Impact of pharmaceutical prior authorization policies: a systematic review of the literature

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Abstract

A systematic review of published articles determining the effects of policies consisting of or including prior authorization (PA) of pharmaceutical prescription on drug use, healthcare utilization, healthcare expenditures, and health outcomes was conducted to give an overview of these policies for controlling drug spending which have been increasingly implemented by public and private insurers in the last decade, especially in the US context. We did a literature search in the electronic databases PUBMED (which includes MEDLINE), ECONLIT, Web of Science, and online sources including Google Scholar from 1985 to September 2006; and also reference lists of retrieved articles. Peer-reviewed studies that provided empirical results about the impact of pharmaceutical PA policies, including randomized controlled trials, non-randomized controlled trials, repeated measures studies, interrupted time series analyses, and before-and-after studies were included.

The most important conclusion is that pharmaceutical use and/or expenditure per patient or enrollee of drugs directly affected by PA restrictions and overall drug expenditure significantly decreased (increased) after policy implementation (removal). Health outcome changes attributed to PA policies were not directly evaluated. In most cases, except for cimetidine, PA implementation was not associated with significant changes in the utilization of other medical services. Even though the literature indicates a reduction in drug expenditure and a non-negative impact on use of other health services, policy recommendations still require improved study designs, and evidence cannot be easily transferred from one setting to another. The evidence still remains excessively limited to US Medicaid settings and to a small number of drug classes; there is a lack of consideration of implications of PA policies as heterogeneous interventions; there is an incomplete outcome measurement; and there is a notable lack of evidence of medium and long-term policy effects.

Introduction

It has been widely reported that prescription drug expenditures are one of the fastest growing components of health expenditures in public and/or private health systems around the world.[1] Several pharmaceutical utilization programmes such as prior authorization (PA) policies (administrative interventions) for controlling drug spending have been increasingly implemented by insurers in the last decade, especially in the US[2-4] and Canada,[5] but they are also rapidly gaining popularity among European public insurers (Denmark, France, Norway, Spain, etc.).

PA policies restrict the use of certain medications by requiring advance approval by the insurance company before reimbursement of specific drugs (prior to dispensing). These policies require submission of individual clinical information for review before the insurer accepts to cover the cost of the prescription of some usually high-cost or risky drugs. PA policies may also adopt the form of "fail first" mechanisms (requiring patients to have failed a lower-cost treatment before use of a more expensive agent),[6] prior approval for non-preferred drugs, individual reimbursement for specific drugs (patient specific, based on individual applications), etc.[7,8]

The main goal of PA policies is to reduce pharmaceutical expenditure by substituting less expensive drugs for higher-priced drugs when therapeutically equivalent alternatives exist and/or to reduce inappropriate prescription (i.e., prescription outside restrictive clinical conditions for which reimbursement has been approved) of risky and expensive medicines.

In practice, PA policies respond to at least two different and not always convergent objectives. First, PA policies have been justified on safety or clinical grounds when applied to medicines with a high probability of adverse effects. If this were the case, the

optimal setting for the policy would be centralized decisions for whole health system affecting all prescriptions, independently of the specific insurer. In fact, the main goal of this type of PA policy would be to reduce negative health outcomes by improving prescription quality, independently of its impact on pharmaceutical expenditure. And second, PA policies have been implemented by insurers mainly as a cost containment measure applied to high-cost medicines or treatments with a high incremental cost-effectiveness ratio (i.e., cost per quality-adjusted life year or QALY) when prescribed outside the high-risk target population for which efficacy has been established. In this more common case, it is clear that the optimal setting for the policy is the decentralized reimbursement decisions of each individual insurer (coverage decisions), which should be dependent on their willingness to pay for health improvements.

