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Pharmaceutical policies: effects of educational or regulatory policies targeting prescribers (Review)

Suleman F, Movik E

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[Intervention Review]

Pharmaceutical policies: effects of educational or regulatory policies targeting prescribers

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ABSTRACT

Background

Pharmaceuticals make an important contribution to people's health. Medicines, however, are frequently not used appropriately. Improving the use of medicines can improve health outcomes and save resources. On the other hand, regulatory and educational policies may have unintended effects on health and costs.

Objectives

To assess the effects of pharmaceutical educational and regulatory policies targeting prescribers on medicine use, healthcare utilisation, health outcomes and costs (expenditures).

Search methods

We searched CENTRAL, MEDLINE, Embase, and two trial registries in March 2018 and several other databases between 2014 and 2018. We reviewed the reference lists of included studies and other relevant reviews, contacted authors of relevant reviews and studies to identify additional studies, and did a citation search for all included studies using ISI Web of Science (searched 05 January 2016).

Selection criteria

Randomised trials, non-randomised trials, interrupted time series studies, repeated measures studies and controlled before–after studies of policies regulating who can prescribe medicines and other policies targeted at prescribers. We included in this category monitoring and enforcement of restrictions, generic prescribing, programmes to implement treatment guidelines, system-wide policies regarding monitoring medicine safety, and legislated or mandatory continuing education or quality improvement specifically targeted at prescribing. We defined 'policies' in this review as laws, rules, financial and administrative orders made by governments, non-governmental organisations or private insurers. We excluded interventions applied at the level of a single facility. For us to include a study, it had to include an objective measure of at least one of the following outcomes: medicine use, healthcare utilization, health outcomes, or costs.

Data collection and analysis

Two review authors independently reviewed abstracts and reference lists of relevant reports, assessed full-text studies for inclusion, extracted data, and assessed risk of bias and certainty of the evidence (GRADE). For all the steps in the above process we resolved disagreements by discussion.

Main results

We identified two studies that met our selection criteria: a controlled interrupted time series study evaluating a regulatory policy involving the monitoring of prescribing of benzodiazepines; and a controlled before–after study of an educational policing involving mailed educational materials on prescribing for physicians and Health Maintenance Organization (HMO) members as well as an intervention to regulate drug reimbursement.

We are uncertain about the effects on medicine use of a regulatory policy involving the monitoring of prescribing with triplicate prescriptions, compared with no regulatory intervention (very low certainty evidence).

We are also uncertain about the effects on medicine use, assessed through doctors' prescribing, and costs of an educational policy involving mailed educational materials on prescribing for physicians and HMO members, compared to no educational intervention or an intervention to regulate drug reimbursement (very low certainty evidence).

Neither of the included studies measured healthcare utilization, health outcomes, or additional costs, if any, to patients.

Authors' conclusions

We are uncertain of the effects of educational or regulatory policies targeting prescribers due to very limited evidence of very low certainty. The impacts of these policies therefore need to be evaluated rigorously using appropriate study designs. Evaluations are needed across a range of settings, including low- and middle-income countries, and across different types of prescribers and medicines.

PLAIN LANGUAGE SUMMARY

The effects of educational or regulatory policies targeting medicine prescribers

The aim of this Cochrane Review was to assess the effects of policies targeting people prescribing medicines. The review authors collected and analysed all relevant studies to answer this question and found two studies.

This review is one of a series of planned or completed reviews that look at the effects of different types of pharmaceutical policies on rational medicine use.

Key messages

We do not know what the effects of educational or regulatory policies are on the prescribing of medicine because the evidence is of very low certainty.

What are educational and regulatory policies?

Large amounts of health care funds are spent on medicines, and these amounts are increasing. And healthcare providers do not always prescribe the right medicines. Policy makers are therefore looking for ways to control the costs of medicines but still making sure that patients get the medicines they need. Governments, non-governmental organisations and health insurers sometimes try to do this through targeting the people who prescribe the medicines.

One way of doing this is to introduce educational policies. This can include laws, rules and regulations that require medicine prescribers to get certain types of information, education or feedback about their prescribing behaviour.

Another approach is to introduce regulatory policies. This can include laws, rules and regulations regarding who can prescribe medicines, what type of medicines they can prescribe and how much they can prescribe. Usually, prescribers are monitored to make sure they follow these policies.

What are the main results of the review?

The review authors found two relevant studies. Both of these studies were from the USA and both assessed policies that were introduced in the late 1990s.

The first study assessed a policy that aimed to get doctors to prescribe antihistamines that were cheaper but considered to be just as good as other antihistamines. In one part of the study, letters were sent to doctors and to their patients telling them about the new policy, and giving them information about the antihistamine. In another part of the study, letters were only sent to doctors.

The second study assessed a policy that aimed to get doctors to prescribe fewer benzodiazepines to certain types of patients. This policy required doctors in the State of New York to fill in three copies of the same form each time they prescribed benzodiazepines. Pharmacies then sent one of these copies to a state surveillance unit that monitored what doctors were prescribing. The study compared these doctors to doctors in the State of New Jersey, who were not monitored in the same way.

Because the evidence from both of these studies was of very low certainty, we do not know what effects these policies had on people's medicine use. We also do not know whether these policies had any effect on people's health or their use of healthcare services or on costs because the studies did not measure this.

How up to date is this review?

The review authors searched for studies that had been published up to March 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Regulatory policy: use of a prescribing monitoring tool compared to no regulatory intervention

Regulatory policy: use of a prescribing monitoring tool compared to no regulatory intervention

Participants: prescribers of benzodiazepines to Medicaid beneficiaries

Setting: United States of America (USA)

Intervention: regulatory policy intervention - prescribing monitoring tool (Triplicate Prescription Program)

Comparison: no regulatory policy intervention

Outcomes	Impact	No. of studies	Certainty of the evidence (GRADE)
Medicine use	We are uncertain about the effects on medicine use of a regulatory policy involving monitoring prescribing with triplicate prescriptions, compared with no regulatory intervention (48.1% relative decrease in benzodiazepine use (95% CI, −50.0% to −46.2%) as compared with predicted levels had the policy not been implemented)	1 ITS[A]	⊕⊖⊖⊖ **Very low**[B]
Health care utilization	Not reported	-	-
Health outcomes	Not reported	-	-
Costs	Not reported	-	-

GRADE Working Group grades of evidence
High certainty**:** further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty**:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty**:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty**:** we are very uncertain about the estimate.

[A] (Simoni-Wastila 2004)
[B] Interrupted times series (ITS) study downgraded due to very serious indirectness (single study set in a high income country with particular health system arrangements, and with the intervention targeting a particular insured group of patients). Note that within the GRADE system evidence from ITS studies is downgraded to low certainty due to risk of bias

Summary of findings 2. Educational policy: mailed educational materials on prescribing for physicians compared to no educational intervention

Educational policy: mailed educational materials on prescribing for physicians compared to no educational intervention

Patient or population: prescribers or patients that are subjected to educational interventions in prescribing due to government, non-government or third party payer policies

Setting: United States of America (USA)

Intervention: mailed educational materials on prescribing for physicians (HMO C)

Comparison: no educational policy intervention (HMO D)

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
Medicine use	We are uncertain about the effects on medicine use of an educational policy involving educational materials on prescribing mailed to physicians, compared to no intervention The share of prescribing for the preferred drug (fexofenadine) increased by 2.3 % (95% CI 0.6% to 4%) in the HMO that implemented educational materials for physicians compared to an increase of 1.6% (95% CI 0.4% to 2.8%) in the control HMO The share of prescribing for the less preferred drug (loratadine) decreased by −5% (95% CI −7.0% to −3.0%) in the HMO that implemented educational materials for physicians compared to a decrease of −3.6% (95% CI −5.2% to −2.0%) in the control HMO	1 CBA[A]	⊕⊖⊖⊖ **Very low[B]**
Health care utilization	Not reported	-	-
Health outcomes	Not reported	-	-
Costs	The average cost per prescription increased 5.0% (from USD 47.95 to USD 50.34) in the group that implemented an educational policy involving educational materials on prescribing for physicians. The average cost per prescription increased 4.2% in the control group.	1 CBA[A]	Not assessed

* GRADE Working Group grades of evidence

High certainty = this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty = this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

Low certainty = this research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

Very low certainty = this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different = a large enough difference that it might affect a decision

A (Benedetto 2000)
B Downgraded due to.high risk of bias and indirectness (the inclusion of a single study from a high income country)

Summary of findings 3. Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to no educational intervention

Educational policy: educational materials on prescribing for physicians and HMO members compared to no educational intervention

Patient or population: prescribers or patients that are subjected to regulatory and educational interventions in prescribing due to government, non-government or third party payer policies

Setting: USA

Intervention: mailed educational materials on prescribing for physicians and HMO members (HMO B)

Comparison: no educational policy intervention (HMO D)

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
Medicine use	We are uncertain about the effects on medicine use of an educational policy involving educational materials on prescribing mailed to physicians and HMO members, compared to no intervention The share of prescribing for the preferred drug (fexofenadine) increased by 9.5% (95% CI 7.9% to 11.1%) in the HMO that implemented educational materials for physicians and HMO members compared to an increase of 1.6 % (95% CI 0.4% to 2.8%) in the control HMO The share of prescribing for the less preferred drug (loratadine) decreased by −12.5% (95% CI −14.6% to −10.4%) in the HMO that implemented educational materials for physicians and HMO members compared to a decrease of −3.6% (95% CI −5.2% to −2.0%) in the control HMO	1 CBA[A]	⊖⊖⊖⊖ **Very low[B]**
Health care utilization	Not reported	-	-
Health outcomes	Not reported	-	-
Costs	The average cost per prescription for the antihistamines increased from USD 38.79 to USD 41.98 or 2% in the educational policy intervention group. The average cost per prescription increased 4.2% in the control group.	1 CBA[A]	Not assessed

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[A] (Benedetto 2000)
[B] Downgraded due to high risk of bias and indirectness (the inclusion of a single study from a high income country)

Summary of findings 4. Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to mailed educational materials on prescribing for physicians only

Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to mailed educational materials on prescribing for physicians only

Patient or population: prescribers or patients that are subjected to educational or regulatory interventions in prescribing due to government, non-government or third party payer policies

Setting: USA

Intervention: mailed educational materials on prescribing for physicians and HMO members (HMO B)

Comparison: mailed educational materials on prescribing for physicians (HMO C)

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
Medicine use	We are uncertain about the effects on medicine use of an educational policy involving educational materials on prescribing for physicians and HMO members, compared to educational materials mailed to physicians only. The share of prescribing for the preferred drug (fexofenadine) increased by 9.5% (95% CI 7.9% to 11.1%) in the HMO that implemented educational materials for physicians and HMO members compared to an increase of 2.3% (95% CI 0.6% to 4.0%) in the HMO that implemented educational materials on prescribing for physicians only. The share of prescribing for the less preferred drug (loratadine) decreased by −12.5% (95% CI −14.6% to −10.4%) in the HMO that implemented educational materials for physicians and HMO members compared to a decrease of −5.0% (95% CI −7.0% to −3.0%) in the HMO that implemented educational materials for physicians only.	1 CBA[A]	⊖⊖⊖⊖ **Very low**[B]
Healthcare utilization	Not reported	-	-
Health outcomes	Not reported	-	-
Costs	The average cost per prescription increased 8.2% (from USD 38.79 to USD 41.98) in the group that implemented an educational policy involving educational materials on prescribing for physicians and HMO members. The average cost per prescription increased 5% in the comparison group.	1 CBA[A]	Not assessed

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[A] (Benedetto 2000)
[B] Downgraded due to high risk of bias and indirectness (the inclusion of a single study from a high-income country)

Summary of findings 5. Educational policy: mailed educational materials on prescribing for physicians only compared to an intervention to regulate drug reimbursement

Educational policy: mailed educational materials on prescribing for physicians only compared to an intervention to regulate drug reimbursement

Patient or population: prescribers or patients that are subjected to educational or regulatory interventions in prescribing due to government, non-government or third party payer policies

Setting: USA

Intervention: mailed educational materials on prescribing for physicians (HMO C)

Comparison: intervention to regulate drug reimbursement (HMO A)

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
Medicine use	We are uncertain about the effects on medicine use of an educational policy involving educational materials on prescribing mailed to physicians, compared to an intervention to regulate drug reimbursement The share of prescribing for the preferred drug (fexofenadine) increased by 2.3 % (95% CI 0.6% to 4.0%) in the HMO that implemented educational materials for physicians compared to an increase of 45.6% (95% CI 42.3% to 48.9%) in the HMO that regulated drug reimbursement The share of prescribing for the less preferred drug (loratadine) decreased by −5.0% (95% CI −7.0% to −3.0%) in the HMO that implemented educational materials for physicians compared to a decrease of −54.4% (95% CI −57.7% to −51.0%) in the HMO that regulated drug reimbursement	1 CBA[A]	⊖⊖⊖⊖ **Very low**[B]
Healthcare utilization	Not reported	-	-
Health outcomes	Not reported	-	-
Costs	The average cost per prescription increased 5.0% (from USD 47.95 to USD 50.34) in the group that implemented an educational policy involving educational materials on prescribing for physicians. The average cost per prescription decreased by 22.3% in the comparison group.	1 CBA[A]	Not assessed

