

Impact of Pharmaceutical Prior Authorisation Policies

A Systematic Review of the Literature

Jaume Puig-Junoy and Iván Moreno-Torres

Research Centre for Economics and Health (CRES), Department of Economics and Business, Universitat Pompeu Fabra, Barcelona, Spain

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Abstract

Policies consisting of or including prior authorisation (PA) of pharmaceutical prescriptions have been increasingly implemented by public and private insurers in the last decade, especially in the US, in order to control drug spending. We conducted a systematic review of published articles determining the effects of these policies on drug use, healthcare utilisation, healthcare expenditures and health outcomes.

A literature search was carried out in the electronic databases PubMed (which includes MEDLINE), EconLit, Web of Science and online sources including Google Scholar, from 1 January 1985 to 12 September 2006. Reference lists of retrieved articles were also searched. Peer-reviewed studies that provided empirical results about the impact of pharmaceutical PA policies, including randomised and non-randomised controlled trials, repeated measures studies, interrupted time series analyses and before-and-after studies were included.

Use of, and expenditure on, directly affected drugs per patient, and overall drug expenditure, significantly decreased after PA implementation, or increased after PA 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 utilisation of other medical services. Although 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 mainly 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, outcome measurements require improvement, and there is a notable lack of evidence of medium- and long-term policy effects.

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

PA policies require physicians or pharmacists to receive approval from the insurer before certain drugs may be dispensed. These policies require submission of individual clinical information for review before the insurer agrees to cover the cost of usually high-cost drugs or 'risky' drugs that may cause important adverse effects. PA policies can adopt the form of 'fail first' mechanisms (i.e. requiring a lower-cost treatment to have failed before use of a more expensive agent),^[6] prior approval for non-preferred drugs, and individual reimbursement for specific drugs (e.g. when a serious disease or condition requires long-term treatment, and the accepted products available for general reimbursement are not appropriate, reimbursement for an alternative product can be applied for on an individual basis).^[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 address 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 central-

ised decisions for the whole health system affecting all prescriptions, independent 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, independent of its impact on pharmaceutical expenditure. 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 (ICER) [i.e. cost per QALY] when prescribed outside the 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 decentralised reimbursement decisions of each individual insurer, that is, the insurer decides the pharmaceutical coverage level, which should be dependent on their willingness to pay for health improvements and on the cost containment objective.

For both objectives, there are two implicit hypotheses about prescriber behaviour. The first is that prescribers have imperfect or biased information about health risks and/or costs of pharmaceuticals. The effects of PA policies will then depend on the amount of previous inappropriate prescription from the clinical or economic perspective. The second is that doctors do not have enough incentive to act as perfect agents for the patient and the insurer. The question of knowing whose agent the physician is was addressed by Rochaix^[9,10] and Blomqvist.^[11] As Rochaix^[10] highlighted "Physicians are increasingly requested to take into account the economic consequences of their decisions, with a view to optimise the use of scarce resources allocated to the population. Yet conflicts necessarily arise between the individual and the collective interest, since doing all that can be done at individual level implies less resources for other patients (including future patients). Physicians are placed today at the heart of this trade-off, as agents of two principals: the patient but also the representative of the collective interest, be it the State or the third party payer."

Some authors suggest that PA policies exert a sentinel effect, i.e. a “decrease in services given by providers as a result of having a utilisation reviewer keep tabs on them.”^[12] Then, government and commercial warnings, surveillance mechanisms (e.g. utilisation review), tiered copayments and prescriber incentives would be alternatives to be compared with PA implementation.

Intended and unintended effects of PA policies include drug substitution, drug discontinuation, alteration of adherence to treatment, and changes in pharmaceutical expenditure, healthcare utilisation, health service and health outcomes (mortality, morbidity, quality of life [QOL] and biological outcomes such as cholesterol and blood-sugar levels, blood pressure, etc.). PA policies can also result in appropriate or inappropriate substitution of other health services for drugs (increased use of more expensive physician or institutional care). As appropriate pharmaceutical prescription may be complementary to physician visits and a substitute for hospital care, PA on effective and appropriate drugs may decrease physician visits and increase hospitalisations. In fact, there is evidence that spending on drugs may be related to lower hospital costs for some chronic diseases, such as chronic obstructive pulmonary disease.^[13,14]