In both types of PA policies, there are two implicit hypotheses about prescriber behaviour. The first one is that prescribers have imperfect or biased information about health risks and/or costs of pharmaceuticals. Then, the effects of PA policies will depend on the amount of previous inappropriate prescription from the clinical or the economic perspective. The second hypothesis to justify PA policies is that doctors do not have enough incentive to act as perfect agents for the patient and the insurer. Some authors suggest that PA policies exert a *sentinel effect* resulting in a *"decrease in services given by providers as a result of having a utilization reviewer keep tabs on them"*[9] (cited by Kahan and colleagues[10]). Then, government and commercial warnings, surveillance mechanisms, tiered copayments, and prescriber incentives would be alternatives to be compared with PA implementation. Accordingly, superiority of one policy over the other can only be empirically established for groups of similar medicines or treatments.

Intended and unintended effects of PA policies should cover drug substitution, drug discontinuation, alteration of the adherence to the treatment, and changes in pharmaceutical expenditure, healthcare utilization, health service and health outcomes (mortality, morbidity, and quality of life). Although the overall goal of PA policies is to

reduce costs without negatively affecting health outcomes, there are concerns that under certain conditions they could result in adverse health effects owing to suboptimal treatment or restricted access to appropriate treatments.

The purpose of this paper is to synthesize and summarize the state of knowledge about the impact of pharmaceutical PA policies on drug use (substituting less expensive medication and/or lower drug utilization), healthcare utilization, healthcare expenditure, and health outcomes by systematically reviewing published empirical studies.

Previous reviews of the impact of PA literature summarize evidence related to the effects of the introduction of such policies on economic and clinical outcomes, but the results of these studies are dated and they included very few studies.[3,6,11-13] Some of these reviews[3,6,12,13] evaluated the effects of PA within the context of a broader set of pharmaceutical utilization management measures restricting access to costly drugs (i.e., restrictive formularies) in specific US settings (Medicaid, Managed Care Organizations, etc.). To our knowledge, until now the only published specific review of PA policies[11] included only six papers up to April 2005, and half of them present severe limitations that make their inclusion in the review problematic: one of them evaluates a hospital PA policy that is not comparable with ambulatory interventions;[14] a second one is a simple cross-sectional design without a comparison group;[15] and a third one is a cross-sectional study with a comparison group,[16] but the groups could not be carefully controlled. Other surveys covering PA policies only included three,[6,12] four[3] or five studies.[13]

This review is not intended to replicate the results of prior reviews but rather to provide new updated evidence on a wider range of outcomes, including a more comprehensive and updated survey, a critical assessment of methodologies used, and a discussion of the lessons of the evidence provided by the design of policy interventions outside the US.

Method of Review

We searched English-language articles in PUBMED (which includes MEDLINE), ECONLIT, Web of Science, and online sources including Google Scholar from 1985 to 12th September 2006 using the following keywords: *prior authorization*, *prior authorisation*, *special authorization*, *special authorisation*, *prior approval*, *preauthorization*, and *preauthorisation* in combination with *drugs*, *pharmaceuticals*, and *medicines* when possible. Reference lists of retrieved articles and prior literature surveys were reviewed to identify studies that our search strategy may have missed.

We included studies if they meet all the following requirements: 1) were peer-reviewed published articles providing empirical results quantifying the effect of ambulatory PA policies; 2) isolated the independent effect of PA when it was applied simultaneously to other policy measures (i.e., Cunningham[17]); 3) measured the impact of the policy on outcome variables including drug use, drug expenditure, healthcare utilization, healthcare spending, health outcomes, and/or quality of life; 4) were designed as randomized controlled trials, non-randomized controlled trials, repeated measures studies, interrupted time series analyses, and before-and-after studies.

Interrupted time series analyses had to have at least six data points before and six after the PA implementation to qualify. Interrupted time series that had data for many individual participants (patients, regions or states, etc.) were regarded as repeated measures studies (panel data), resulting in a study with more power than a simple time series.[18]

Confidence in the estimated PA impact may be graded using the approach recommended by the GRADE Working Group[19]: the highest level of evidence corresponds to randomized controlled trials, interrupted time series and repeated measures studies are

graded as moderate quality, and controlled before-and-after studies as low quality. Results of repeated measures and interrupted time series could be considered more compelling (more likely to be correct) than controlled before-and-after studies.[18] The lowest grade of evidence of the included studies corresponds to uncontrolled before-and-after studies.

