crude annual direct health care costs and productivity costs (CAD dollars) per patient

Mean (SD)	All patients (n=483)	Patients stratified by level of pain disability			*P*-values
		Mild disability[a] (n=165)	Moderate disability[b] (n=160)	Severe disability[c] (n=158)	
Direct health care costs					
Hospitalizations					
All hospitalization costs, except physician visits	1,908 (9,877)	1,148 (5,849)	3,117 (15,080)	1,480 (5,583)	0.021
Pain-related hospitalization costs	1,102 (8,304)	739 (5,555)	1,763 (12,610)	810 (4,213)	0.043
General practitioner visits	14 (98)	9 (47)	13 (91)	22 (137)	0.004
Specialist visits	114 (321)	106 (307)	138 (380)	99 (267)	0.508
Total costs	2,036 (10,137)	1,262 (6,053)	3,266 (15,404)	1,600 (5,878)	0.030
Emergency room visits					
Emergency room costs	250 (481)	179 (369)	267 (553)	308 (498)	0.150
General practitioner visits	8 (44)	5 (33)	6 (42)	13 (55)	0.001
Specialist visits	62 (289)	43 (260)	65 (262)	78 (341)	0.455
Total costs	320 (686)	227 (528)	338 (753)	399 (752)	0.148
Outpatient medical consultations					
Primary care visits	231 (247)	211 (205)	204 (233)	278 (291)	0.129
Specialist visits	163 (240)	137 (195)	144 (222)	209 (290)	0.094
All outpatient tests and interventions	145 (170)	132 (163)	149 (186)	152 (161)	0.699
Pain-related tests and interventions	66 (102)	50 (80)	75 (116)	72 (105)	0.115
Total costs	604 (541)	531 (437)	573 (561)	712 (602)	0.048
Complementary health care provider visits					
Psychotherapists	257 (1,276)	160 (902)	279 (1,400)	335 (1,466)	0.103
Physiotherapists	2,337 (5,231)	1,818 (4,382)	2,626 (5,688)	2,586 (5,546)	0.528
Massage therapists	781 (2,830)	521 (1,992)	873 (2,876)	959 (3,457)	0.181
Occupational therapists	343 (1,944)	281 (1,937)	405 (1,861)	345 (2,043)	0.607
Acupuncturists	249 (1,235)	274 (1,153)	243 (1,077)	230 (1,455)	0.875
Osteopaths	339 (1,426)	507 (1,801)	288 (1,326)	216 (1,011)	0.043
Chiropractors	198 (899)	299 (1,131)	108 (587)	185 (880)	0.013
Total costs	4,505 (8,115)	3,860 (6,706)	4,822 (8,599)	4,856 (8,924)	0.640
Prescribed analgesics and medication to treat side effects of medication	1,963 (2,978)	1,304 (1,728)	1,979 (3,029)	2,635 (3,728)	<0.001
Over-the-counter analgesics and medication to treat side effects	136 (601)	150 (709)	150 (708)	108 (275)	0.341
Total direct health care costs	9,565 (13,993)	7,334 (9,276)	11,128 (19,131)	10,311 (11,501)	0.008
Productivity costs					
Absenteeism	5,052 (9,429)	3,068 (7,677)	5,084 (9,743)	7,091 (10,339)	0.082
Presenteeism	2,020 (6,013)	1,455 (4,027)	3,171 (7,804)	1,445 (5,511)	0.057
Total productivity costs	7,072 (11,716)	4,523 (8,951)	8,254 (13,386)	8,536 (12,077)	0.158
Total overall costs	**16,636 (19,182)**	**11,857 (13,685)**	**19,382 (23,228)**	**18,847 (18,734)**	**<0.001**

Notes: [a]Patients in the first BPI tertile (scores ranging from 0–4.3); [b]patients in the second BPI tertile (scores ranging from 4.31–6.4); [c]patients in the third BPI tertile (scores ranging from 6.41–10.0).
Abbreviations: CAD, Canadian; SD, standard deviation; n, number; BPI, Brief Pain Inventory.

losses accounted for more than half of the total costs. Similar observations were also made by Guerriere et al[24] in a population of chronic pain patients waiting for treatment in tertiary care pain clinics. Although they remain insufficiently documented, presenteeism costs should be systematically taken into consideration, as illustrated by an Australian and an American study where these costs accounted for the majority of the CNCP costs.[14,21]