Although the overall goal of PA policies is to reduce costs without negatively affecting health outcomes, there are concerns that, under certain conditions, such policies could result in adverse health effects owing to suboptimal treatment or restricted access to appropriate treatments. Declines in health and/or health-related QOL (HR-QOL) may arise from lower use of essential therapies, substitution of less effective pharmaceuticals for PA drugs, and substitution of older drugs with worse post-treatment health when PA is applied to newer drugs.^[15]

PA policies also work by potentially increasing the costs to physicians or pharmacists of prescribing some drugs. Critics argue that this policy might effectively deter prescribing drugs that require PA because the additional time spent by professionals is not reimbursed. This could reduce the total quantity of prescribed drugs if physicians respond by prescribing nothing for some patients. However, another hypothesis is that it may also reduce price either

through substitution or through greater negotiation power by the payer.

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

1. Review Method

We searched English-language articles in PubMed (which includes MEDLINE), EconLit, Web of Science, and online sources including Google Scholar from 1 January 1985 to 12 September 2006 using the following keywords in both UK and US English: ‘prior authorisation’, ‘special authorisation’, ‘prior approval’ and ‘preauthorisation’. ‘Preauthorisation’ was searched in combination with ‘drugs’, ‘pharmaceuticals’ and ‘medicines’. 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 met all the following requirements: (i) were peer-reviewed published articles providing empirical results quantifying the effect of ambulatory PA policies; (ii) isolated the independent effect of PA when it was applied simultaneously with other policy measures (i.e. Cunningham^[16]); (iii) measured the impact of the policy on outcome variables including drug use, drug expenditure, healthcare utilisation, healthcare spending, health outcomes and/or QOL; and (iv) were designed as randomised or non-randomised controlled trials, repeated measures studies, interrupted time series analyses and 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. We also excluded cross-sectional studies.^[15,17] Studies that concentrated their analysis on the so-called ‘spillover effects’ of closed formularies and PA policies were not included (the influence on physician prescribing behaviour for patients covered by other insurers). 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.^[18-20]

From a maximum number of items reported in the search (Google Scholar = 1760, PubMed = 81, Web of Science = 56, EconLit = 6), we identified 15 studies that met our criteria. More than two-thirds (11/15) of the studies reviewed had not been addressed in prior reviews.

Using a standardised extraction form, the following information was extracted from the included studies: drugs affected by the PA policy; type of study (randomised trial, non-randomised 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.^[21]

2. Descriptive Analysis

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 4 of 15 studies (26.6%) were published before 2001, and 9 of 15 (60%) were 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*) [see table I].

Eight of the PA studies included here-in^[23,25-27,29,31,33,34,36] evaluated the impact of PA policies on the use of NSAIDs and/or cyclo-oxygenase-2 (COX-2) selective inhibitors, such as celecoxib. This may be a clear indication that PA policies have been extensively applied to NSAIDs, and especially to COX-2 inhibitors, as non-systematic descriptive information for PA policy implementation confirms.

Despite the increasing interest in, and use of, PA policies outside the US, only 2 of the 15 studies (13.3%) evaluated the impact of this policy in a non-US setting (one each in Israel^[28] and British Colum-

bia, Canada^[5]). Most US-based studies evaluated PA policies implemented by the public programme, Medicaid. None of the studies were in a European setting.

Administrative intervention measures evaluated in 14 of the 15 studies consisted of PA implementation; in one,^[33] the differential effect of implementing PA at market entry or implementing it 2 years after market entry for COX-2 inhibitors was evaluated. Only one study evaluated the impact of PA removal.^[30]

The main outcome measures used in all except one^[31] of the studies were changes in pharmaceutical use and/or in pharmaceutical expenditure (see table II). Only 7 of the 15 studies (46.6%) evaluated the impact of PA policies on change in some other health service use and/or expenditure. And only one of the 15 studies^[31] evaluated the impact on HR-QOL. In terms of financing source, pharmaceutical companies financed 5 of the 15 studies (33.3%).