We excluded studies if they only described policy details and/or provided descriptive data after policy implementation without a control group. Cross-sectional studies[16,20] with a comparison group were excluded from this review because the groups could not be carefully controlled and they also lack a before-and-after comparison. Studies evaluating PA policies applied to hospital-administered drugs and other healthcare services were also excluded. Finally, forecasting and modelling exercises dealing with the impact of PA policies not based on observational data were not included in the review.[21-23]

From a maximum number of items reported in the search of 1,760 in Google Scholar, 81 in PUBMED, 56 in Web of Science, and 6 in ECONLIT, we finally identified 15 studies that met our criteria. More than two thirds (11/15) of the studies reviewed herein had not been addressed in prior reviews.

The following information was extracted from the included studies using a standardized extraction form: drugs affected by the PA policy; type of study (randomized trial, non-randomized trial, repeated measures study, interrupted time series, and before-and-after study); study setting (country and study duration); characteristics of the participants (patients and insurer); main outcome measures; and the results for the main outcome measures.

We did not use formal meta-analytic techniques because the included studies used many different effect measures and some did not report the parameters necessary to calculate an effect size.[11]

Results

The table below (Table I) includes the following information for the fifteen studies included herein: study identification, drugs under PA, type of study, study setting, characteristics of the participants, and main outcome measures.

[Insert Table I about here]

Despite the reported use of PA by private and public health insurers for many years, the literature on the impact of PA policies is very recent: only four out of fifteen studies (26.6%) were published before 2001, and nine out of fifteen (60%) have been published after December 2003. Only four health services research journals published more than one of the studies included in this review (*The American Journal of Managed Care*, *Clinical Therapeutics*, *The New England Journal of Medicine*, and *Medical Care*).

Eight of the PA studies included herein[16,24-30] evaluated the impact of the implementation of this policy on non-steroidal anti-inflammatory drugs (NSAIDs) and/or cyclooxygenase-2 (Cox-2) selective inhibitors (a relatively new class of NSAIDs which are relatively costly and about which there is uncertainty regarding their safety and efficacy), such as celecoxib. This may be a clear indication that PA policies have been extensively applied to NSAIDs, and especially to Cox-2, as non-systematic descriptive information for PA policy implementation confirms.

Despite the increasing interest in and use of PA policies outside the US, only two of the fifteen studies (13.3%) evaluated the impact of this policy in a non-US setting: one of them analysed the effect of a PA policy in Israel,[10] and the other one in British Columbia, Canada.[5] Most US-based studies evaluated PA policies implemented by the

public programme Medicaid. None of the studies evaluated the impact of this policy in a European setting.

Administrative intervention measures evaluated in fourteen out of the fifteen studies consist of PA implementation; in one of the studies,[28] the differential effect of implementing PA at market entry or implementing it two years after market entry for Cox-2 inhibitors was evaluated. Only one study evaluated the impact of PA removal.[31]

The main outcome measures used in most of the evaluation studies of PA policies included in this review (all except one) used measures of change in pharmaceutical use and/or in pharmaceutical expenditure. Only seven out of the fifteen studies (46.6%) evaluated the impact of PA policies using measures of change in some other health services use and/or health service expenditures. And only one of the fifteen studies[27] evaluated the impact of this policy on health-related quality of life. In terms of financing source, pharmaceutical companies financed five out of the fifteen studies (33.3%).

A second table (Table II) has been prepared to include study identification and the results for the main outcome measures grouped into pharmaceutical use and expenditure, healthcare services use and expenditure, and health outcomes and quality of life.

[Insert Table II about here]

Impact on pharmaceutical use and/or expenditure

All the studies except one[27] estimated the impact of PA on pharmaceutical use and/or expenditure. Only two of these studies reported changes in outcome variables related indirectly to the appropriateness of pharmaceutical prescription or utilization,[10,31] and twelve reported changes in use and/or pharmaceutical spending.[5,10,24-26,28-30,32-35]

In accordance with their intended policy objectives, ten reviewed studies[5,10,24-26,28-30,33-35] showed that pharmaceutical use and/or expenditure per patient or enrollee of drugs directly affected by PA restrictions significantly decreased (increased) after policy implementation (removal).