When combined, the direct health care costs and productivity costs led to mean annual total costs of CAD $16,636 per patient, which compares with previous estimates in fibromyalgia (US $15,000 [2009 values]; CAD $15,489 [2011 values]),[56] chronic low back pain (US $19,473 [2002 values]; CAD $23,566 [2011 values]),[54] and osteoarthritis (US $16,146 [2005 values]; CAD $18,189 [2011 values]).[57] Other studies have also reported that economic burden increases with the severity of pain disability. For example, among individuals with rheumatoid arthritis, increases in self-report disability status, as measured by the Health Assessment Questionnaire, were associated with higher costs.[17,18,58,59] Costs incurred by chronic low back pain and by neuropathic pain were also found to vary as a function of the degree of disability levels.[54,60] However, the present study is the first to demonstrate this association for a variety of chronic pain diagnoses in a primary care setting.

Table 5 Adjusted annual direct health care costs and productivity costs (CAD dollars) per patient

Mean (95% CI)	Mild disability[a] (n=165)	Moderate disability[b] (n=160)	Severe disability[c] (n=158)	*P*-values
Direct health care costs				
Hospitalization				
All-cause hospitalizations	897 (415; 1,380)	2,857 (1,348; 4,365)	2,021 (849; 3,193)	0.012
Pain-related hospitalizations	326 (146; 507)	1,700 (707; 2,693)	883 (224; 1,542)	0.001
Emergency room visits	228 (137; 319)	339 (202; 476)	400 (238; 563)	0.149
Outpatient consultation visits	532 (441; 622)	574 (475; 673)	713 (589; 837)	0.048
Complementary health care provider visits	4,165 (2,553; 5,776)	4,279 (2,638; 5,921)	4,345 (2,665; 6,024)	0.989
Prescribed analgesics	1,428 (1,143; 1,713)	1,976 (1,589; 2,363)	2,330 (1,848; 2,812)	0.004
Over-the-counter analgesics	112 (74; 150)	138 (91; 185)	116 (76; 155)	0.646
Total	7,374 (5,819; 8,930)	10,524 (8,383; 12,665)	9,546 (7,502; 11,590)	0.051
Productivity costs				
Absenteeism	2,320 (1,179; 3,460)	3,175 (1,587; 4,763)	4,922 (2,449; 7,395)	0.108
Presenteeism	826 (368; 1,284)	1,761 (841; 2,681)	300 (130; 469)	0.000
Total	3,005 (1,587; 4,422)	5,083 (2,647; 7,519)	5,385 (2,789; 7,981)	0.194
Total direct health care and productivity costs				
Including all cause hospitalizations	12,913 (10,534; 15,292)	17,970 (14,782; 21,159)	17,292 (14,075; 20,510)	0.024
Including pain-related hospitalizations	12,118 (9,844; 14,393)	18,278 (14,909; 21,648)	19,216 (15,538; 22,894)	0.001

Notes: [a]Patients in the first BPI tertile (scores ranging from 0–4.3); [b]patients in the second BPI tertile (scores ranging from 4.31–6.4); [c]patients in the third BPI tertile (scores ranging from 6.41–10.0).
Abbreviations: CAD, Canadian; CI, confidence interval; n, number; BPI, Brief Pain Inventory.

Strengths and limitations

Like any other study, the present one has some limitations that must be taken into consideration. Patients were recruited only if they had an active analgesic prescription from a primary care physician in their pharmacy chart. Our results cannot be extrapolated to those having no active analgesic prescriptions or only prescriptions from a specialist. Furthermore, some of our results are based on patient self-reports and may be influenced by social desirability (tendency to answer questions in a manner that will be viewed favorably by others) and memory biases. However, the research assistants who conducted the telephone interviews were well trained and used a structured interview protocol. Self-administered questionnaires were used to document more sensitive information such as levels of depression and anxiety. Some assumptions were also made to estimate the annual costs. Annual productivity costs, as well as annual use of over-the-counter medication and complementary health care services, were estimated using data covering a 6-month period. This may have resulted in an overestimation or underestimation of costs, as resource utilization rates may have changed over time. Furthermore, the frequency of use was not precisely documented. Finally, we took into account the direct costs to patients associated with different self-management techniques (eg cost of physiotherapy). However, we did not consider the impact this may have on caregiver time (eg time absent from work for the patient's wife).