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[A] (Benedetto 2000)
[B] Downgraded due to high risk of bias and indirectness (the inclusion of a single study from a high income country)

Summary of findings 6. Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to an intervention to regulate drug reimbursement

Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to an intervention to regulate drug reimbursement

Patient or population: prescribers or patients that are subjected to educational or regulatory interventions in prescribing due to government, non-government or third party payer policies

Setting: USA

Intervention: mailed educational materials on prescribing for physicians and HMO members (HMO B)

Comparison: intervention to regulate drug reimbursement (HMO A)

Outcomes	Impact	No of participants (studies)	Certainty of the evidence

			(GRADE)
Medicine Use	We are uncertain about the effects on medicine use of an educational policy involving educational materials on prescribing mailed to physicians and HMO members, compared to an intervention to regulate drug reimbursement The share of prescribing for the preferred drug (fexofenadine) increased by 9.5% (95% CI 7.9% to 11.1%) in the HMO that implemented educational materials for physicians and HMO members compared to an increase of 45.6% (95% CI 42.3% to 48.9%) in the HMO that regulated drug reimbursement The share of prescribing for the less preferred drug (loratadine), decreased by −12.5% (95% CI −14.6% to −10.4%) in the HMO that implemented educational materials for physicians and HMO members compared to a decrease of −54.4% (95% CI −57.7% to −51.0%) in the HMO that regulated drug reimbursement	1 CBA[A]	⊕⊖⊖⊖ **Very low**[B]
Healthcare utilization	Not reported	-	-
Health outcomes	Not reported	-	-
Costs	The average cost per prescription increased 8.2% (from USD 38.79 to USD 41.98) in the group that implemented an educational policy involving educational materials on prescribing for physicians and HMO members. The average cost per prescription decreased by 22.3% in the comparison group.	1 CBA[A]	Not assessed

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[A] (Benedetto 2000)
[B] Downgraded due to high risk of bias and indirectness (the inclusion of a single study from a high income country)

BACKGROUND

Promotion of medicines can lead to over-prescribing, poor-quality prescribing and medicine use, and increased risk of adverse effects and healthcare costs (Ziganshina 2010).

Most countries face large increases in expenditures on pharmaceuticals. Expenditures on medicines account for between 6.8% and 29.2% of spending on healthcare in OECD (Organisation for Economic Co-operation and Development) countries (OECD 2015). Increasing expenditures on medicines puts pressure on policymakers to control medicine costs and ensure that this money is well spent. Pharmaceuticals make an important contribution to people's health. However, medicines are frequently not used appropriately. Improving the use of medicines can improve health outcomes and, in many circumstances, can result in large savings without adverse health consequences. On the other hand, regulatory and educational policies targeted at prescribers may have unintended effects on health and costs; for example, regulatory interventions can reduce appropriate prescribing due to surveillance of prescribing. This in turn can lead to adverse health outcomes in patients and therefore increased costs of health care. Educational policies targeted at prescribers may be expensive and may result in increased costs to the health system with modest savings due to changes in prescriber behaviour.

According to OECD 2009, OECD countries in 2009 faced a total pharmaceutical bill of more than USD 700 billion (this accounts for around 19% of health spending at that time). Spending on pharmaceuticals accounted for more than a sixth (17%) of all health expenditure on average across OECD countries in 2011 (due to economic recession), making it the third largest spending component after inpatient and outpatient care (OECD 2013). The average spending on pharmaceuticals has risen by almost 50% in real terms since 2000, but there are variations across countries in terms of consumption patterns and pharmaceutical policies.

Description of the condition

With the advent of new medicines and their increasing costs, more efforts are being made by regulators in terms of policy interventions designed to improve prescriber behaviour. In times of economic recession, the economic and clinical aspects of inappropriate prescribing can be immense (Soumerai 1989; Machado-Alba 2013; Schultz 2014). There are a number of contributing factors to inappropriate prescribing such as failure to keep abreast of new clinical information and developments, promotion strategies by pharmaceutical manufacturers, lack of consideration of costs of medicines, patient demand for specific medications, and third party involvement in patient-physician relationships that insulate both prescriber and patient from cost considerations.

Regulators can target consumption of pharmaceuticals and regulations can be directed at prescribers, dispensers or patients. Examples of such restrictions include requirement for patients to have a special permit or restrictions on care settings where medicines can be prescribed, restrictions on prescribing privileges to limited physician specialties, dose limits, restrictions on the number of days' supply that can be prescribed at one time and restrictions on the sites of medicine dispensing (Cherny 2010). Access to effective medicines can be restricted, however, by inadequate formulary availability and overregulation.

Education of prescribers is also important. Prescribers have control over pharmaceuticals through their prescribing; they are also in positions of influence as instructors or supervisors of younger doctors. Thus, if the training or education of prescribers in good prescribing practices is sound, this can have a cascading effect. Most undergraduate curricula do not include prescribing in their training (McLellan 2012; Ross 2012), nor is in-service training or continuing education mandated in many countries in order to keep abreast of changes in the use of medicines. Some prescribers may rely on promotional material for their information (Ziganshina 2010). This can lead to irrational and inappropriate prescribing leading to increased costs of medicines.

Description of the intervention

We considered two types of interventions for this review: regulatory interventions; and educational interventions by governments, non-governmental organisations or private insurers.

Regulatory strategies are used to address inappropriate prescribing practices, and seek to use laws and regulations to influence prescribing through restrictions and requirements. Regulatory interventions aim to enforce decisions that are intended to improve prescribing. Prescribing limitations may take the form of:

- medicine formularies used to direct prescribing;
- generic prescribing being mandatory;
- prescribing privileges by level of use (facility level or competence level of prescriber);
- limiting the number of medicines prescribed per patient (Chalker 2012);
- monitoring prescribing practices through surveillance, especially for medicines that can be abused by patients.

Educational policies are laws, rules, financial or administrative orders made by governments, non-governmental organisations or private insurers regarding the use of such interventions. Educational interventions are commonly used to address inappropriate prescribing practices. They include printed materials, educational meetings and educational outreach. Educational interventions not included in this review but covered in other EPOC reviews can be further described as follows (Oxman 1995; Chalker 2012).

- Educational materials: distribution of published or printed recommendations for clinical therapy, including clinical treatment guidelines, audiovisual materials and electronic publications (Giguère 2012).
- Educational meetings: participation of prescribers in conferences, lectures, workshops or traineeships outside their practice settings (Forsetlund 2009).
- Outreach visits: use of a trained person who meets prescribers in their practice settings to provide information that may include feedback on the prescriber's performance (O'Brien 2007).
- Local opinion leaders: use of prescribers acknowledged by their colleagues to be "educationally" influential (Flodgren 2019).
- Audit and feedback: providing summaries of the practices of prescribers over a specified period, with or without recommendations (Ivers 2012).
- Reminders: providing manual or computerized prompts to prescribers (Arditi 2017).

How the intervention might work

Regulatory policies concerning generic prescribing might be applied to increase generic prescribing at the level of the individual or small units such as general practices. Generic prescribing involves the prescription of a chemically equivalent but less expensive medicine in place of a brand-name product that has an expired patent (Moe-Byrne 2014). Surveillance of physician prescribing by health care payers is an increasingly common strategy intended to reduce inappropriate medicine use, abuse, and medicine expenditures. Tools which monitor prescribing, such as triplicate prescription programmes (TPPs), require physicians to order targeted medicines on triplicate forms with one copy forwarded by pharmacies to a state surveillance unit that monitors prescriptions to detect 'unusual' patterns of prescribing and dispensing. Tools which monitor prescribing do not directly restrict freedom to prescribe, but critics contend that they can reduce appropriate care by creating an environment that discourages prescribing of targeted medicines due to fear of sanctions, procedural obstacles, or confidentiality concerns (Ross-Degnan 2004).

Restriction of prescribing can be limited to an approved formulary for a country or institution, or based on treatment guidelines. Restrictions can also limit prescribing of specialised or expensive medicines to specialised prescribers. Regulatory policies that limit who can prescribe opioid medicines, as well as monitoring the prescribing and use of opioid medicines, are common (Vranken 2014). Prescription monitoring programmes in the USA and Asia on reducing abuse and diversion of controlled substances are especially common (Vranken 2014).

Educational policies seek to improve prescribing behaviours by informing, persuading or training prescribers. The most common educational interventions aim to inform prescribers, usually in the form of mailed printed materials or advisory letters; protocols and guidelines without any other reinforcements; self-educational materials; and mailed materials as parts of national warning campaigns, generally when medicines are identified as causing severe adverse effects (Soumerai 1989). Feedback interventions, in which physicians' past prescribing patterns are presented and compared to either peer behaviour or accepted standards (or both), aim to improve prescriber behaviour both by informing and influencing prescribers. Educational meetings, outreach visits and local opinion leaders can aim to inform, persuade or train prescribers. Reminders aim to help prescribers to recall information.

Why it is important to do this review

A wide variety of educational and regulatory policies are being used with the intention of improving prescribing. There are no previous reviews that focus specifically on the effects of educational or regulatory policies targeted at prescribers.

The aim of this review is to support informed decisions about educational and regulatory pharmaceutical policies targeted at prescribers and to guide future evaluations by preparing an up-to-date, comprehensive summary of what is known from well-designed research about the effects of these policies for improving rational (appropriate and efficient) medicine use. This review is one of 13 planned or completed reviews of the effects of different types of pharmaceutical policies on rational medicine use (Aaserud 2006a). Pharmaceutical policies that are complementary to the regulation of the provision of medicine insurance are addressed in other reviews. These include policies regarding the effects of financial incentives for prescribers (Rashidian 2015), sales and dispensing policies (Peñaloza 2015), caps and co-payments (Luiza 2015), policies that place restrictions on reimbursement for medicines that are covered (Green 2010), policies that regulate pricing and purchasing (Acosta 2014), and policies that regulate drug insurance schemes (Pantoja 2015).

OBJECTIVES

To assess the effects of pharmaceutical educational and regulatory policies targeting prescribers on medicine use, healthcare utilisation, health outcomes and costs (expenditures).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials, non-randomised trials, repeated measures studies, interrupted time series (ITS) studies, and controlled before–after (CBA) studies. For controlled interrupted time series studies, we planned to assess the time series arm of the studies for risk of bias independently from the control arm, using the criteria for ITS studies. We planned to assess the control series arm of the study using risk of bias criteria for controlled before–after studies. If the control arm had a high risk of bias, we would not have included it in the analysis and the study would have been classified as interrupted time series. If we had assessed the risk of bias as low, we would have used the control data in the review.

We excluded randomised trials, non-randomised trials and controlled before–after studies with only one intervention or control site. We also excluded interrupted time series and repeated measures studies that did not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention (EPOC 2017a).

Types of participants

Health care consumers and providers within a large jurisdiction or system of care. Jurisdictions could have been regional, national or international. We excluded studies within organisations, such as health maintenance organisations, if the organisation was multi-sited and served a large population.

Types of interventions

Regulatory and educational policies targeted at prescribers, including monitoring and enforcement of restrictions, generic prescribing, programmes to implement treatment guidelines, system-wide policies regarding monitoring medicine safety, and legislated or mandatory continuing education or quality improvement specifically targeted at prescribing, including printed materials. We defined 'policies' in this review as laws, rules, financial and administrative orders made by governments, non-governmental organisations or private insurers. We excluded interventions applied at the level of a single facility.

Types of outcome measures

To be included a study had to include an objective measure of at least one of the following outcomes.

- Medicine use
- Healthcare utilization
- Health outcomes
- Costs (and where appropriate, expenditure)

We did not include adverse events or unanticipated consequences.

Search methods for identification of studies

The EPOC Trials Search Co-ordinator (TSC) (Marit Johansen), in consultation with the authors, developed the search strategies. Search strategies comprised keywords and controlled vocabulary terms. We did not apply language limits. We searched all databases from database start date to date of search. We used two methodology search filters to limit retrieval to appropriate study designs: a modified version of the Cochrane Highly Sensitive Search Strategy (sensitivity- and precision-maximizing version – 2008 revision) to identify randomised trials (cf. *Cochrane Handbook for Systematic Reviews of Interventions* 6.4d); and an EPOC methodology filter to identify non-RCT designs.

Electronic searches

We searched the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) for related systematic reviews.