Overall pharmaceutical expenditure per patient dropped significantly after policy implementation in all eleven studies that evaluated the impact of specific PA implementation on overall drug spending.[5,24-26,28-30,32-35] The extent of substitution and expenditure decrease after PA varies according to medication class and type of policy design and objectives. The greater decrease in spending after PA was reported in a study evaluating the impact of PA on all proton pump inhibitor prescriptions.[33] A major decrease in pharmaceutical spending after PA (53%) was also reported in two studies[29,34] evaluating the impact of applying PA to brand-name drugs when generic substitutes exist; in this case, the expected impact mainly depends on price differentials between brand-name and generic drugs. In other PA implementations, the impact on pharmaceutical spending is heavily dependent on price differentials between restricted and non-restricted active ingredients (i.e., those studies evaluating PA restrictions on new Cox-2 inhibitors).

One study[36] only reported a reduction in the share of restricted drugs, but it did not report evidence of changes in use and/or expenditure per patient or enrollee.

Although appropriate prescription and use is usually claimed as one of the main purposes of PA, none of the reviewed studies provided an estimation of changes in inappropriate prescription or use after PA implementation. Kahan and colleagues[10] provides information about disease distribution of cases treated with cefuroxime before, during and post PA implementation. The post-intervention prescribing rates for each diagnostic category returned to the patterns observed before PA; however, these simple results are

not useful in order to obtain evidence on changes in inappropriate prescribing. In another study McCombs and colleagues[31] estimated the rate of drug therapy completion (patient compliance) for fluoxetine and paroxetine after PA removal; the authors concluded that in the unrestricted period physicians might have expanded the use of fluoxetine and paroxetine to treat less severely ill patients.

Impact on health services use and/or expenditure

Seven studies[5,25,26,29,32-34] analysed the extended impact of pharmaceutical PA on the use and expenditure of other health services. An increase in the utilization of other medical services (outpatient medical visits, emergency department visits, or inpatient admissions) after PA may indicate poor health outcomes or the occurrence of adverse events. In most cases, PA implementation was not associated with significant changes in the utilization of medical services such as physician office or ambulatory visits,[5,25,29,33,34] emergency department visits,[25,26] and inpatient admissions.[5,25,26,29,33,34]

Only one study,[32] which analysed the impact of PA restrictions applied to cimetidine in 1981-83, reported an increase in monthly physician payments and inpatient hospital costs that may have offset pharmaceutical savings from PA implementation.

Impact on health outcomes and health-related quality of life

We found only one study that addressed the impact of PA for branded-NSAIDs on the health-related quality of life (HRQoL) of chronic NSAIDs users[27] using a mail survey at eight weeks' follow-up from a very limited number of completed surveys (n=181). In this study, HRQoL was evaluated using self-reported information for nine domains (mobility, walking and bending, hand and finger function, self care, household tasks, social activities, arthritis pain, level of tension, and mood) and overall health. The conclusion was that PA for branded NSAIDs did not compromise patients' HRQoL.

Administrative costs of operating PA policies were rarely included in PA impact evaluations,[30,33,35] and when included they lacked accurate descriptions of how costs were measured, and what they comprised.[11] Carroll et al.[30] pointed out that an automated electronic PA system programme like that implemented in the Medicaid programme of Missouri in 2002 resulted in substantial savings in administrative costs and patients', physicians', and pharmacists' time compared with what would have been expected in a traditional PA programme.

Study quality

To determine the influence of methodological quality on study results, we stratified the fifteen reports on the basis of the type of study design. Only one study[5] assessed PA impact using a randomized controlled trial. Three studies reported PA impact in the framework of a repeated measures study with control series.[5,24,28] Five impact studies were designed as interrupted time series analyses with control series.[26,29,33,34,36] Four other studies employed a simpler before-and-after design with a control group.[25,27,30,31] And finally, three studies were designed as before-and-after analyses without any control group.[10,32,35]

The randomized controlled trial study[5] followed a policy exempted group and an intervention group for six months, which only allowed the authors to obtain limited short-term impact measures for PA implementation that cannot be extrapolated to a longer period of time after policy implementation.