Despite those limitations, this study offers a comprehensive description of the direct health care costs and productivity costs associated with CNCP. The use of administrative databases and pharmacy charts enabled the precise documentation of prescribed pharmacological treatments of participants, as well as their use of health care resources. Furthermore, we also assessed the use of over-the-counter medication and complementary health care services, both documented through telephone interviews with the patients. The structured interview protocol also allowed for the documentation of productivity losses due to pain or its treatment, which were further translated into productivity costs based on the method previously described by Hu et al.[42]

Conclusion

CNCP among primary care patients is associated with substantial economic burden not only for the health care system and the workforce, but also for patients themselves. These costs tend to increase as pain causes more limitations in a patient's daily activities. Further research is clearly needed to improve the management of CNCP in primary care. Finding efficient strategies to reduce further chronicity of pain problems is certainly an avenue that needs to be explored, as it could alleviate not only the burden of illness, but also its associated costs.

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Supplementary materials

Table S1 Hospitalization codes related or possibly related to chronic pain

- Adhesive capsulitis of shoulder
- Algoneurodystrophy, unspecified
- Arthritis, unspecified
- Articular ankylosis
- Articular ankylosis – knee joint
- Carpal tunnel syndrome
- Cervicalgia
- Chronic intractable pain
- Chronic salpingitis and oophoritis
- Coxarthrosis, unspecified
- Endometriosis of uterus
- Endometriosis, unspecified
- Fibromyalgia
- Gonarthrosis, unspecified
- Gout, unspecified
- Idiopathic gout – elbow joint
- Idiopathic gout – hand joints
- Irritable bowel syndrome with diarrhea
- Irritable bowel syndrome without diarrhea
- Lateral epicondylitis
- Low back pain
- Osteoarthritis, unspecified
- Other cervical disc displacement
- Other dorsalgia
- Other specified arthrosis
- Other specified disorders of bone – leg
- Other specified intervertebral disc displacement
- Other specified spondylopathies – cervical region
- Pain in limb – scapular region
- Radiculopathy – dorsal region
- Rheumatoid arthritis, unspecified
- Rotator cuff syndrome
- Spinal instabilities – lumbar region
- Spinal stenosis – cervical region
- Spinal stenosis – lumbar region
- Spondylosis, unspecified – lumbar region

Table S2 Documented analgesics

Therapeutic class	International common denomination
Anticonvulsants	
Carboxylic acid derivatives	Valproic acid
Gamma-aminobutyric acid analogs	Gabapentin, Pregabalin
Iminostilbene	Carbamazepine, Oxcarbazepine
Other anticonvulsants	Divalproex, Lamotrigine, Topiramate
Antidepressants	
Selective serotonin reuptake inhibitors	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Trazodone
Serotonin and noradrenaline reuptake inhibitors	Duloxetine, Venlafaxine
Tricyclic and tetracyclic antidepressants	Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Mirtazapine, Nortriptyline, Trimipramine
Other antidepressants	Bupropion
Antiretroviral	Acyclovir, Famciclovir, Valacyclovir
Disease-modifying antirheumatic drugs	Auranofin, Aurothioglucose, Aurothiomalate, Azathioprine, Chloroquine, Cyclosporine, D-penicillamine, Hydroxychloroquine, Leflunomide, Methotrexate, Sulfasalazine
Muscle relaxants	
Benzodiazepine	Diazepam, Tetrazepam
Carbamic acid derivatives	Methocarbamol
Centrally acting myorelaxants	Cyclobenzaprine, Tizanidine
Gamma-aminobutyric acid derivatives	Baclofen
Other muscle relaxants	Thiocolchicoside
Nonsteroidal antiinflammatory	
Acetic acids	Diclofenac, Etodolac, Indomethacin, Ketorolac, Nabumetone
Acetylsalicylic acid	
Coxibs	Celecoxib
Fenamates	Meclofenamate, Mefenamic acid
Oxicams	Meloxicam, Piroxicam
Propionic acids	Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Oxaprozin
Opioids	
Agonist–antagonist derivatives	Buprenorphine, Butorphanol, Nalbuphine, Pentazocine
Antagonists	Naloxone
Benzomorphan derivatives	Pentazocine
Centrally acting analgesics	Tramadol
Meperidine-like agonists	Fentanyl, Meperidine
Methadone-like agonists	Methadone, Propoxyphene
Morphine-like agonists	Codeine, Hydrocodone, Hydromorphone, Levorphanol, Morphine, Oxycodone, Oxymorphone
Natural cannabinoids	Tetrahydrocannabinol, Cannabidiol
Synthetic cannabinoids	Dronabinol, Nabilone