3. Impact of Prior Authorisation Policies

3.1 Pharmaceutical Use and/or Expenditure

Only two studies^[28,30] reported changes in outcome variables related indirectly to the appropriateness of pharmaceutical prescription or utilisation, and 12 reported changes in use and/or pharmaceutical spending.^[5,22-29,32-34]

In accordance with their intended policy objectives, ten reviewed studies^[5,23-29,32-34] 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 PA implementation in all 11 studies that evaluated such impact.^[5,22-27,29,32-34] The extent of substitution and expenditure decrease after PA varied according to medication class and type of policy design and objectives. The greatest decrease in spending after PA was reported in a study evaluating the impact of PA on all proton pump inhibitor prescriptions.^[24] A major decrease (53%) in pharmaceutical spending after the introduction of PA was also reported in two studies^[29,34] evaluating the impact of applying PA to brand-name

Table 1. Studies evaluating the impact of pharmaceutical prior authorisation (PA) policies on selected outcomes

Study	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 ^[22]	Cimetidine	Before-and-after study without control group	10 152 patients with peptic ulcer disease; Medicaid	US, West Virginia (1981–3)	Outpatient pharmaceutical expenditure for peptic ulcer disease; inpatient hospital and physician expenditure for peptic ulcer disease
Carroll et al. ^[23]	COX-2 inhibitors	Before-and-after study with control group	42 262 continuously eligible patients with a before COX-2 claim; Medicaid	US, Missouri (2002–3)	Expenditures for and prescriptions of COX-2 inhibitors, NSAIDs, other pain drugs and GI-protective drugs
Delate et al. ^[24]	Proton pump inhibitors	Interrupted time series with control series	5 965 potential antiseizure medication users; Medicaid	US (2001–3)	Pharmaceutical expenditure; ambulatory services use and expenditure; inpatient care use and expenditure
Fischer et al. ^[25]	COX-2 inhibitors	Repeated measures study with control group	50 states; Medicaid	US (1999–2003)	DDD of NSAIDs; NSAIDs and COX-2 inhibitor expenditure; proportion of COX-2 inhibitor DDDs
Gleason et al. ^[26]	COX-2 inhibitors	Before-and-after study with control group	737 patients with a before COX-2 prescription; a large corporation	US (2002–3)	Pharmaceutical use and expenditure; medical expenditure
Hartung et al. ^[27]	Celecoxib	Interrupted time series with control series	245 600 patients; Medicaid	US, Oregon (1999–2000)	Pharmaceutical use and expenditures; ED visits; hospitalisations
Kahan et al. ^[28]	Cefuroxime	Before-and-after study without control group	Not reported; Leumit Health Fund	Israel (2001–5)	Prescriptions of cefuroxime; disease distribution of cases treated with cefuroxime
Kotzan et al. ^[29]	Single-source ^a NSAIDs	Interrupted time series without control series	80 064 eligible recipients of NSAIDs; Medicaid	US, Georgia (1989–90)	Pharmaceutical expenditure; other medical services
McCombs et al. ^[30]	Fluoxetine and paroxetine	Before-and-after PA removal study with control group	6 409 patient treatment episodes; Medicaid	US, California (1994–9)	Patient compliance; drug switching
Momani et al. ^[31]	Brand-name NSAIDs	Before-and-after study with control group	181 patients; Medicaid	US, Virginia (1996)	HR-QOL at 8 weeks' follow-up
Phillips and Larson ^[32]	16 categories of individual drugs	Before-and-after study without control group	250 000 insured people; Medicaid	US, Iowa (1993–5)	Administrative cost; pharmaceutical expenditure
Roughead et al. ^[33]	COX-2 inhibitors	Repeated measures study with control group	50 states; Medicaid	US (1996–2003)	DDD and expenditure for COX-2 inhibitors and NSAIDs
Schnee Weiss et al. ^[35]	Nebulised respiratory medication	Randomised controlled trial, repeated measures study with control group	5 463 patients; Pharmicare	Canada, British Columbia (1997–9)	Utilisation and expenditure of respiratory drugs; number of contacts with doctors; emergency admissions to hospital
Smailey et al. ^[34]	Non-generic NSAIDs	Interrupted time series with control series	495 821 enrollees; Medicaid	US, Tennessee (1988–91)	Expenditure for NSAIDs; expenditure for other medical care
Virabhak and Shinogle ^[35]	Cardiovascular medications	Interrupted time series with control series	Not reported; Medicaid	US, Illinois and Louisiana (2002–3)	Prescription share changes of drugs under PA

a Multiple-source drugs are defined as those with two or more drug products determined to be therapeutically equivalent. Single-source drugs are those without therapeutically equivalent products.

COX-2 = cyclo-oxygenase-2 inhibitor; DDD = daily defined dose; GI = gastrointestinal; HR-QOL = health-related quality of life.