Some interrupted time series studies and repeated measures studies suffer serious limitations because the analysis did not include sufficient time points to adjust for differential prior trends in outcome variables. Two interrupted time series studies[26,36] and two repeated measures studies[5,24] modelled observations for less than one year

before policy implementation. Only three of these studies evaluated the impact of PA for a period of at least two years after implementation.[24,28,29] Therefore, most of the results obtained in these studies are only valid as short-term impact measures (immediate policy effects). The relative (or absolute) change in level during the period after PA implementation was reported in all interrupted time series and repeated measures studies. However, only two studies clearly reported information on immediate change separately of changes in month rate (i.e., the slope). Hartung and colleagues[26] reported a significant decline in the monthly rate use of celecoxib during the eleven months after PA implementation. Instead, Fischer and colleagues[24] reported *"a slight upward trend of 1.6 percent in the slope of the curve of coxib use in the six quarters after"*.

Two controlled before-and-after studies[25,27] present some limitations arising from using a small patient sample for the control and/or intervention group, and from using very short periods of pre and/or post PA observation which limit conclusion validity to immediate short time effects. McCombs and colleagues[31] used a logistic regression model, and controlled for observable and unobservable selection bias, to obtain reliable estimates of the odds ratio for outcome variables.

The three before-and-after studies without a control group[10,32,35] present serious limitations that may affect the validity of their conclusions. Even though these uncontrolled before-and-after studies were included in this review, they represent a weak non-experimental design given the absence of a control group. Bloom and Jacobs[32] compared short before and after PA periods (nine months), but in the post-PA period they excluded all those patients that discontinued treatment after PA restrictions, which resulted in an inadequate comparison. Kahan and colleagues[10] only observed a short period of 3 months before PA and did not attempt to consider time trend or other effects in order to make the before-and-after comparison. Phillips and Larson[35] also simply compared a so-called *"baseline period prior to the initiation of the PA program"* observation with a post-intervention observation without any consideration of potential

time trend or the effects of other environmental or policy variables affecting the post-PA outcomes.

The impact of specific PA policies on pharmaceutical expenditure is usually estimated as the impact on those drugs that are considered therapeutically equivalent or close drug substitutes. However, two different approaches for considering equivalent drugs have been employed in this literature: some studies only consider the impact on those drugs that belong to the same therapeutic class as the one directly affected by PA restrictions, i.e., all NSAIDs when PA is applied to Cox-2 inhibitors.[24-26,28] In contrast, other studies estimate the impact of PA on overall spending on drugs indicated for the same disease, i.e., antisecretory drugs when PA is applied to proton pump inhibitors.[33] This latter approach may provide a more comprehensive and accurate picture of the overall impact of the policy on pharmaceutical spending.

The units of measure for pharmaceutical utilization were the number of defined daily doses (DDDs) in two studies[24,28] and days' supply per person-year in one study.[26] However, the rough number of prescriptions was used in one study.[10]

Discussion

Some authors[11,12] reported that PA policies, like many other pharmaceutical administrative interventions, had not been adequately evaluated. Since then, we have observed that the number of evaluation studies has increased moderately and the quality of the study designs has notably improved, including a randomized controlled trial, several repeated measures, and controlled interrupted time series studies. However, despite some progress in the quantity and quality of the literature and a growing international interest in implementing PA policies, several limitations still remain in some

important aspects of this literature, and should be addressed by future research. These limitations demand caution in directly using the evidence provided by this literature to make policy recommendations. First, the evidence still remains excessively limited to US Medicaid settings and to a small number of drug classes (i.e., NSAIDs), despite the fact that PA has been extended to many countries and drug categories. Second, there is a lack of consideration of implications of PA policies as heterogeneous interventions (i.e., objectives, previous situation, existence of substitute drugs, price of substitutes, coincident environment and policy changes, etc.). Third, an incomplete outcome measurement is observed in the literature that is heavily concentrated on pharmaceutical expenditure effects, although PA policies are usually justified on the grounds of improving appropriate pharmaceutical utilization, and despite their potentially high administrative costs. There is a lack of reliable data on the implementation of PA policies to examine the effects of PA programmes on patients' health and satisfaction, on physicians' and pharmacists' satisfaction, and on administrative costs. And finally, a notable lack of evidence of medium and long-term policy effects has been observed.