We searched the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL), 2014, Issue 11, part of Cochrane Library. www.cochranelibrary.com (searched 22 March 2018)
- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE 1946 to Present, Ovid (searched 22 March 2018)
- Embase 1974 to 2018 March 21, Ovid (searched 22 March 2018)
- Dissertations and Theses Database, 1861 to present, ProQuest (searched 09 December 2014)
- EconLit 1969-present, ProQuest (searched 09 December 2014)
- PAIS International 1914-present, ProQuest (searched 09 December 2014)
- Worldwide Political Science Abstracts 1975-present, (searched 09 December 2014)
- International Political Science Abstracts (IPSA) 1951 – present, EbscoHost (searched 09 December 2014)
- NHS Economic Evaluation Database 2014, Issue 4, in the Cochrane Library. www.cochranelibrary.com (searched 09 December 2014)
- INRUD Bibliography, International Network for Rational Use of Drugs (searched 09 December 2014)
- PubMed, NLM (searched 09 December 2014 for relevant journals not indexed in MEDLINE)
- World Health Organization Library Information System (WHOLIS), VHL (searched 09 December 2014)
- Science Citation Index and Social Sciences Citation Index 1975 to present, and Emerging Sources Citation Index 2015 to present, ISI Web of Science (searched 05 January 2016 for studies that cite the included studies in this review)

Searching other resources

Grey Literature

- Grey Literature Report (New York Academy of Medicine) www.nyam.org/library/online-resources/grey-literature-report (searched 24 February 2018)
- Word Health Organization (WHO) www.who.int/ictrp/en (searched 24 February 2018)·

Trial Registries

- International Clinical Trials Registry Platform (ICTRP) (searched 24 February 2018)
- ClinicalTrials.gov, US National Institutes of Health (NIH) ClinicalTrials.gov (searched 24 February 2018)

We also reviewed reference lists of all included studies, relevant systematic reviews/primary studies.

All strategies used are provided in Appendix 1.

Data collection and analysis

Selection of studies

Two authors (FS and EM) independently reviewed all of the search results, abstracts and reference lists of relevant reports. We retrieved the full text of potentially relevant reports (if one or both authors thought it was potentially relevant) and the authors independently assessed the full reports of all potentially relevant studies for inclusion using an eligibility form based on the inclusion and exclusion criteria. Both authors extracted data from included studies independently of each other. For all the steps in the above process, they resolved disagreements by discussion.

Data extraction and management

The following additional information was extracted from included studies using a standardised data extraction form.

- Type of study (randomised trial, non-randomised trial, repeated measures study, interrupted time series, controlled before–after).
- Study setting (country, key features of the healthcare system and concurrent pharmaceutical policies).
- The sponsors of the study.
- Characteristics of the participants (consumers, physicians, practices, hospitals, etc.).
- Characteristics of the policies.
- Main outcome measures and study duration.
- The results for the main outcome measures.

In addition, we attempted to identify important factors that might be taken into consideration by anyone contemplating implementing any of the policy alternatives, including: possible trade-offs (of the expected benefits versus harms and costs); short- versus long-term effects; and limitations of the available evidence and other important factors that might affect the translation of the available evidence into practice in specific settings. We recorded our judgements and justifications in 'Risk of bias' tables for each included study and we used these judgements while grading

the overall quality of evidence for outcomes in the 'Summary of findings' tables for each comparison.

Assessment of risk of bias in included studies

Two review authors (EM and FS) independently used the criteria recommended by EPOC to assess the risk of bias of studies included in EPOC reviews (EPOC 2017b).

Each of the data extractors assessed overall limitations for each main outcome within each study using the following guidelines (Higgins 2011).

- Low risk of bias = all criteria scored as 'low risk'. Plausible bias unlikely to seriously alter the results.
- Unclear risk of bias = one or two criteria scored as 'unclear risk' or 'high risk'. Plausible bias that raises some doubt about the results.
- High risk of bias = more than two criteria scored as 'unclear' or 'high risk'. Plausible bias that seriously weakens confidence in the results.

Measures of treatment effect

Had there been sufficient numbers of comparisons for similar outcomes across studies, we would have used graphical displays (box and whisker plots) to visually explore heterogeneity of the results across studies. The following potentially explanatory factors would have been considered: differences in the characteristics of the policies; differences in the settings; and differences in study quality. We would have supplemented these visual analyses with multivariate statistical analyses (metaregression), if appropriate, to examine how the size of observed effects are related to characteristics of the policies, differences in settings and differences in study quality.

As there are just two studies that fit the inclusion criteria, we present the results as they appear in the original papers. Benedetto 2000 used measures such as monthly per cent market share for each medicine; per cent prescribing for each medicine; cost per medicine prescription; mean costs per prescription; and estimated cost savings. Simoni-Wastila 2004 used measures such as number of benzodiazepine users per 100 study-eligible individuals per month; probably problematic use; possibly problematic use; and probably nonproblematic use of benzodiazepines.

Unit of analysis issues

We performed all included analyses at the same level as the allocation to avoid unit of analysis errors.

Dealing with missing data

All of the included results are available in published reports. We made no efforts to obtain missing data.

Assessment of heterogeneity

We did not statistically combine the results, as there was one study for the regulatory intervention and one for the educational intervention. We considered the following potential explanatory factors, which might limit the applicability of the findings, as well as explain differences in results.

- The characteristics of the policies, i.e. the length of period for policy implementation as well as the time at which impact of the policy was studied. The longer the follow-up, the smaller the effect, as most effects can be expected to diminish over time due to other factors, including adjustments or interventions by industry, that influence prescribing.
- The settings, i.e. geographical location of the intervention, as high-resource settings may be able to afford multiple educational interventions and the resources those required, including monitoring systems, whereas low-resource settings might not be able to duplicate such interventions; presence of strong regulatory systems in some countries would enable better implementation, monitoring and sustainability of interventions.

We were also prepared to consider the contexts — policy, professional, economic and regulatory — in which prescribers operate in each country, as well as the knowledge of prescribers and patients. Factors such as the relationship between public and private sector services, and the existence of laws, regulations and methods to enforce these, as well as the political willingness and capacity of governments, can all influence the impact of educational and regulatory interventions to improve prescribing.

Assessment of reporting biases

There was an insufficient number of studies for us to assess the risk of publication bias. We considered selective outcome reporting as a risk-of-bias criterion for the included studies.

Data synthesis

We prepared a table for each of the included studies with the main results. We prepared tables for each subcategory of intervention including the following information: study identification; characteristics of the intervention; drug use; healthcare utilisation; health outcomes; and expenditures.

Summary of findings

We prepared 'Summary of findings' tables for the main intervention comparisons and included the main outcomes in order to draw conclusions about the certainty of the evidence. Two review authors independently assessed the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* and the EPOC worksheets (Higgins 2011 and EPOC 2017c, respectively), using GRADEpro software (GRADE 2004). We resolved disagreements on certainty ratings by discussion. Our decisions to down- or upgrade are presented in footnotes in the tables. We use plain language statements to report these findings in the review (EPOC 2017d)

Subgroup analysis and investigation of heterogeneity

We could perform no subgroup analyses due to the insufficient number of studies.

Sensitivity analysis

We performed no sensitivity analyses.

RESULTS

Description of studies

Results of the search

A broad search for pharmaceutical educational and regulatory policies in the databases and resources outlined under Electronic searches above resulted in 29,867 records. Including reference lists from grey literature added another 52 records. We therefore screened 29,919 records in total (without duplicates). We identified and retrieved in full text a total of 71 papers that evaluated potentially relevant interventions. Sixty-six of these papers were excluded, most of them because they did not meet the intervention or participant-inclusion criteria. These were primarily non-policy studies, studies of financial regulatory policies, studies with no data points from before the intervention, and before–after studies without a control group. Most of the interventions we evaluated were not implemented by governments, non-governmental organisations or third party payers. We then evaluated five studies for the review. However, we found three were subsequently to be more relevant to other EPOC reviews on pharmaceutical policies such as interventions on pre-authorisation, generic substitution, and sales and dispensing policies. See Figure 1 for a PRISMA flow diagram.

Figure 1. Study flow diagram.

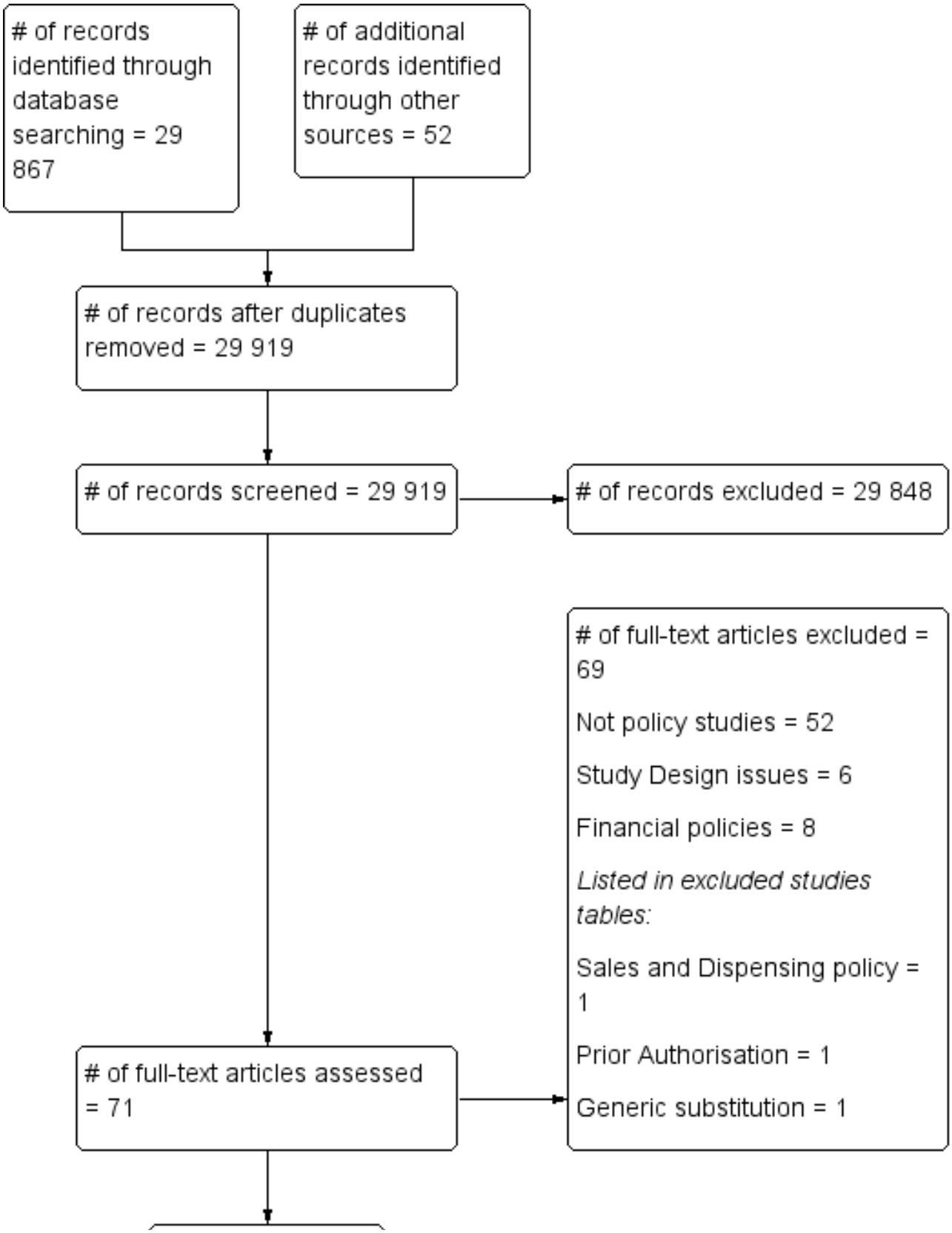
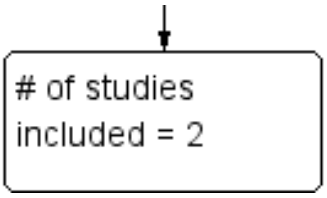


Figure 1. (Continued)



Included studies

Study designs

We identified two studies that met the selection criteria: a controlled interrupted time series (ITS) analysis (Simoni-Wastila 2004); and a controlled before–after study (see Characteristics of included studies) (Benedetto 2000). One compared a policy of mailed printed educational materials on prescribing to no policy and to a policy that restricted reimbursement for antihistamines (Benedetto 2000) (see Table 1). The other evaluated the effects of a tool to monitor prescribing of benzodiazepines (Simoni-Wastila 2004)

Characteristics of settings and patients

Both of the studies were conducted in the USA. One study was set in the States of New York and New Jersey, and participants were continuously enrolled Medicaid beneficiaries, 19 years or older, in three categories: Aid to Families with Dependent Children; Old Age Assistance; and Aid to the Permanently and Totally Disabled (Simoni-Wastila 2004). The second study included four independent practice-association model Health Maintenance Organizations (HMOs) from the Northeast, Midwest and West Coast (Benedetto 2000), with 540,000 members in the intervention HMOs (A, B and C) and 430,000 members in the control HMO (D).