Table II. Results of the studies evaluating the impact of pharmaceutical prior authorisation (PA) policies on selected outcomes

Study	Impact on pharmaceutical use and expenditure	Impact on (non-pharmaceutical) healthcare use and expenditure
Bloom and Jacobs ^[22]	Pharmaceutical cost per patient-month declined by 78.9%	Monthly physician payments increased by 3.1%; monthly inpatient (non-pharmaceutical) hospital costs increased by 23.6%
Carroll et al. ^[23]	Expenditures for COX-2 inhibitors, NSAIDs, other pain drugs and GI-protective drugs were \$US256 higher, \$US56 lower, \$US21 higher and \$US198 higher after PA implementation, respectively, in the control state among low-risk patients vs patients in the PA group; and \$US102 higher, \$US12 lower, \$US21 lower and \$US185 higher, respectively, in the control state among high-risk patients. Results were similar for drug utilisation	
Delate et al. ^[24]	A 90.9% decrease in PPIs per member-per-month expenditures and a 223.2% increase in H2A in the first month after PA implementation; mean expenditures for antisecretory drugs decreased 49.9%	Enrolees who received an H2A or no antisecretory drugs were not more likely to have incurred greater (non-pharmaceutical) medical care expenditures than enrollees who received a PPI after PA implementation
Fischer et al. ^[25]	Initial 15% reduction in the proportion of NSAID doses made up of COX-2 inhibitors, with a much smaller rise in use subsequently, corresponding to an 18% decrease in the cost per NSAIDs prescription after PA implementation; states with more restrictive PA criteria had lower levels of use of COX-2 inhibitors after PA implementation	
Gleason et al. ^[26]	84.1% of members (previous COX-2 inhibitor users) had no claims for a COX-2 after PA implementation, 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	(Non-pharmaceutical) medical costs of the 84.1% of members (previous users of COX-2 inhibitors) that had no claims for a COX-2 declined by 18.7% after PA implementation; in the subgroup who tried to get a COX-2 prescription filled but were denied coverage, (non-pharmaceutical) medical costs initially declined by 10.3%, and then returned to baseline
Hartung et al. ^[27]	Use of celecoxib after PA implementation was immediately reduced by 58.9% per person-year; the monthly rate of increase also decreased; utilisation changes were not observed in other drug classes	An 18% non-significant increase in ED 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. ^[28]	Prescription of cefuroxime declined during the PA period (8% of eligible antibacterial prescriptions) and rose in the period after PA was removed (4.3%)	

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Table II. Contd

Study	Impact on pharmaceutical use and expenditure	Impact on (non-pharmaceutical) healthcare use and expenditure
Kozaan et al. ^[29]	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 ^a NSAIDs decreased; monthly NSAIDs expenditures decreased by 53% after PA	No additional (non-pharmaceutical) costs were observed for inpatient, outpatient or other categories of medical services
McCombs et al. ^[30]	Drug therapy completion dropped from 23.2% in the PA period to 20.5% after PA removal, without a corresponding increase in the likelihood of switching therapies	
Momani et al. ^[31]		
Phillips and Larson ^[32]	Proportions of generic anti-arthritic and benzodiazepine use were much higher 2 years after PA vs before implementation; total net savings after considering administrative costs for anti-arthritics, benzodiazepines, anti-ulcers and antihistamines were estimated between \$US2.51 million and \$US3.83 million	
Roughead et al. ^[33]	Implementing PA for COX-2 inhibitors at market entry was effective in restricting uptake; states implementing PA 2 years after market entry approached utilisation levels of the early adopting states within 1 year	
Schneebeiss et al. ^[5]	A reduction of \$Can24 per patient-month in all nebulised drug use and an increase of \$Can3 per patient-month in all expenditure for inhalers was observed after PA in the observational analysis; the randomised study found savings of \$Can8 per patient-month for nebulisers and no increase in all expenditure for inhalers	Contacts with doctors and emergency admissions to hospital did not increase after PA
Smalley et al. ^[34]	Expenditures for NSAIDs prescriptions decreased by 53% during the next 2 years after PA implementation; 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 (non-pharmaceutical) expenditures for other medical care after PA implementation
Virabhak and Shinogle ^[35]	There was a decrease of 9% and 6.2% in the prescription share of restricted cardiovascular drugs for Illinois and Louisiana, respectively after PA implementation	
<p>^a Multiple-source drugs are defined as those with two or more drug products determined to be therapeutically equivalent. Single-source drugs are those without therapeutically equivalent products.</p> <p>COX-2 = cyclo-oxygenase-2 inhibitor; GI = gastrointestinal; H2A = histamine receptor antagonist; PPI = proton pump inhibitor.</p>		

drugs when generic substitutes existed; the impact mainly depended on price differentials between brand-name and generic drugs. In other PA implementations, the impact on pharmaceutical spending was heavily dependent on price differentials between restricted and non-restricted active ingredients (e.g. those studies evaluating PA restrictions on new COX-2 inhibitors).