Results cannot be easily transferred from one institutional setting (country and institutional coverage) to another, or from one therapeutic class to another, or even between states or regions with the same institutional coverage and in the same country, due to differences in the implementation of these policies (Fischer and colleagues[37] found that state Medicaid PA policies were heterogeneous in terms of criteria required to obtain a coxib). Conclusions from Medicaid studies, which include a disproportionate number of the elderly and children, cannot be easily generalized to the rest of the population.[12]

The impact of PA in a specific drug class is also heavily dependent on the inclusion of generic products in this class; the existing price differences in the market between brand name and generic products and also between on-patent medicines in the same class; the degree of therapeutic advantage of one active ingredient over another; whether they are

used to treat a symptomatic problem of mild to moderate severity (as is the case of NSAIDs) or to treat acute severe problems; and the risk associated with a therapeutic failure derived from trying a different agent from the class (hospitalization, use of other expensive health services, or serious adverse effects on patients' health). Generalization of results is even more difficult when studies fail to distinguish between cost savings resulting from switching to generic or less expensive medicines and those resulting from lower drug utilization.[11]

Conclusions

This review of the literature on the impact of PA policies indicates that pharmaceutical use and/or expenditure per patient or enrollee of drugs directly affected by PA restrictions and overall drug expenditure significantly decreased (increased) after policy implementation (removal). Health outcome changes attributed to PA policies were not directly evaluated, although changes in the use of other health services may provide an indirect indication of complication or adverse health effects. In most cases, except for cimetidine, PA implementation was not associated with significant changes in the utilization of other medical services.

Although the existing literature is not enough to support firm assertions about the overall impact of PA policies on health and welfare for future policy implementation in other drug categories, institutional settings, and countries, some implications may be cautiously raised from this literature review, and from the list of tentative principles for policy making enumerated by Soumerai.[6] First, greater improvements in use, cost, and health outcomes may be expected from implementing PA policies for drugs with high prior inappropriate prescribing and utilization, and with higher relative prices in comparison to therapeutically equivalent substitutes. Second, the cost-effectiveness of PA policies may be greater when applied to drug categories in which heterogeneity in patient responses

to different active ingredients is low, and where delayed treatment will not result in adverse health outcomes. Third, cost-effectiveness of PA policies may also be improved by minimizing the bureaucratic and administrative burden of the policy design on patients, physicians, and pharmacies. Fourth, PA implementation for specific drugs should be based on scientific evidence and expert independent consensus or recommendations in order to gain credibility among the agents involved in pharmaceutical prescription. Fischer and colleagues[37] stressed the need for greater consistency between evidence-based medicine and PA policy requirements in cases such as coxib where there is consensus about risk factors that identify patients likely to benefit from it. And fifth, PA policies, as insurance coverage and pharmaceutical management decisions, are only one of the vast array of policy alternatives that insurers have at their disposal, and before implementation there should be careful study to ascertain which is the most cost-effectiveness policy alternative.

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Table I. Studies evaluating the impact of pharmaceutical prior authorization policies on selected outcomes