Characteristics of interventions

Both policies in the studies were introduced in the late 1990s (Benedetto 2000; Simoni-Wastila 2004). One study evaluated a regulatory policy intervention and one study evaluated an educational policy intervention.

Simoni-Wastila 2004 reported on a mandatory prescribing monitoring tool, a regulatory intervention that was a form of surveillance of physicians' prescribing patterns. Triplicate prescription programmes (TPPs) require physicians to use multiple copy forms when ordering medicines covered by an insurance plan or other funder. TPPs are a strategy used by health insurers to identify unusual or unexpected patterns of prescribing, dispensing, and medicine consumption. This study assessed changes in the use of benzodiazepines and other psychoactive medicines by clinically vulnerable patients in the New York Medicaid programme (the prescribing monitoring tool site) and in a control state (New Jersey Medicaid). Changes were assessed 12 months before and 24 months after the addition of benzodiazepines to the New York site (from January 1988 to December 1990), using the Medicaid Management Information System. The regulatory policy required New York physicians linked to Medicaid to order benzodiazepines on triplicate prescription forms with one copy forwarded by pharmacies to a state surveillance unit. This constituted an extension of the existing TPP policy. New Jersey is an adjoining state with a similar medicine reimbursement programme but did not have any regulations targeting benzodiazepines during the 3-year study period.

Benedetto 2000 compared an educational policy of mailed printed educational materials on prescribing to no policy and to a policy that restricted reimbursement for antihistamines, In this study, the four included HMOs were similar in structure and in their control over prescribing. Physicians at these HMOs were routinely monitored for compliance to formularies and generic product prescribing. This information was then fed back to the physicians by the HMOs on a quarterly basis. In some cases the notification was a simple report card. In others a financial bonus was provided if certain rates set by the HMO were reached. Each HMO performed four to eight interventions related to drug utilization per year, so the physicians were familiar with such interventions. In Benedetto 2000, the educational policy interventions were targeted at shifting prescribing of a formulary-listed antihistamine to a new antihistamine, based on cost data for the two antihistamine options (clinical safety and efficacy were deemed to be similar). All interventions were undertaken by a pharmacy benefit management company. The study included three different interventions — for a summary of these interventions see Table 1.

Two HMOs implemented voluntary switching to the new antihistamine by means of an educational policy involving educational mailings. In one HMO, letters were mailed to physicians and HMO members indicating the preferred antihistamine that should be used, together with an educational fact sheet on the drug in order to aid prescribing (HMO B). In a second HMO, letters were mailed to physicians only, together with a step-wise guide as to when the prescription antihistamine should be used in patients (HMO C).

A third HMO used a 'mandatory lockout' of one antihistamine, loratadine, in favour of another, fexofenadine — only fexofenadine was reimbursable while loratadine was not reimbursable (HMO A). We considered this to be a form of reimbursement policy. This intervention is included in the review only as a comparison as while this could be viewed as a type of regulation, it is primarily about reimbursement policies which are covered by another EPOC review (Green 2010). In addition, coverage limitations were instituted, restricting the antihistamine to one dose per day and suggesting two other alternate medicines for an evening dose. A month later the restriction was increased to two doses per day.

In all three intervention HMOs, USD 10 manufacturer coupons were used as incentives to encourage prescribing of the new antihistamine. The HMO that implemented the reimbursement intervention (HMO A) sent the coupon to members for whom prescriptions were written for the antihistamine on formulary, along with an educational pamphlet offering information on an allergy centre that provided information to patients and families

on allergies at no cost. The HMO that implemented educational interventions for both physicians and HMO members sent the coupon to members of the scheme with the clinical information sheet sent to prescribers, as well as a free consultation at the allergy centre. The HMO that implemented an educational intervention for physicians only sent the coupon to the prescribers directly, to be used in conjunction with the first antihistamine prescription.

All three HMOs were compared to a control HMO that did not restrict member benefits in any way (HMO D). The study took place in 1998, and measured time points six months before and six months after the intervention in each HMO.

Characteristics of outcomes

The studies provided data on medicine use; i.e. percentage utilization of medicine or prescriptions per 100 enrolees (Simoni-Wastila 2004) (see Table 2), percentage market share and percentage prescribed for each medicine (Benedetto 2000) (see Table 3). Only one study reported on total expenditure before and after the intervention programmes, and on the costs of the intervention (Benedetto 2000) (see Table 4). Health outcomes and healthcare utilisation were not reported.

Excluded studies

We excluded three studies of policies that might appear to be targeted at prescribers because, in practice, these policies were not directly targeted at prescribers. One interrupted time series study evaluated the effects of enforcement of restrictions on prescribing using pre-authorisation (Lu 2011), which is addressed by another review (Green 2010). One controlled before–after study evaluated the effects of separating prescribing and dispensing functions for outpatient services on expenditures and on physicians' prescribing practices (Chou 2003), a type of dispensing policy (Peñaloza 2015). One interrupted time series study evaluated the effects of mandatory generic substitution on pharmaceutical expenditures (Anderson 2007), also a type of dispensing policy. See Characteristics of excluded studies.

Risk of bias in included studies

Details of our assessment of the risk of bias for the included studies are presented in the Characteristics of included studies table. The 'Risk of bias' assessments for both studies are also shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

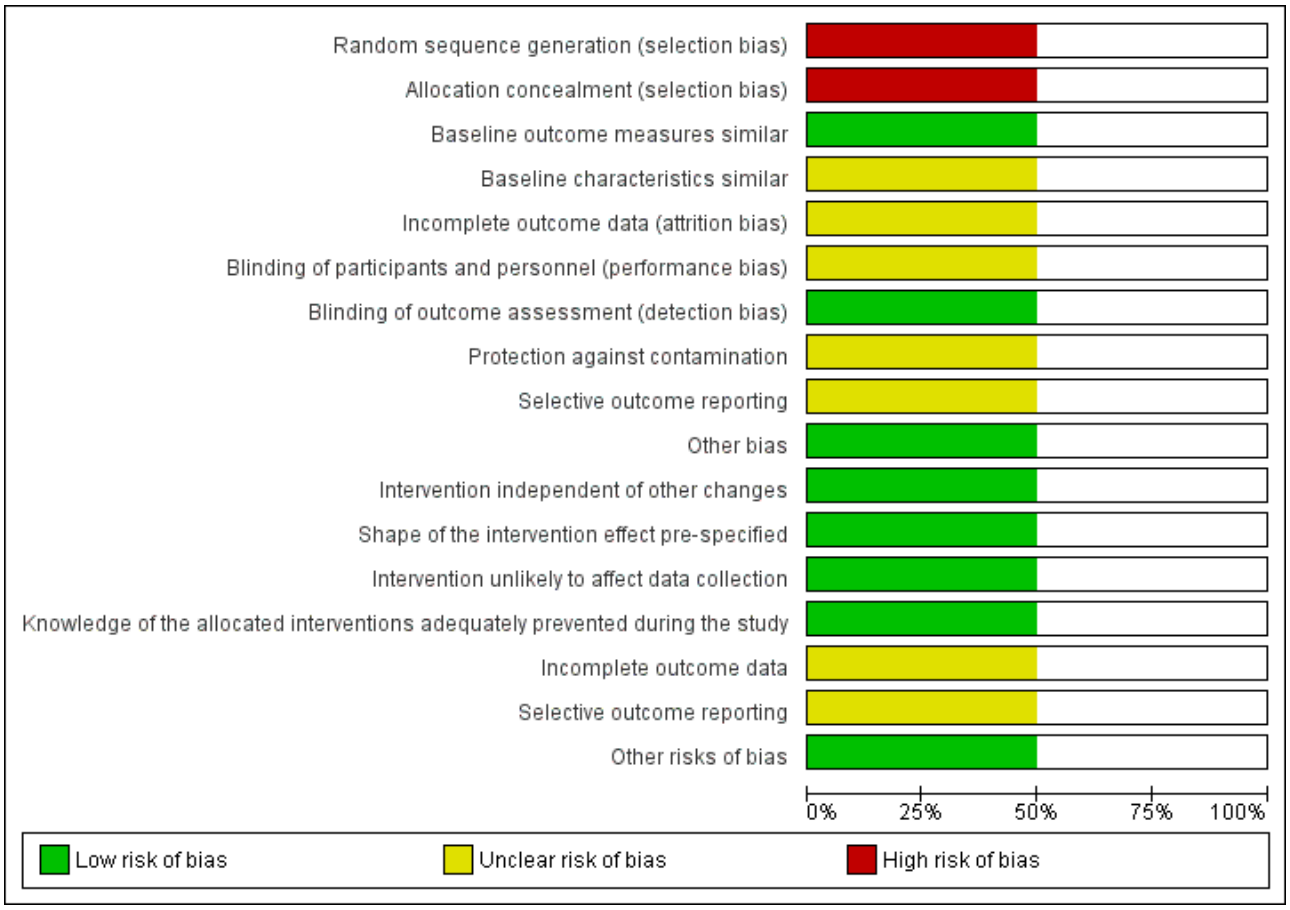
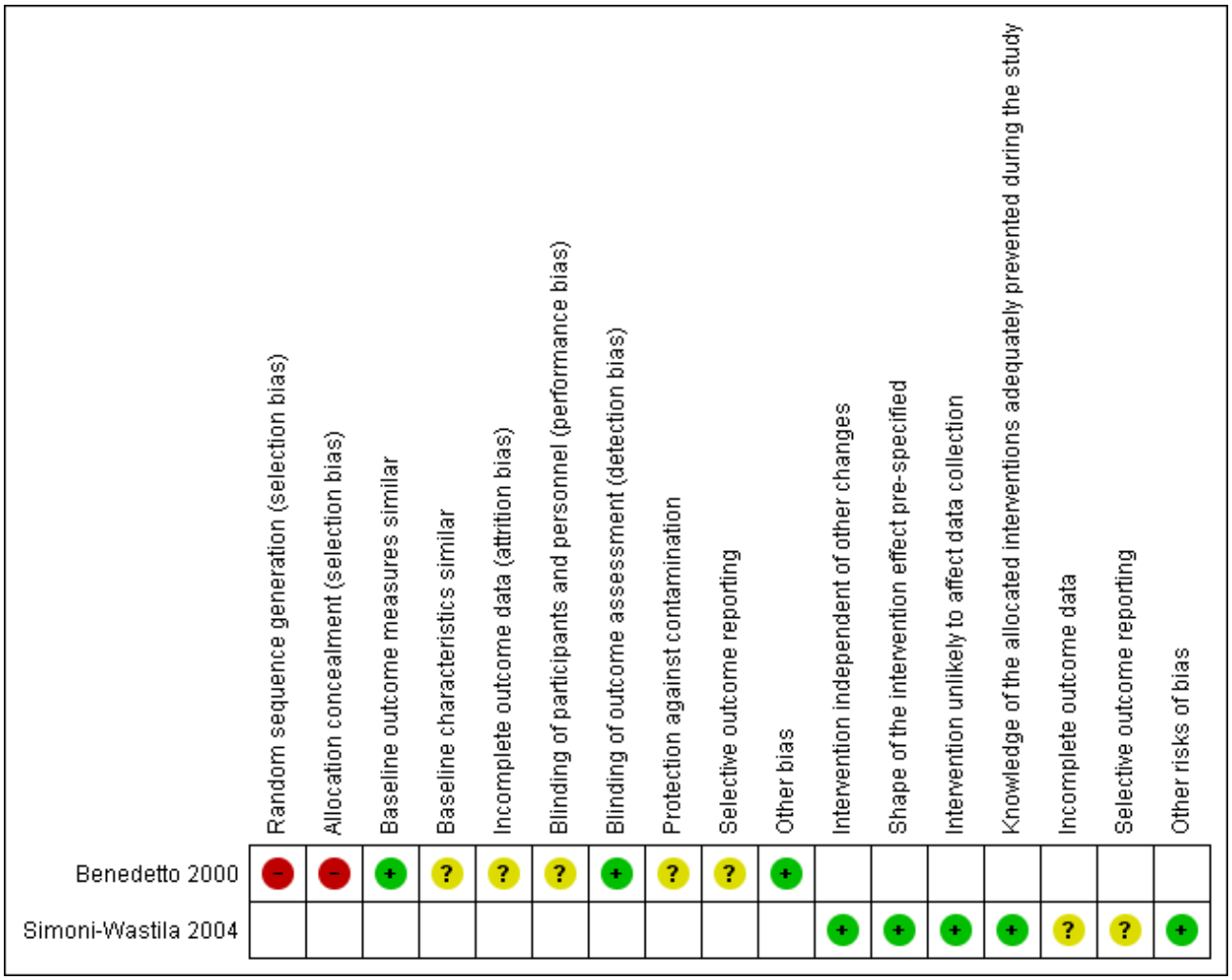


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We judged Simoni-Wastila 2004 to be at low risk of bias for all criteria for interrupted time series studies, apart from the completeness of outcome data and selective outcome reporting, for which we assessed the risk as 'unclear'. The study clearly defined the population for inclusion in the study, namely Medicaid beneficiaries with schizophrenia, schizophreniform disorder, schizoaffective disorder, schizoid personality disorder, or schizotypal personality disorder; bipolar disorder; epilepsy; panic disorder, and agoraphobia without history of panic disorder. Baseline characteristics in the intervention and control sites were similar.

