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COMPUS

Interventions for Appropriate Prescribing of Proton Pump Inhibitors: A Literature Review

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À l'appui des décisions éclairées

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ABBREVIATIONS

CI	confidence interval
DUR	drug utilization review
GERD	gastrointestinal reflux disease
GI	gastrointestinal
H_2RA	histamine H_2-receptor agonist
H. pylori	Helicobacter pylori
HTA	health technology assessment
OR	odds ratio
PPI	proton pump inhibitor
PUD	peptic ulcer disease
RCT	randomized controlled trial

GLOSSARY

Before-and-after study: a study design in which subjects are observed before and after a therapy or the introduction of an intervention.

Case control study: a type of observational study in which past exposures to one or more putative risk factors are measured in a group of subjects with a disease or outcome of interest (cases), and in a group without this outcome (controls), to ascertain the degree of association between risk factor and outcome.

Cluster randomized control trial: a randomized control trial in which the investigator randomly allocates units (such as clinics or physicians) to one or more intervention groups and a control group.

Cohort study: a type of observational study in which a comparison of the risk of disease or other outcome is made between a group of subjects exposed to a putative risk factor, and a group that is unexposed, to ascertain the degree of association between risk factor and outcome.

Controlled clinical trial: a prospective study designed to test the effectiveness of an intervention in which the investigator allocates subjects to one or more intervention groups and a control group using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier).

Defined daily dose (DDD): the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a unit of measurement and does not necessarily agree with the recommended or prescribed daily dose.

Drug cost or expenditure: the amount of money that is spent by a drug plan on prescription drugs.

Drug utilization: describes the pattern or profile of drug use – assessing which alternative drugs are being used for particular conditions, in a particular time period, and to what extent.

General practitioner (GP): or family physician (FP) is a physician who provides primary care. A GP/FP treats acute and chronic illnesses, provides preventive care and health education for all ages and both sexes.

Group practices: the practice of medicine by a group of physicians, each of whom is usually confined to some special field, but all of whom share a common facility.

***H. pylori* triple therapy**: a combination of three drugs – two antibiotics and an acid suppressor (H_2RA or PPI) or bismuth salt for H. pylori eradication.

Health care expenditure: the amount of money that is spent by an organization on hospitalization, surgical procedures or laboratory tests.

Health care utilization: the number of hospital admissions, surgical procedures or laboratory tests.

Interrupted time series: a study design that collects multiple observations over time on the same units or individuals that are 'interrupted' by an intervention to determine whether an intervention has had an effect significantly greater than the underlying trend.

Prescribed daily dose (PDD): the average dose prescribed according to a representative sample of prescriptions.

Randomized controlled trial: a prospective study designed to test the effectiveness of an intervention in which the investigator randomly allocates subjects to one or more intervention groups and a control group.

Step-down therapy: the initial use of potent acid suppression, followed by decreased doses or the use of less potent agents to tailor therapy according to individual response.

Step-up therapy: the initial use of less potent agents or lower doses of acid suppressive therapies, followed by increased doses or more potent agents if there is an inadequate response.

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1 EXECUTIVE SUMMARY

1.1 Objectives

To review all published studies on interventions that focused on enhancing appropriate prescribing and use of proton pump inhibitors (PPIs).

1.2 Method

A review of literature was undertaken using multiple bibliographic databases, supplemented by an extensive gray literature search. The search strategy was broad as the goal was to locate material describing any intervention related to the prescribing and use of PPIs. The selection of included studies was not limited by study designs.

1.3 Results

Twenty-four studies were identified that focused on: professional interventions (five studies); disease management interventions (three studies); dissemination strategies for dyspepsia guidelines (three studies); policy-related interventions (10 studies); and patient interventions (three studies). The majority of the studies were non-randomized control studies with poor study design. Synthesis of the evidence was limited by study designs and the wide variation in population, setting, interventions and outcomes. In general, studies included in this review suggest that multifaceted interventions may have a positive impact in controlling the prescription and cost of PPIs. This appears to be especially true when passive interventions such as educational materials (guidelines) were reinforced by active interventions such as outreach visits (academic detailing). Formulary-based interventions and drug utilization review (DUR)-based interventions were shown to be effective in controlling PPI cost. However, the effect on patient's health outcomes was not addressed. Only one study showed that targeting patients by educational interventions may reduce long-term use of PPIs.