Study, Year (Reference)	Drugs under PA	Type of study	Characteristics of the participants (patients or jurisdictions, insurer)	Study setting (country, study duration)	Main outcome measures
Bloom and Jacobs,[32] 1985	Cimetidine	Before-and-after study without control group	10,152 patients with peptic ulcer disease Medicaid	US, West Virginia 1981-1983	Outpatient pharmaceutical expenditure for peptic ulcer disease Inpatient hospital and physician expenditure for peptic ulcer disease
Carroll et al.,[30] 2006	Cox-2	Before-and-after study with control group	42,262 continuously eligible patients with a before Cox-2 claim Medicaid	US, Missouri 2002-2003	Expenditures for and prescriptions of Cox-2 inhibitors, NSAIDs, other pain drugs, and GI-protective drugs
Delate et al.,[33] 2005	Proton pump inhibitors	Interrupted time series with control series	5,965 potential antisecretory medication users Medicaid	US 2001-2003	Pharmaceutical expenditure Ambulatory services use and expenditure Inpatient care use and expenditure
Fischer et al.,[24] 2004	Cox-2	Repeated measures study with control group	50 states Medicaid	US 1999-2003	DDDs of NSAIDs NSAIDs and Cox-2 expenditure Proportion of Cox-2 DDDs
Gleason et al., [25] 2005	Cox-2	Before-and-after study with control group	737 patients with a before Cox-2 prescription A large corporation	US 2002-2003	Pharmaceutical use and expenditure Medical expenditure
Hartung et al., [26] 2004	Celecoxib	Interrupted time series with control series	245,600 patients Medicaid	US, Oregon 1999-2000	Pharmaceutical use and expenditures Emergencydepartment visits Hospitalizations
Kahan et al.,[10] 2006	Cefuroxime	Before-and-after study without control group	Not reported Leumit Health Fund	Israel 2001-2005	Prescriptions of cefuroxime Disease distribution of cases treated with

					cefuroxime
Kotzan et al.,[34] 1993	Single source NSAIDs	Interrupted time series without control series	80,064 eligible recipients of NSAIDs Medicaid	US, Georgia 1989-1990	Pharmaceutical expenditure Other medical services
McCombs et al.,[31] 2002	Fluoxetine and paroxetine (PA removal)	Before-and-after study with control group	6,409 patient treatment episodes Medicaid	US, California 1994-1999	Patient compliance Drug switching
Momani et al.,[27] 2002	Brand-name NSAIDs	Before-and-after study with control group	181 patients Medicaid	US, Virginia 1996	Health-related quality of life at 8 weeks follow-up
Phillips and Larson,[35] 1997	16 categories of individual drugs	Before-and-after study without control group	250,000 insured people Medicaid	US, Iowa 1993-1995	Administrative cost Pharmaceutical expenditure
Roughead et al.,[28] 2006	Cox-2	Repeated measures study with control group	50 states Medicaid	US 1996-2003	DDDs and expenditure for Cox-2 and NSAIDs
Schneeweiss et al.,[5] 2004	Nebulized respiratory medication	Randomized controlled trial Repeated measures study with control group	5,463 patients Pharmacare	Canada, British Columbia 1997-1999	Utilization of and expenditure of respiratory drugs Number of contacts with doctors Emergency admissions to hospital
Smalley et al.,[29] 1995	Non-generic NSAIDs	Interrupted time series with control series	495,821 enrollees Medicaid	US, Tennessee 1988-1991	Expenditure for NSAIDs Expenditure for other medical care
Virabhak and Shinogle,[36] 2005	Cardiovascular medications	Interrupted time series with control series	Not reported Medicaid	US, Illinois and Louisiana 2002-2003	Prescription share changes of drugs under PA

Cox-2 = cyclooxigenase (Cox)-2 inhibitor. **DDD** = daily defined dose. **NSAIDs** = non-steroidal anti-inflammatory drugs.

Table II. Results of the studies evaluating the impact of pharmaceutical prior authorization policies on selected outcomes