As a controlled before–after study, we assessed Benedetto 2000 as being at high risk of bias in relation to random sequence generation and allocation concealment. We assessed the study as being at unclear risk of bias in relation to the similarity of baseline characteristics; the completeness of outcome data; blinding of participants and personnel; protection against contamination; and selective outcome reporting. In addition, we assessed the study as being at low risk of bias in relation to blinding of outcome assessment as outcome data were drawn from a central pharmacy claims database run by the HMOs in the study and can therefore be considered objective.

Effects of interventions

See: **Summary of findings for the main comparison** Regulatory policy: use of a prescribing monitoring tool compared to no regulatory intervention; **Summary of findings 2** Educational policy: mailed educational materials on prescribing for physicians compared to no educational intervention; **Summary of findings 3** Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to no educational intervention; **Summary of findings 4** Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to mailed educational materials on prescribing for physicians only; **Summary of findings 5** Educational policy: mailed educational materials on prescribing for physicians only compared to an intervention to regulate drug reimbursement; **Summary of findings 6** Educational policy: mailed educational materials on prescribing for physicians and HMO members compared to an intervention to regulate drug reimbursement

Regulatory policies

One included study assessed a regulatory policy intervention in the form of a prescribing monitoring tool — the Triplicate Prescription

Program — and reported on medicine use (Simoni-Wastila 2004) (Table 2). Healthcare utilization, health outcomes, and costs were not reported in this study.

Comparison 1: Regulatory policy involving use of a prescribing monitoring tool (Triplicate Prescription Program) compared to no regulatory intervention

See Summary of findings for the main comparison.

Medicine use

The impacts of a regulatory policy involving use of a prescribing monitoring tool were assessed through relative changes in the use of benzodiazepines. We are uncertain about the effects of monitoring prescribing using triplicate prescriptions on prescribing of benzodiazepines at 6 months among patients with one or more of the specified diagnostic conditions, compared to no policy (very low certainty evidence) (48.1% relative decrease in benzodiazepine use as compared with predicted levels had the policy not been implemented, after controlling for baseline trends (95% confidence interval (CI) −50.0% to −46.2%)). The control group did not demonstrate any decrease in benzodiazepine use. There was a small increase in the use of substitute medicines in the intervention group following the intervention, but this did not counteract the reductions in benzodiazepine use. The effects of the intervention were sustained for seven years of follow-up. We judged the certainty of the evidence as very low due to risk of bias (ITS study) and very serious indirectness (single study from a high-income country with particular health system arrangements, and with the intervention targeting to a particular insured group of patients).

The study reported a number of other very low certainty findings, as follows.

- The largest reduction in benzodiazepine use was observed among people with epilepsy (a 59.9% relative decrease at 6 months, 95% CI −63.9% to −55.9%).
- The intervention had the greatest impact on nonproblematic benzodiazepine use. Nonproblematic use was defined as use in patients that were on long-term or short-term use, but there was no filling of the prescription at 2 pharmacies within 7 days or use of the drug at high dose (2 times more than the maximum recommended daily dose) (see Table 2).
- The following groups were more likely to experience greater reductions in benzodiazepine use: women (compared with men (RR = 1.15 [1.01, 1.32])); and Medicaid members living in urban areas (RR = 1.47 [1.26, 1.72]), in areas that were mainly Black (RR = 1.23 [1.11, 1.37]), or in areas that had a high density of poor households (RR = 1.33 [1.19, 1.49]).

Educational policies

One included study assessed three different interventions including an educational policy involving mailed educational materials on prescribing for physicians and HMO members and an intervention to regulate drug reimbursement (Benedetto 2000) (Table 1). The study reported on medicine use and costs. Healthcare utilization and health outcomes were not reported in the study.

We have reported the post-intervention change (expressed as a factor) relative to prescribing in per cent, not number of prescriptions or market share, in order to express the estimated effect sizes in relative terms as well as the absolute differences in per cent.

Comparison 2: Educational policy involving mailed educational materials on prescribing for physicians compared to no educational intervention

See Summary of findings 2.

Medicine use

We are uncertain about the effects on medicine use of an educational policy involving mailed educational materials on prescribing for physicians, compared to no intervention (very low certainty evidence). We judged the certainty of the evidence as very low due to high risk of bias and indirectness (single study from a high-income country, with particular regulatory and health systems arrangements).

For the preferred drug (fexofenadine), the HMO that implemented educational materials for physicians showed a pre-post intervention increase in the share of prescribing of 2.3% (95% CI 0.6% to 4%; very low certainty evidence). In the control HMO, the pre-post intervention difference in the share of prescribing for the preferred drug was 1.6% (95% CI 0.4% to 2.8%; very low certainty evidence).

For the less preferred drug (loratadine), the HMO that implemented educational materials for physicians showed a pre-post intervention decrease in the share of prescribing (−5%, 95% CI −7.0% to −3.0%; very low certainty evidence). In the control HMO, the pre-post intervention difference in the share of prescribing for the less preferred drug also decreased (−3.6%, 95% CI −5.2% to −2.0%; very low certainty evidence) (Table 3).

We are uncertain about the effect of mailed educational materials on prescribing for physicians on the change in market share from the less preferred drug to the more preferred drug, compared to no intervention. This is because the certainty of the evidence is very low (Table 5).

Costs

For the HMO that implemented educational materials for physicians, the average cost per prescription increased 5.0%, from USD 47.95 to USD 50.34. For the control HMO, the average cost per prescription increased 4.2%. The certainty of these cost data was not assessed.

The total cost of the intervention (from the perspective of the pharmacy benefit management company, including the personnel time to implement the programmes as well as the supply, printing and mailing costs) was USD 5517 at the HMO that implemented mailed educational materials for physicians (HMO C).

Comparison 3: Educational policy involving mailed educational materials on prescribing for physicians and HMO members compared to no educational intervention

See Summary of findings 3

Medicine use

We are uncertain about the effects on medicine use of an educational policy involving mailed educational materials on prescribing for physicians and HMO members, compared to no

educational intervention (very low certainty evidence). We judged the certainty of the evidence as very low due to high risk of bias and indirectness (single study from a high-income country, with particular regulatory and health systems arrangements).

For the preferred drug (fexofenadine), the HMO that implemented educational materials for physicians and HMO members showed a pre-post intervention increase in the share of prescribing of 9.5% (95% CI 7.9% to 11.1%; very low certainty evidence). In the control HMO, the pre-post intervention difference in the share of prescribing for the preferred drug was an increase of 1.6% (95% CI 0.4% to 2.8%; very low certainty evidence).

For the less preferred drug (loratadine), the HMO that implemented educational materials for physicians and HMO members showed a pre-post intervention decrease in the share of prescribing (−12.5%, 95% CI −14.6% to −10.4%; very low certainty evidence). In the control HMO, the pre-post intervention share of prescribing for the less preferred drug also decreased (−3.6%, 95% CI −5.2% to −2.0%; very low certainty evidence) (Table 3).

We are uncertain about the effect of mailed educational materials on prescribing to physicians and HMO members on the change in market share from the less preferred drug to the more preferred drug, compared with no intervention. This is because the certainty of the evidence is very low (Table 5).

Costs

In the intervention HMO (HMO B), the average cost per prescription for the antihistamines increased from USD 38.79 to USD 41.98, or 8.2%. The cost of the antihistamines continued to rise despite the promotion of a switch from loratadine to fexofenadine. In HMO that received no intervention (HMO D), the average cost per prescription increased 4.2%. The certainty of these cost data was not assessed.

The total cost of the intervention (from the perspective of the pharmacy benefit management company, including the personnel time to implement the programmes as well as the supply, printing and mailing costs) was USD 7539 at the HMO that mailed educational materials and coupons to members and physicians (HMO B).

Comparison 4: Educational policy involving mailed educational materials on prescribing for physicians and HMO members compared to mailed educational materials on prescribing for physicians only

See Summary of findings 4.

Medicine Use

We are uncertain about the effects on medicine use of an educational policy involving mailed educational materials on prescribing for physicians and HMO members, compared to educational materials mailed to physicians only (very low certainty evidence). We judged the certainty of the evidence as very low due to high risk of bias and indirectness (single study from a high-income country, with particular regulatory and health systems arrangements).

For the preferred drug (fexofenadine), the HMO that implemented educational materials for physicians and HMO members showed a pre-post intervention increase in the share of prescribing of 9.5% (95% CI 7.9% to 11.1%; very low certainty evidence). In the HMO that implemented educational materials for physicians only, the pre-post intervention difference in the share of prescribing for the preferred drug was an increase of 2.3% (95% CI 0.6% to 4.0%; very low certainty evidence).

For the less preferred drug (loratadine), the HMO that implemented educational materials for physicians and HMO members showed a pre-post intervention decrease in the share of prescribing (−12.5%, 95% CI −14.6% to −10.4%; very low certainty evidence). In the HMO that implemented educational materials for physicians only, the pre-post intervention share of prescribing for the less preferred drug also decreased (−5.0%, 95% CI −7.0% to −3.0%; very low certainty evidence) (Table 3).

We are uncertain about the effect of mailed educational materials on prescribing to physicians and HMO members on the change in market share from the less preferred drug to the more preferred drug, compared to educational materials for physicians only. This is because the certainty of the evidence is very low (Table 5).

Costs

The average cost per prescription increased 8.2% (from USD 38.79 to USD 41.98) in the group that implemented an educational policy involving educational materials on prescribing for physicians and HMO members. The average cost per prescription increased 5% in the comparison group. The certainty of these cost data was not assessed.

The total cost of the intervention (from the perspective of the pharmacy benefit management company, including the personnel time to implement the programmes as well as the supply, printing and mailing costs) was USD 7539 at the HMO that mailed educational materials and coupons to members and physicians (HMO B).

Comparison 5: Educational policy involving mailed educational materials on prescribing for physicians only compared to an intervention to regulate drug reimbursement

See Summary of findings 5.

Medicine Use

We are uncertain about the effects on medicine use of an educational policy involving educational materials for physicians only, compared to an intervention to regulate drug reimbursement (very low certainty evidence). We judged the certainty of the evidence as very low due to high risk of bias and indirectness (single study from a high-income country, with particular regulatory and health systems arrangements).

For the preferred drug (fexofenadine), the HMO that regulated drug reimbursement showed a pre-post intervention increase in the share of prescribing of 45.6% (95% CI 42.3% to 48.9%; very low certainty evidence). In the HMO that implemented educational materials for physicians only, the pre-post intervention difference in the share of prescribing for the preferred drug was a small increase of 2.3% (95% CI 0.6% to 4.0%; very low certainty evidence).

For the less preferred drug (loratadine), the HMO that regulated drug reimbursement showed a pre-post intervention decrease in the share of prescribing (−54.4%, 95% CI −57.7% to −51.0%; very low certainty evidence). In the HMO that implemented educational materials for physicians only, the pre-post intervention share of

prescribing for the less preferred drug also decreased (−5.0%, 95% CI −7.0% to −3.0%); very low certainty evidence) (Table 3).

We are uncertain about the effect of mailed educational materials for physicians only on the market share from the less preferred drug to the more preferred drug, an intervention to regulate drug reimbursement (Table 5).

Costs

The average cost per prescription increased 5.0% (from USD 47.95 to USD 50.34) in the group that implemented an educational policy involving educational materials on prescribing for physicians. The average cost per prescription decreased by 22.3% in the comparison group. The certainty of these cost data was not assessed.

The total cost of the intervention (from the perspective of the pharmacy benefit management company, including the personnel time to implement the programmes as well as the supply, printing and mailing costs) was USD 5517 at the HMO that implemented mailed educational materials for physicians (HMO C).

Comparison 6: Educational policy involving mailed educational materials on prescribing for physicians and HMO members compared to an intervention to regulate drug reimbursement

See Summary of findings 6

Medicine use

We are uncertain about the effect on medicine use of an educational policy involving educational materials for physicians and HMO members compared to an intervention to regulate drug reimbursement (very low certainty evidence). We judged the certainty of the evidence as very low due to indirectness (single study from a high-income country, with particular regulatory and health systems arrangements).