One study^[35] reported a reduction in the prescription 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 drug 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 et al.^[28] provided information about disease distribution of cases treated with cefuroxime before, during and after 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 et al.^[30] 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.

3.2 Health Services Use and/or Expenditure

Seven studies^[5,22,24,26,27,29,34] analysed the extended impact of pharmaceutical PA on the use and expenditure of other health services. An increase in the utilisation of other medical services (outpatient medical visits, ED visits or inpatient admissions) after the introduction of 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 utilisation of medical services such as physician office or ambulatory visits,^[5,24,26,29,34] ED visits^[26,27] and inpatient admissions.^[5,24,26,27,29,34]

Only one study,^[22] which analysed the impact of PA restrictions applied to cimetidine in 1981–3, reported an increase in monthly physician payments

and inpatient hospital costs that may have offset pharmaceutical savings from PA implementation.

3.3 Health Outcomes and Health-Related Quality of Life

We found only one study that addressed the impact of PA for branded NSAIDs on the HR-QOL of long-term NSAIDs users.^[31] A mail survey was sent at 8 weeks' follow-up. HR-QOL 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' HR-QOL. However, only a very limited number of surveys were completed (n = 181).

3.4 Administration Costs

Administrative costs of operating PA policies were rarely included in PA impact evaluations,^[23,24,32] and, when included, they lacked accurate descriptions of how costs were measured, and what they comprised.^[21] Carroll et al.^[23] pointed out that an automated electronic PA system programme such as that implemented in the 2002 Missouri Medicaid programme 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.

4. Study Quality

To determine the influence of methodological quality on study results, we stratified the 15 reports based on the type of study design. Only one study^[5] assessed PA impact using a randomised controlled trial. Three studies reported PA impact in the framework of a repeated measures study with control series.^[5,25,33] Five impact studies were designed as interrupted time series analyses with control series.^[24,27,29,34,35] Four other studies employed a simpler before-and-after design with a control group.^[23,26,30,31] And finally, three studies were designed as before-and-after analyses without any control group.^[22,28,32]

The randomised controlled trial study^[5] followed a policy-exempted group and an intervention group

for 6 months, which only allowed the authors to obtain limited short-term impact measures for PA implementation that cannot be extrapolated any further.

Some of the interrupted time series and repeated measures studies suffered serious limitations because the analyses did not include sufficient time points to adjust for differential prior trends in outcome variables. Two interrupted time series studies^[27,35] and two repeated measures studies^[5,25] modelled observations for <1 year before policy implementation. Only three studies evaluated the impact of PA for a period of at least 2 years after implementation.^[25,33,34] Therefore, most of the results obtained in the aforementioned studies are only valid as short-term impact measures (immediate policy effects). The relative (or absolute) change in the level of the outcomes 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, that is, short-term level variation of the outcomes due to the policy implementation, separately of changes in month rate (i.e. slope or trend variations after PA introduction). Hartung et al.^[27] reported a significant decline in the monthly rate use of celecoxib during the 11 months after PA implementation. Alternatively, Fischer et al.^[25] reported "a slight upward trend of 1.6 percent in the slope of the curve of COX-2 inhibitor use in the six quarters after."

Two controlled before-and-after studies^[26,31] suffered 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 et al.^[30] 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^[22,28,32] have 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^[22] compared short before-and-after PA periods (9 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 et al.^[28] 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^[32] 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 the use of those drugs that are considered therapeutically equivalent or close drug substitutes. However, two different approaches for considering equivalent drugs have been employed in the literature: some studies only considered the impact on those drugs that belong to the same therapeutic class, i.e. all NSAIDs when PA is applied to COX-2 inhibitors.^[25-27,33] In contrast, other studies estimated the impact of PA on overall spending on drugs indicated for the same disease, i.e. anti-secretory drugs when PA is applied to proton pump inhibitors.^[24] This latter approach may provide a more comprehensive and accurate picture of the overall impact of PA policies on pharmaceutical spending.