Study, Year (Reference)	Impact on pharmaceutical use and expenditure	Impact on healthcare use and expenditure	Impact on health outcomes and health-related quality of life
Bloom and Jacobs,[32] 1985	Pharmaceutical cost per patient-month declined by 78.9%.	Monthly physician payments increased by 3.1%. Monthly inpatient hospital costs increased by 23.6%.	
Carroll et al.,[30] 2006	Expenditures for Cox-2 inhibitors, NSAIDs, other pain drugs, and GI-protective drugs were $256 higher, $56 lower, $21 higher, and $198 higher respectively in the control state among low-risk patients; and $102 higher, $12 lower, $21 lower, and $185 higher respectively in the control state among high-risk patients. Results were similar for drug utilization.		
Delate et al.,[33] 2005	A 90.9% decrease in PPIs per member-per-month expenditures and a 223.2% increase in histamine receptor antagonists (H_2A) in the first month; mean expenditures for antisecretory drugs decreased 49.9%.	Enrollees who received an H_2A or no antisecretory drugs were not more likely to have incurred greater medical care expenditures than enrollees who received a PPI.	
Fischer et al.,[24] 2004	Initial 15% reduction in the proportion of NSAID doses made up of coxibs, with a much smaller rise in use subsequently, corresponding to an 18% decrease in the cost per NSAIDs prescription; states with more restrictive PA criteria had lower levels of use of coxibs after PA implementation.		
Gleason et al.,[25] 2005	84.1% of members (previous Cox-2 users) had no claims for a Cox-2, and their pharmacy costs declined by 40%; in a subgroup who tried to get a Cox-2 prescription filled but were denied coverage, pharmacy costs initially declined by 48.1%, remaining significantly lower.	Medical costs of the 84.1% of members (previous users of Cox-2) that had no claims for a Cox-2 declined by 18.7%; in the subgroup who tried to get a Cox-2 prescription filled but were denied coverage, medical costs initially declined by 10.3%, and then returned to baseline.	

Hartung et al.,[26] 2004	Use of celecoxib was immediately reduced by 58.9% per person-year; the monthly rate of increase also decreased; utilization changes were not observed in other drug classes.	An 18% non-significant increase in emergency department visits was observed in the entire sample after PA; a similar change was not observed in the secondary analysis of prior NSAID users.	
Kahan et al.,[10] 2006	Prescription of cefuroxime declined during the PA period (8% of eligible antibiotic prescriptions) and rose in the post-PA period (4.3%).		
Kotzan et al.,[34] 1993	The combined monthly prescription volume of single- and multiple-source NSAIDs prescriptions decreased by 21.3%; multiple-source NSAID prescriptions and analgesic prescriptions increased as the single-source NSAIDs decreased; monthly NSAIDs expenditures decreased by 53% after PA.	No additional costs were observed for inpatient, outpatient, or other categories of medical services.	
McCombs et al.,[31] 2002	Drug therapy completion dropped from 23.2% to 20.5% after PA removal, without a corresponding increase in switching.		
Momani et al.,[27] 2002			Patients who were restricted to generic NSAIDs did not report deterioration in HRQoL.
Phillips and Larson,[35] 1997	Proportions of generic antiarthritic and benzodiazepine use were much higher than before PA two years after; total net savings were estimated after considering administrative costs for antiarthritics, benzodiazepines, antiulcers, and antihistamines.		
Roughead et al.,[28] 2006	Implementing PA for Cox-2 at market entry was effective in restricting uptake; states implementing PA 2 years after market entry approached utilization levels of the early adopting states within 1 year.		
Schneeweiss et al.,[5] 2004	A reduction of $C24 per patient-month in all nebulized drug use and an increase of $C3 per patient-month in all expenditure for inhalers was observed after PA; the randomized study found savings of $C8 per	Contacts with doctors and emergency admissions to hospital did not increase after PA.	

	patient-month for nebulizers and no increase in all expenditure for inhalers.		
Smalley et al.,[29] 1995	Expenditures for NSAIDs prescriptions decreased by 53% during the next two years; this reduction resulted in an increased use of generic NSAIDs, as well as a 19% decrease in overall NSAIDs use.	There was no concomitant increase in expenditures for other medical care.	
Virabhak and Shinogle,[36] 2005	There was a decrease of 9 percentage points and 6.2 percentage points in the prescription share of restricted cardiovascular drugs for Illinois and Louisiana respectively; for physicians with a high percentage of prescriptions paid for by Medicaid, the share loss was estimated to be more than 37% for the non-Medicaid prescriptions (*spillover effect*).		

Cox-2 = cyclooxigenase (Cox)-2 inhibitor. **DDD** = daily defined dose. **H_2A** = histamine receptor antagonist. **NSAIDs** = non-steroidal anti-inflammatory drugs. PPI = proton pump inhibitor.