For the preferred drug (fexofenadine), the HMO that regulated drug reimbursement showed a pre-post intervention increase in the share of prescribing of 45.6% (95% CI 42.3% to 48.9%; very low certainty evidence). In the HMO that implemented educational materials for physicians and HMO members, the pre-post intervention difference in the share of prescribing for the preferred drug was an increase of 9.5% (95% CI 7.9% to 11.1%; very low certainty evidence).

For the less preferred drug (loratadine), the HMO that regulated drug reimbursement showed a pre-post intervention decrease in the share of prescribing (−54.4%, 95% CI −57.7% to −51.0%; very low certainty evidence). In the HMO that implemented educational materials for physicians and HMO members, the pre-post intervention share of prescribing for the less preferred drug also decreased (−12.5%, 95% CI −14.6% to −10.4%); very low certainty evidence) (Table 3).

We are uncertain about the effect of educational materials for physicians and HMO members on the change in market share from the less preferred drug to the more preferred drug, compared to an intervention to regulate drug reimbursement. This is because the certainty of the evidence is very low (Table 5).

Costs

The average cost per prescription increased 8.2% (from USD 38.79 to USD 41.98) in the group that implemented an educational policy involving educational materials on prescribing for physicians and HMO members. The average cost per prescription decreased by 22.3% in the comparison group. The certainty of these cost data was not assessed.

The total cost of the intervention (from the perspective of the pharmacy benefit management company, including the personnel time to implement the programmes as well as the supply, printing and mailing costs) was USD 7539 at the HMO that mailed educational materials and coupons to members and physicians (HMO B).

DISCUSSION

Summary of main results

We identified only two studies that met our selection criteria. Due to very low certainty evidence, we are uncertain about the effects of a regulatory policy - monitoring prescribing with triplicate prescriptions - on medicine use (Simoni-Wastila 2004). We are also uncertain about the effects on medicine use and costs of an educational policy that included mailed education materials on prescribing for physicians and HMO members because the certainty of the evidence was very low (Benedetto 2000). Neither of the studies measured patient health outcomes or additional costs, if any, to patients.

Overall completeness and applicability of evidence

Little evidence is available on the effects of educational or regulatory policies targeting prescribers. We did not find any studies that evaluated policies that regulate who can prescribe medicines, the monitoring and enforcement of restrictions (other than formularies and dosing), generic prescribing policies, programmes to implement treatment guidelines, system-wide policies regarding monitoring drug safety and legislated or mandatory continuing education. A number of countries have implemented prescribing restrictions based on the level of care and on the competence of the prescriber, e.g. USA, Canada, Australia, New Zealand, the Republic of Ireland, Finland, Sweden, the Netherlands, Spain, and the UK. However, no studies assessing this policy were found. We also did not find any studies of quality improvement policies specifically targeting prescribers.

The two included studies were undertaken in a high-income country (the USA), although participants in Simoni-Wastila 2004 were low-income patients (Medicaid beneficiaries). We did not find any eligible studies conducted in low- or middle-income countries. Continuing education systems for prescribers and regulatory systems differ across high-, middle- and low-income countries. Because of these differences, it is uncertain whether a regulatory policy such as monitoring prescribing using triple prescriptions, or another method, would have the same effects in other settings as were found in the USA. Implementing an educational policy on the use of mailed educational materials may not be practical in low-income countries, and the effects of printed educational materials are likely to be modest at best (Giguère 2012). The sustainability of the effects of the interventions is also uncertain as the studies did not measure impacts beyond 6 months (Benedetto 2000) and 24 months following the intervention (Simoni-Wastila 2004).

Regulatory authorities in many countries require pharmaceutical companies to send letters to prescribers regarding adverse events or new indications for medicines. Yet very few well-planned and executed studies have looked at the impact of these or other common policies.

Quality of the evidence

Both studies were conducted in the USA. Due to risk of bias (as a consequence of the study designs used) and concerns regarding the directness of the evidence in relation to similar policies in other settings, the certainty of the evidence is very low for all of the outcomes evaluated in this review.

Potential biases in the review process

The main limitation of this review is that we were able to find only two studies that met our selection criteria. It is possible that we failed to identify eligible studies, particularly unpublished studies, or difficult-to-find and access grey literature. Our search was relatively thorough, however, and we screened over 20,000 records in total.

Agreements and disagreements with other studies or reviews

The use of educational policy interventions by governments, non-governmental organizations or third party payers can be compared to several reviews that have looked at educational strategies implemented in other organisations (and therefore not eligible for this review), and these may provide some insights into the possible outcomes that can be expected. The findings of a systematic review of the effects of printed educational materials indicate that printed educational materials may slightly improve practice outcomes among health care providers, when used alone and compared to no intervention, and that the effects of printed educational materials on patient outcomes are uncertain as very few studies included in the review assessed these outcomes (Giguère 2012). Educational interventions using printed materials may slightly improve prescribing outcomes. Of the 45 studies included in the Giguère 2012 review, 44 were from high-income countries. The authors note that rigorous studies from low-income countries are needed to assess the impacts of printed educational materials on professional practice and health outcomes in these setting, and it is possible that more studies have been done since this review was undertaken.

A Cochrane Review on continuing education meetings and workshops found that educational meetings alone or combined with other interventions probably improve professional practice and healthcare outcomes for patients and that educational meetings alone probably improve professional practice as much as multifaceted interventions that include educational meetings (Forsetlund 2009). Educational meetings did not appear to be effective for complex behaviours, they appeared to be less effective for less serious outcomes, and more effective for educational meetings with high attendance.

O'Brien 2007 found that educational outreach visits alone or combined with other interventions improve the quality of care delivered to patients, and that for prescribing, the effects are relatively consistent and small but potentially important.

The Triplicate Prescription Program (TPP) Intervention could be compared to the results of audit and feedback (Ivers 2012), as the intended mechanism of action was auditing prescribing practices. Ivers 2012 found that audit and feedback probably leads to small but potentially important improvements in professional practice compared with usual care.

AUTHORS' CONCLUSIONS

Implications for practice

It is difficult to draw out implications for practice from this review as the available evidence is very limited and is all of very low certainty.

Implications for research

We identified very few studies that evaluated the effects of educational or regulatory policies targeting prescribers. The impacts of these policies should therefore be evaluated rigorously, ideally using robust designs such as randomised trials or interrupted time series studies. Studies are needed across a range of settings, including in low- and middle-income countries, and across different types of prescribers and medicines.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [author-defined order]

Benedetto 2000

Methods	Controlled before–after study
Participants	General practitioners, patients, and private insurers in Health Maintenance Organizations (HMOs) in the USA
Interventions	Switching of therapy (1 mandatory policy to restrict reimbursement and 2 voluntary educational policies). See Table 1 for further details.
Outcomes	Medicine use in terms of market share, percentage switch to fexofenadine and back to loratadine after the intervention; per cent prescribing for each medicine Costs in terms of cost per antihistamine prescription; cost saving for each intervention (estimated); cost of intervention
Notes	HMOs spread across the USA (HMO A, 60,000 members - Northeast; HMO B 250,000 members - Midwest; HMO C 230,000 members - West Coast; HMO D – control HMO – 430,000 members - Northeast. The HMOs were similar in structure and in their control over prescribing. Physicians at these HMOs were not directly at risk for pharmacy benefits, but were monitored for compliance to formularies and generic product prescribing. This information was then fed back to the physicians by the HMOs on a quarterly basis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	As this is a CBA study, randomisation was not used. The paper does not specify how the intervention and control HMOs were selected
Allocation concealment (selection bias)	High risk	As this is a CBA study, it was assessed to be at high risk of selection bias
Baseline outcome measures similar	Low risk	Baseline outcome measures appeared to be similar across the 4 sites in the study for drug market share (%) and prescribing (%), although this was not tested statistically (Table 1, p1783)
Baseline characteristics similar	Unclear risk	No report of characteristics in text or tables or if there are differences between control and intervention providers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified in the paper.
Blinding of participants and personnel (performance bias)	Unclear risk	No blinding was used and it is unclear if participants of personnel may have behaved differently as a result of the interventions

Benedetto 2000 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, though the outcomes (number of prescriptions etc.) came from a central pharmacy claims database run by the HMOs in the study and can therefore be considered objective (p1779)
Protection against contamination	Unclear risk	Although allocation was by HMO, it is possible that communication between intervention and control professionals could have occurred (for example), leading to contamination
Selective outcome reporting	Unclear risk	It is not clear what outcomes were planned to be assessed at the protocol stage, and whether there are any that were not reported. Outcomes such as adverse events or unanticipated consequences were not reported.
Other bias	Low risk	

Simoni-Wastila 2004

Methods	Controlled interrupted time series study
Participants	Prescribers, and continuously enrolled Medicaid beneficiaries who were 19 years or older in 3 categories: Aid to Families with Dependent Children; Old Age Assistance; and Aid to the Permanently and Totally Disabled
Interventions	A regulatory restrictive prescribing policy, using a triplicate prescription programme for benzodiazepine use in Medicaid patients with chronic psychiatric and neurologic disorders. Triplicate prescription programmes (TPPs) require physicians to order covered medicines using multiple copy forms. The intervention aimed to reduce inappropriate drug use.
Outcomes	Medicine use in terms of use of benzodiazepines in per cent or per 100 enrolees
Notes	Although TPPs do not directly restrict physicians' freedom to prescribe, it has been suggested that they can reduce access to appropriate medicines by creating a "chilling effect" that discourages prescribing of the covered medicines due to physicians' fears of sanctions from the insurer

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes	Low risk	No other interventions were reported for the study time period. p323: control state similar to intervention state but for policy “New Jersey is a proximate state with a similar medicine reimbursement program but without any regulations targeting BZs during the 3-year study period.”
Shape of the intervention effect pre-specified	Low risk	p323: point of analysis identical with point of intervention
Intervention unlikely to affect data collection	Low risk	Data were extracted from monthly enrolment, medical claims, and medicine claims files from the computerized Medicaid Management Information System of the 2 study states for the years 1988 through 1990 and the year 1995
Knowledge of the allocated interventions adequately prevented during the study	Low risk	p328: assessment not blinded, but objective outcomes (BZ use and prescription rate)

Simoni-Wastila 2004 *(Continued)*

Incomplete outcome data	Unclear risk	There were some prescriptions excluded, but the data on this were not reported in the paper (p325: some prescriptions written in 1988 were not filled immediately, January 1989 was excluded from estimates of TPP effects). No further information on the completeness of the outcome data was provided
Selective outcome reporting	Unclear risk	As we did not have access to a study protocol, it is not clear what outcomes were planned to be assessed at the protocol stage, and whether there are any that were not reported in the published study
Other risks of bias	Low risk	Appropriate design and analysis was performed. p325: appropriate time-series analysis: "Autocorrelation and first-order autoregressive effects were assessed and corrected in all models using the Statistical Analysis System Autoreg procedure (SAS Institute, Inc., Cary, North Carolina). Standardized regression coefficients from these models were used to compare post-TPP changes in levels of and trends in use of BZs and other psychoactive medicines in the study state." p323: "Using an interrupted time series with comparison series design, this study assessed changes in the use of BZs and other psychoactive medicines by clinically vulnerable patients in the New York Medicaid program and in a control state (New Jersey Medicaid) 12 months before and 24 months after the addition of BZs to the New York TPP."