The units of measure for pharmaceutical utilisation were the number of defined daily doses in two studies^[25,33] and days' supply per person-year in one study.^[27] However, the approximate number of prescriptions was used in one study.^[28]

5. Discussion

There are very few other reviews that summarise the evidence on the effects of PA policies on economic and clinical outcomes, and those that do exist are dated.^[3,6,21,37,38] Some authors^[3,6,37,38] evaluated the effects of PA within the context of a broader set of pharmaceutical utilisation management measures restricting access to costly drugs (i.e. restrictive formularies) in specific US settings (Medicaid, managed care organisations, etc.). To our knowledge, until now the only published specific review of PA policies^[21] included only six papers up to April 2005, and half of them present severe limitations

that make their inclusion in the review problematic: one^[39] evaluated a hospital PA policy that was not comparable with ambulatory interventions; a second^[40] was a simple cross-sectional design without a comparison group; and a third^[36] was a cross-sectional study with a comparison group, but the difference between groups could not be carefully controlled. Other surveys covering PA policies only included three,^[6,37] four^[3] or five studies.^[38]

In 2001, two reviews^[21,37] reported that PA policies, like many other pharmaceutical administrative interventions, had not been evaluated adequately. 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 randomised controlled trial and 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, which should be addressed by future research. These limitations demand caution in directly using the existing evidence to make policy recommendations.

The evidence still remains mainly limited to US Medicaid settings and to a small number of drug classes (e.g. NSAIDs), despite the fact that PA has been extended to many countries and drug categories. There is a lack of consideration of PA policies as heterogeneous interventions (i.e. objectives, previous situation, existence of substitute drugs, price of substitutes, coincident environment and policy changes, etc.). Furthermore, outcome measurement is heavily concentrated on pharmaceutical expenditure effects, despite PA policies usually justified on the grounds of improving appropriate pharmaceutical utilisation, and having potentially high administrative costs. There is a lack of reliable data examining the effects of PA programmes on patients' health and satisfaction, on physicians' and pharmacists' satisfaction, and on administrative costs. And finally, there is a notable lack of evidence of medium and long-term policy effects. As has been mentioned above, a great number of the evaluated studies only concentrated their attention on short-term policy implementation effects, but did not provide evidence on use and expenditure trend variations. In

comparison, Fischer et al.^[25] reported information for a period >2 years after PA implementation and on short-term change separately of trend changes.

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. For example, Fischer et al.^[41] found that state Medicaid PA policies were heterogeneous in terms of criteria required to obtain a COX-2 inhibitor. Conclusions from Medicaid studies that include a disproportionate number of the elderly and children, cannot be easily generalised to the rest of the population.^[37]

The impact of PA in a specific drug class is also heavily dependent on the inclusion of generic products in the 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 the disease being treated is a symptomatic problem of mild to moderate severity (as is the case of NSAIDs) or an acute severe problem; and the risk associated with a therapeutic failure derived from trying a different agent from the class (hospitalisation, use of other expensive health services or serious adverse effects on patients' health). Generalisation 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 utilisation.^[21]

Although the existing literature is not enough to support firm assertions for future policy implementation about the overall impact of PA policies on health and welfare in drug categories, institutional settings and countries different from those to which impact studies refer, 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, despite not being directly addressed in the reviewed studies, greater improvements in use and cost of pharmaceuticals and health outcomes could be expected from implementing PA policies for drugs with high prior inappropriate prescribing and

utilisation, and with higher relative prices in comparison with therapeutically equivalent substitutes. Second, it may also be hypothesised that 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, PA implementation for specific drugs should be based on scientific evidence on outcomes and costs and expert independent consensus or recommendations in order to gain credibility among the agents involved in prescribing pharmaceuticals. And fourth, 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-effective policy alternative.

6. Conclusion

According to the reviewed literature, pharmaceutical use and/or expenditure per patient or enrollee of drugs directly affected by PA restrictions and overall drug expenditure significantly decreases (increases) after PA policy implementation (removal). Health outcome changes attributed to PA policies have not been 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 utilisation of other medical services.

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Correspondence: Dr *Jaume Puig-Junoy*, Department of Economics and Business, Universitat Pompeu Fabra, Ramon Trias Fargas 25-27, Barcelona, 34-08005, Spain.
E-mail: jaume.puig@upf.edu