BZ: Benzodiazepines
CBA: Controlled before–after
HMO: Health Maintenance Organizations
TPP: Triplicate prescription programmes
USA: United States of America

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 2007	ITS. Excluded because of study intervention. Generic substitution not targeted at prescribers but rather at sales and dispensing policies review. Sweden.
Chou 2003	CBA. Excluded because of study intervention. Separation of dispensing and prescribing function of prescribers which is part of Dispensing policy review. China
Lu 2011	ITS. Excluded because of study intervention. Prior Authorisation is part of another policy review. USA

CBA: Controlled before–after
ITS: interrupted time series
USA: United States of America

ADDITIONAL TABLES

Table 1. Interventions delivered in Benedetto 2000 *(Continued)*

	Intervention to restrict reimbursement[1]	Educational Interventions		Control
	HMO A	HMO B	HMO C	HMO D

Table 1. Interventions delivered in Benedetto 2000 *(Continued)*

Type of Intervention	*Mandatory lockout*	*Voluntary switch*	*Voluntary switch*	*Did not restrict member benefits in any way*
Description of intervention	Only fexofenadine listed in the formulary	Educational letter and fact sheet	Educational letter and fact sheet	None
Intervention components				
Letters to physicians	List of members that needed to be switched	Stated that fexofenadine was now the preferred antihistamine; explained the formulary change; identified all patients who were currently taking loratadine. Also contained an educational fact sheet with clinical information on fexofenadine to aid in prescribing the medicine	Informed physicians that fexofenadine was now the preferred antihistamine; attached was a list of patients currently receiving loratadine; asked to review their therapy and consider using fexofenadine rather than loratadine if prescription antihistamines are appropriate. Included an educational fact sheet with clinical information on non-sedating antihistamines that focused on prescribing fexofenadine	None
Letters to HMO members	Educational pamphlet describing a resource centre	Members received a similar mailing to that received by physicians and that detailed the change; also informed that switching to fexofenadine qualified them to consult the Aller Days Resource Center at no cost.	None	None
Letters to pharmacists	Contained samples of materials sent to physicians and members	None	None	None
Other	Coverage limited to two doses per day. A USD 10 manufacturer coupon to be applied toward the co-payment for the first fexofenadine prescription	A USD 10 manufacturer coupon to be applied toward the co-payment for the first fexofenadine prescription	As part of the physician letter, a USD 10 manufacturer coupon for members to be applied toward the co-payment for the first fexofenadine prescription	None

1. This intervention is included here only as a comparison for the educational interventions as policies regarding drug reimbursement are covered by another EPOC review (Green 2010)

Table 2. Effects of a prescribing monitoring tool (Triplicate Prescription Program (TPP)) policy on benzodiazepine use[1,2] *(Continued)*

Category	Intervention area (New York)			Control area (New Jersey)			Difference in change between intervention and control areas (%)	Certainty of the evidence
	1988	1990	Change (%)	1988	1990	Change (%)		
Probably problematic benzodiazepine use[3]	7.1	2.4	−4.7	4.0	3.4	−0.6	−4.1	Very low[6]
Possibly nonproblematic benzodiazepine use[4]	16.2	10.6	−5.6	12.8	15.2	2.4	−8.0	Very low[6]
Probably nonproblematic benzodiazepine use[5]	18.0	8.6	−9.4	17.1	13.6	−3.5	−5.9	Very low[6]

[1]Among 125,837 continuously enrolled patients before (1988) and after (1990) implementation of the TPP (Simoni-Wastila 2004)
[2]All values are shown as percentages. All effects were reported to be significant at P < 0.001
[3] Pharmacy hopping (filling a prescription for same benzodiazepine in 2 different pharmacies within 7 days) or high-dose use (maximum recommended dose is 10 diazepam milligram equivalent doses (DMEs) for elderly patients and 20 DMEs for adults aged < 65 years).
[4]Long-term use (episode > 120 days) only; no pharmacy hopping and no high-dose use
[5]Short-term use (episode </= 120 days) only; no pharmacy hopping and no high-dose use
[6]ITS study downgraded due to risk of bias and very serious indirectness

Table 3. Share of prescribing for antihistamines, pre- and post-intervention

Fexofendadine (preferred drug)				
	No intervention (HMO D)	**Intervention to restrict drug reimbursement (HMO A)**	**Educational materials on prescribing for physicians and HMO members (HMO B)**	**Educational materials on prescribing for physicians (HMO C)**
Preintervention (prescribing %)	14.5%	14.8%	11.6%	15.8%
Postintervention (prescribing %)	16.1%	60.4%	21.1%	18.1%
Change in prescribing share	1.6%	45.6 %	9.5%	2.3%
95% confidence interval	0.4% to 2.8%	42.3% to 48.9%	7.9% to 11.1%	0.6% to 4%
Chi^2; P value	Chi^2 = 6.76, P = 0.0093	Chi^2 = 539, P = < 0.0001	Chi^2 = 130, P = < 0.0001	Chi^2 = 7.4, P = 0.0065
Loratadine (less preferred drug)				
	No intervention (HMO D)	**Intervention to restrict drug reimbursement (HMO A)**	**Educational materials on prescribing for physicians and HMO members (HMO B)**	**Educational materials on prescribing for physicians (HMO C)**
Preintervention (prescribing %)	67.0%	67.4%	72.6%	72.5%
Postintervention (prescribing %)	63.4% ≈	13.0%	60.1%	67.5%
Change in prescribing share	−3.6%	−54.4 %	−12.5 %	−5.0%
95% confidence interval	−5.2% to −2.0%	−57.7% to −51%	−14.6% to −10.4%	−7% to −3%
Chi^2; P value	Chi^2 = 19.8, P = < 0.0001	Chi^2 = 822, P = < 0.0001	Chi^2 = 138, P = < 0.0001	Chi^2 = 23.5, P = < 0.0001

Table 4. Estimated total dollar value of intervention programmes at each HMO[1] *(Continued)*

Intervention	**Total expenditure on drugs evaluated in the study (USD)**		**Cost of intervention (USD)**	**Change in expenditure[2]**	
	Before the intervention	**After the intervention**		**USD**	**Per cent**
Regulation of drug reimbursement (HMO A)	190,923	148,698	5040	−37,185	−19.5
Educational materials on prescribing for physicians and clients (HMO B)	1,136,586	1,230,056	5517	98,987	8.7

Table 4. Estimated total dollar value of intervention programmes at each HMO[1] *(Continued)*

Educational materials on prescribing for physicians (HMO C)	2,000,570	2,100,285	7539	107,254	5.4
No intervention (HMO D)	1,644,460	1,712,996	NA	68,536	4.2

[1]This table is from Benedetto 2000, p1784
[2] Change in expenditure was calculated by adding the total cost in the postintervention period to the cost of the intervention, and then subtracting the total cost of the study drugs during the pre-intervention period

Table 5. Market share and prescribing patterns for antihistamines before and after interventions[a]

Outcome[b]	Total No. Prescriptions for Four Antihistamines	Fexofenadine	Loratadine	Cetirizine	Astemizole
HMO A					
Market share before intervention in % (number of prescriptions)	3804	18.9 (719)	62.3 (2370)	17.2 (654)	1.7 (65)
Market share after intervention in % (number of prescriptions)	7923	65.2 (5166)	8.7 (689)	26.1 (2068)	0.0 (0)
Prescribing before intervention in % (number of prescriptions)	1066	14.8 (158)	67.4 (718)	16.9 (180)	0.9 (10)
Prescribing after intervention in % (number of prescriptions)	1565	60.4 (945)	13.0 (203)	26.5 (415)	0.1 (2)
HMO B					
Market share before intervention in % (number of prescriptions)	29,301	14.8 (4337)	67.5 (19,778)	16.3 (4776)	1.4 (410)
Market share after intervention in % (number of prescriptions)	35,751	21.0 (7508)	58.6 (20,950)	19.4 (6936)	1.1 (393)
Prescribing before intervention in % (number of prescriptions)	3874	11.6 (449)	72.6 (2813)	15.3 (593)	0.5 (19)
Prescribing after intervention in % (number of prescriptions)	4053	21.1 (855)	60.1 (2436)	18.3 (742)	0.5 (20)
HMO C					
Market share before intervention in % (number of prescriptions)	41,722	20.7 (8636)	70.5 (29,414)	8.6 (3588)	0.2 (83)
Market share after intervention in % (number of prescriptions)	31,953	23.8 (7605)	65.3 (20,865)	10.8 (3451)	0.2 (64)
Prescribing before intervention in % (number of prescriptions)	4418	15.8 (698)	72.5 (3203)	11.5 (508)	0.2 (9)
Prescribing after intervention in % (number of prescriptions)	3606	18.1 (653)	67.5 (2434)	14.2 (512)	0.2 (7)
HMO D					

Table 5. Market share and prescribing patterns for antihistamines before and after interventions[a] *(Continued)*

Market share before intervention in % (number of prescriptions)	39,616	17.3 (6854)	63.0 (24,958)	18.0 (7131)	1.7 (673)
Market share after intervention in % (number of prescriptions)	46,346	19.1 (8852)	60.4 (27,993)	19.3 (8945)	1.2 (556)
Prescribing before intervention in % (number of prescriptions)	6638	14.5 (963)	67.0 (4447)	17.2 (1142)	1.2 (80)
Prescribing after intervention in % (number of prescriptions)	7471	16.1 (1203)	63.4 (4737)	19.5 (1457)	1.0 (75)

[a]Data from Benedetto 2000, Table 1 (p1783).
[b]Number of prescriptions was calculated by the review authors by multiplying the total number of prescriptions for all four antihistamines by the per cent prescribing for each drug (presented in Table 1 of Benedetto). Because of rounding, the number of prescriptions for each drug may not equal exactly the total number of prescriptions
Per cent market share for each drug was calculated by the study authors by dividing the number of prescriptions for that drug by the total number prescriptions for all four antihistamines each month and multiplying by 100.
Per cent prescribing for each drug was calculated by the study authors by dividing the number of prescriptions for each drug was calculated by dividing the number of prescriptions for each drug by the total number of prescriptions for all four drugs and multiplying by 100. Per cent prescribing was calculated only for the 25 physicians who prescribed loratadine most frequently before the interventions.

APPENDICES

Appendix 1. Search Strategies

CENTRAL, Cochrane Library (including the EPOC Register)

ID	Search	Hits
#1	MeSH descriptor: [Practice Patterns, Physicians'] this term only	1357
#2	MeSH descriptor: [Drug Prescriptions] this term only	559
#3	#1 and #2	155
#4	MeSH descriptor: [Physicians] explode all trees	1866
#5	MeSH descriptor: [Nurses] explode all trees	1223
#6	MeSH descriptor: [Family Practice] this term only	2211
#7	(physician* or nurse or nurses or doctor or doctors or general next practitioner* or general next practice* or family next practice* or prescriber*):ti,ab	44354
#8	#4 or #5 or #6 or #7	45381
#9	rational near/3 (drug or drugs or pharmaceutic* or medicine* or medicament* or medicat*):ti,ab	87
#10	prescribing next (practice* or behavior* or behaviour* or pattern*):ti,ab	501
#11	generic near/3 (substitution or prescribing):ti,ab	46

(Continued)

#12	generic near/6 (shift* or switch* or chang*):ti,ab	122
#13	prescri* near/3 (shift* or switch* or chang* or improve* or appropriat*):ti,ab	1041
#14	(prescribing or medication) next error*:ti,ab	342
#15	(co next prescri* or coprescri*):ti,ab	118
#16	prescri* near/3 (duplicat* or double):ti,ab	19
#17	market next share:ti,ab	36
#18	prescri* near/3 (saving* or cost* or expenditure*):ti,ab	355
#19	(reduc* or decreas* or increas*) near/3 (drug or drugs or pharmaceutic* or medicine* or medicament* or medicat*) near/3 (cost* or expenditure*):ti,ab	403
#20	(rate or rates) near/3 (prescri* or "drug use"):ti,ab	557
#21	(number near/1 medication*):ti,ab	35
#22	(class or classes or type or types) near/3 medication*:ti,ab	855
#23	(prescribing next intervention* or prescribing next program* or prescription next program*):ti,ab	40
#24	(influenc* near/3 prescri*):ti,ab	145
#25	(#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)	3916
#26	#8 and #25	1280
#27	#3 or #26 in Trials	1178

MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE 1946 to Present, Ovid

#	Searches	Results
1	Practice Patterns, Physicians'/	51590
2	Drug Prescriptions/	25236
3	1 and 2	3841
4	exp Physicians/	118999
5	exp Nurses/	81908
6	Family Practice/	63771

(Continued)

7	(physician? or nurse? or doctor? or general practitioner? or general practice? or family practice? or prescriber?).ti,ab,kf.	704300
8	or/4-7	810922
9	(rational adj3 (drug? or pharmaceutic? or medicine? or medicament? or medicat$)).ti,ab,kf.	4399
10	(prescribing adj (practice? or behavior? or behaviour? or pattern?)).ti,ab,kf.	5824
11	(generic adj3 (substitution or prescribing)).ti,ab,kf.	852
12	(generic adj6 (shift$ or switch$ or chang$)).ti,ab,kf.	859
13	(prescri$ adj3 (shift$ or switch$ or chang$ or improve$ or appropriat$)).ti,ab,kf.	7743
14	((prescribing or medication) adj error?).ti,ab,kf.	5234
15	(co prescri$ or coprescri$).ti,ab,kf.	1057
16	(duplicat$ adj3 prescri$).ti,ab,kf.	76
17	market share.ti,ab,kf.	1514
18	(prescri$ adj3 (saving? or cost? or expenditure?)).ti,ab,kf.	2776
19	((reduc$ or decreas$ or increas$) adj3 (drug? or pharmaceutic? or medicine? or medicament? or medicat$) adj3 (cost? or expenditure?)).ti,ab,kf.	1835
20	(rate? adj3 (prescri$ or "drug use")).ti,ab,kf.	4415
21	number of medication?.ti,ab,kf.	2278
22	((class or classes or type?) adj2 medication?).ti,ab,kf.	4025
23	(prescribing intervention? or prescribing program* or prescription program*).ti,ab,kf.	216
24	(influenc$ adj3 prescri$).ti,ab,kf.	1441
25	or/9-24	38730
26	8 and 25	11791
27	3 or 26	14574
28	randomized controlled trial.pt.	455869
29	random$.tw.	963042
30	intervention$.tw.	799921
31	control$.tw.	3331897
32	evaluat$.tw.	2958841
33	or/28-32	6525426

(Continued)

34	exp Animals/	21381818
35	Humans/	16946757
36	34 not (34 and 35)	4435061
37	review.pt.	2355141
38	meta analysis.pt.	85984
39	news.pt.	186440
40	comment.pt.	709453
41	editorial.pt.	453083
42	cochrane database of systematic reviews.jn.	13499
43	comment on.cm.	709450
44	(systematic review or literature review).ti.	108054
45	or/36-44	7836346
46	33 not 45	4756410
47	27 and 46	6185

Embase 1974 to 2018 March 21, Ovid

#	Searches	Results
1	*Clinical Practice/	34824
2	*Physician/	52885
3	1 or 2	87134
4	*Prescription/	33768
5	3 and 4	1390
6	exp Physician/	609437
7	exp Nurse/	152582
8	General Practice/	77743
9	(physician? or nurse? or doctor? or general practitioner? or general practice? or family practice? or prescriber?).tw.	901151
10	or/6-9	1318466

(Continued)

11	(rational adj3 (drug? or pharmaceutic? or medicine? or medicament? or medicat$)).tw.	6300
12	(prescribing adj (practice? or behavior? or behaviour? or pattern?)).tw.	9172
13	(generic adj3 (substitution or prescribing)).tw.	1474
14	(generic adj6 (shift$ or switch$ or chang$)).tw.	1358
15	(prescri$ adj3 (shift$ or switch$ or chang$ or improve$ or appropriat$)).tw.	12604
16	((prescribing or medication) adj error?).tw.	8170
17	(co prescri$ or coprescri$).tw.	1763
18	(duplicat$ adj3 prescri$).tw.	131
19	market share.tw.	2356
20	(prescri$ adj3 (saving? or cost? or expenditure?)).tw.	4420
21	((reduc$ or decreas$ or increas$) adj3 (drug? or pharmaceutic? or medicine? or medicament? or medicat$) adj3 (cost? or expenditure?)).tw.	3033
22	(rate? adj3 (prescri$ or "drug use")).tw.	6747
23	number of medication?.tw.	3869
24	((class or classes or type?) adj2 medication?).tw.	6567
25	(prescribing intervention? or prescribing program* or prescription program*).tw.	445
26	(influenc$ adj3 prescri$).tw.	2143
27	or/11-26	61036
28	10 and 27	20013
29	5 or 28	21003
30	Randomized Controlled Trial/	493929
31	random$.tw.	1283136
32	experiment$.tw.	1999300
33	Time Series Analysis/	20454
34	(time adj series).tw.	26922
35	(pre test or pretest or post test or posttest).tw.	32080
36	impact.tw.	1078436
37	intervention$.tw.	1093316
38	chang$.tw.	3394103

(Continued)

39	evaluat$.tw.	4075906
40	effect?.tw.	5834608
41	compar$.tw.	6079408
42	control$.tw.	4288389
43	or/30-42	16083478
44	nonhuman/	5370387
45	review.pt.	2347490
46	editorial.pt.	559157
47	cochrane database of systematic reviews.jn.	11691
48	(systematic review or literature review).ti.	128258
49	or/44-48	7825120
50	43 not 49	11714057
51	29 and 50	14569
52	limit 51 to embase	7350

EconLit, ProQuest

ALL(rational NEAR/3 drug* OR rational NEAR/3 pharmaceutic* OR rational NEAR/3 medicine* OR rational NEAR/3 medicament* OR rational NEAR/3 medicat* OR prescri* NEAR/3 practice* OR prescri* NEAR/3 behavior* OR prescri* NEAR/3 behaviour* OR prescri* NEAR/3 pattern* OR generic NEAR/3 substitution OR generic NEAR/3 prescri* OR generic NEAR/6 shift* OR generic NEAR/6 switch* OR generic NEAR/6 chang* OR prescri* NEAR/3 shift* OR prescri* NEAR/3 switch* OR prescri* NEAR/3 chang* OR prescri* NEAR/3 improve* OR prescri* NEAR/3 appropriat* OR prescri* NEAR/3 error* OR medication NEAR/3 error* OR co PRE/0 prescri* OR coprescri* OR duplicate* NEAR/3 prescri* OR double NEAR/3 prescri* OR prescri* NEAR/3 saving* OR prescri* NEAR/3 cost* OR prescri* NEAR/3 expenditure* OR reduc* NEAR/3 drug OR decreas* NEAR/3 drug OR increase* NEAR/3 drug OR reduc* NEAR/3 drugs OR decreas* NEAR/3 drugs OR increase* NEAR/3 drugs OR reduc* NEAR/3 pharmaceutic* OR decreas* NEAR/3 pharmaceutic* OR increase* NEAR/3 pharmaceutic* OR reduc* NEAR/3 medicine* OR decreas* NEAR/3 medicine* OR increase* NEAR/3 medicine* OR reduc* NEAR/3 medicament* OR decreas* NEAR/3 medicament* OR increase* NEAR/3 medicament* OR reduc* NEAR/3 medicat* OR decreas* NEAR/3 medicat* OR increase* NEAR/3 medicat*) AND **ALL**(cost* OR expenditure* OR rate* NEAR/3 prescri* OR rate* NEAR/3 "drug use" OR number NEAR/1 medication* OR class NEAR/3 medication* OR classes NEAR/3 medication* OR type* NEAR/3 medication* OR prescri* NEAR/3 intervention* OR influenc* NEAR/3 prescri*) AND **ALL**(randomi* OR randomly OR intervention* OR control* OR evaluat* OR effect*)

PAIS International, ProQuest, and **Worldwide Political Science Abstracts, ProQuest**

ALL(prescrib* OR prescrip*) AND **ALL**(drug OR drugs OR pharmaceutic* OR medicine* OR medicament* OR medicat*) AND **ALL**(random* OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR longitud* OR repeated PRE/0 measure* OR pretest OR posttest OR "pre test" OR "post test" OR impact* OR chang* OR effect* OR experiment*)

International Political Science Abstracts (IPSA), EbscoHost

TX ((prescrib* OR prescrip*)) AND **TX** ((drug OR drugs OR pharmaceutic* OR medicine* OR medicament* OR medicat* OR therapy OR therapies)) AND **TX** ((random* OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR longitud* OR "repeated measure" OR "repeated measures" OR pretest OR posttest OR "pre test" OR "post test" OR impact* OR chang* OR effect* OR experiment*))

NHSEED, Cochrane Library

#1	(prescri* near/6 practice*) or (prescri* near/6 behaviour*) or (prescri* near/6 behavior*) or (prescri* near/6 pattern*) or (prescri* near/6 shift*) or (prescri* near/6 switch*) or (prescri* near/6 chang*) or (prescri* near/6 improv*) or (prescri* near/6 appropriate*) or (prescri* near/6 err) or (prescri* near/6 error*) or (prescri* near/6 duplicate*) or (prescri* near/6 double) or (prescri* near/6 intervention*) or (prescri* near/6 influence*) or (prescri* near/6 impact*) or coprescri* or (co near/6 prescri*) or (rational near/6 drug) or (rational near/6 drugs) or (rational near/6 pharmaceutic*) or (rational near/6 medicin*) or (rational near/6 medicamen*) or (rational near/6 medicat*) in Economic Evaluations	207

INRUD Bibliography

prescri* (In All non-indexed fields) OR prescri* (In All Indexed fields)

PubMed, NLM (not indexed in MEDLINE)

#1 Search Physician's Practice Patterns[Mesh] AND Prescriptions[Mesh]

#2 Search "rational drug use"[tiab] or "rational drug usage"[tiab]

#3 Search ("prescription"[tiab] or "prescriptions"[tiab] or "prescriber"[tiab] or "prescribers"[tiab] or "prescribe"[tiab] or "prescribing"[tiab]) AND ("practice"[tiab] or "practices"[tiab] or "behaviour"[tiab] or "behavior"[tiab] or "pattern"[tiab] or "patterns"[tiab]) AND ("drug"[tiab] or "drugs"[tiab] or "pharmaceuticals"[tiab] or "medicines"[tiab] or "medicament"[tiab] or "medicaments"[tiab] or "medication"[tiab])

#4 Search "randomized controlled trial"[pt] or randomised[tiab] or randomized[tiab] or randomly[tiab] or intervention[tiab] or interventions[tiab] or control[tiab] or controlled[tiab] or evaluat[tiab] or evaluated[tiab] or evaluation[tiab] or evaluations[tiab] or evaluating[tiab] or effect[tiab] or effects[tiab] or impact[tiab] or impacts[tiab]

#5 Search (#1 or #2 or #3) and #4

#6 Search (#5 AND pubmednotmedline [sb])

WHOLIS, VHL

(tw:(prescrib$ OR prescrip$)) AND (tw:(legislation OR law OR laws OR act OR acts OR policy OR policies OR politics OR reform$ OR system OR systems OR plan OR plans OR planning OR program$ OR strategy OR strategies OR regulat$ OR reform$ OR requirement$ OR restrict $ OR monitor$ OR control$))

OECD Publications & Documents

Term used: Prescribing

SourceOECD

Term used: Prescribing

World Bank Documents & Reports

Term used: Prescribing

World Bank e-Library

Term used: Prescribing

JOLIS

Term used: Prescribing

Global Jolis

Term used: Prescribing

Grey Literature Report

Term used: Prescribing

International Clinical Trials Registry Platform (ICTRP): http://apps.who.int/trialsearch/

Advanced Search - Recruitment status: ALL

1. (prescriber OR prescribers OR physician OR physicians OR nurse OR nurses) AND (prescribing) AND (practice OR practices OR behavior OR behaviors OR behaviour OR behaviours OR pattern OR patterns) (in Title)

OR

(prescriber OR prescribers OR physician OR physicians OR nurse OR nurses) AND (prescribing) AND (practice OR practices OR behavior OR behaviors OR behaviour OR behaviours OR pattern OR patterns) (in Condition)

2. prescribing practice OR prescribing practices OR prescribing behavior OR prescribing behaviors OR prescribing behaviour OR prescribing behaviours OR prescribing pattern OR prescribing patterns (in Title)

OR

prescribing practice OR prescribing practices OR prescribing behavior OR prescribing behaviors OR prescribing behaviour OR prescribing behaviours OR prescribing pattern OR prescribing patterns (in Condition)

ClinicalTrials.gov https://clinicaltrials.gov/

Advanced Search - Other terms - Interventional Studies

1. (prescriber OR prescribers OR physician OR physicians OR nurse OR nurses) AND ("drug prescription" OR "drug prescriptions" OR "drug prescribing" OR "prescribing drug" OR "prescribing drugs")

2. (prescriber OR prescribers OR physician OR physicians OR nurse OR nurses) AND (prescribing) AND (practice OR practices OR behavior OR behaviors OR behaviour OR behaviours OR pattern OR patterns)

3. ("prescribing practice" OR "prescribing practices" OR "prescribing behavior" OR "prescribing behaviors" OR "prescribing behaviour" OR "prescribing behaviours" OR "prescribing pattern" OR "prescribing patterns")

Science Citation Index, Social Sciences Citation Index, and Emerging Sources Citation Index, ISI Web of Science

Citation search for: Benedetto 2000; Simoni-Wastila 2004

CONTRIBUTIONS OF AUTHORS

Fatima Suleman: developing search strategies, searching studies, accessing articles, reviewing of articles for inclusion and exclusion, abstraction of data for the included papers, interpretation of results and writing and editing of the review.
Espen Movik: access to articles, reviewing of articles for inclusion and exclusion, abstraction of data for the included papers, review and editing of all drafts, assistance with interpretation of results and approval of the final version of the review.

DECLARATIONS OF INTEREST

Fatima Suleman: Fatima Suleman is the Chair of South Africa's Medicine Pricing Committee.

Espen Movik: Espen Movik was employed by the Norwegian Knowledge Centre for the Health Services and the Norwegian Institute of Public Health for most of the duration of the review. From 5 August 2013 to 1 February 2017 he was employed by Roche Norway. During this period he did not access or work on this review. None of these institutions are involved in the formulation of pharmaceutical policy. Espen's employment at Roche Norway was discussed with the Cochrane Funding Arbiters who determined this employment is not a conflict of interest for this review as Roche does not have a real or potential financial interest in the outcome of the review.

NOTES

This review is one of 13 planned or completed reviews of the effects of different types of pharmaceutical policies on rational medicine use (Aaserud 2006b).