1.4 Conclusion

The studies in the review suggest that combining educational multifaceted interventions that involve both professionals and patients with policy intervention may encourage appropriate prescribing and use of proton pump inhibitors. However, the decision on the selection of interventions should be tailored to address barriers to intervention implementation. It is also worthwhile exploring the cost-effectiveness of any intervention before its implementation.

2 INTRODUCTION

In Canada, drug expenditures have accounted for the second largest share of total health expenditures, after hospitals. Drug expenditures have continued to grow steadily, from $3.8 billion in 1995 to $20.1 billion in 2003, with an average annual growth of 9.9%. This growth rate was expected to increase to 11.0% in 2005.[1] More than 75% of drug costs were spent on brand name drugs whose expenditures grew faster than generic drugs.[2]

There are three main factors driving the recent increases in drug expenditures: increases in the number of prescriptions filled, therapeutic mix (i.e., increased use of newer, more expensive drugs instead of older, less-expensive medications), and price increases for existing drugs.[2]

In terms of per capita spending on drugs, gastrointestinal drugs are the fourth largest therapeutic class after cardiovascular, psychotherapeutic and cholesterol agents. Almost 90% of gastrointestinal drug spending is for acid suppressant. Eighty per cent of the spending is for PPIs, while histamine-receptor antagonists (H_2RA) account for only 10%.[3] Acid suppressants are drugs used to treat peptic ulcer disease (PUD), gastrointestinal reflux disease (GERD) and dyspepsia.

PPIs are proven to be effective in treating PUD, GERD and dyspepsia; however, they are often used where H_2RAs can be an effective lower-cost alternative. The perceived improved effectiveness of PPIs over H_2RAs by patients and physicians play a major role in the rapid growth of the utilization of these agents.[4,5] A recent study conducted in the UK identified several factors that influence a physician's decision to prescribe PPIs.[6] These include the use of guidelines and evidence, endoscopy results, commercial influence and marketing, physician attitude toward different management strategies (step-down or step-up therapies), and the cost and introduction of different PPIs. Another study conducted in the United States found that step-up approach strategies are not used by physicians while a step-down approach is acceptable.[7]

Several interventions have been used to encourage the appropriate prescribing of drugs while minimizing the costs associated with their use. Some of these interventions target physician prescribing behaviour while others are directed toward patients.

2.1 Professional Interventions

Professional interventions are aimed at improving professional practice and the delivery of effective health services. Professional interventions include professional educational interventions, audit and feedback, and reminders.

Educational interventions are designed to increase the understanding of clinical care principles or the awareness of specific practice recommendations.[8] Educational interventions include: the distribution of educational material (electronically published or printed recommendations for clinical care, including clinical practice guidelines and audio-visual materials); educational meetings (gatherings of health care professionals in face-to-face or virtual environments); a local consensus process (a debate and discussion between professionals and other concerned parties toward the establishment of a general consensus on the importance and management of specific clinical problems within a limited, local jurisdiction; educational outreach visits or academic detailing (face-to-face educational meetings between a trained person and a health provider in his or her own setting, aimed at changing the provider's behaviour); and local opinion leaders (use of providers nominated by their colleagues).[9]

Audit and feedback is another strategy that has been widely used to improve physician practice. Audit and feedback can be defined as any summary of clinical performance of health care over a period of time.[9] This summary may also include recommendations for clinical action. In some cases, health care professionals are passive recipients of feedback while in other cases, professionals are actively involved and have specific and formal responsibilities for implementing change. The latter method of audit and feedback may have a larger impact on improving professional practice.[10]

Reminders are another method used to help clinicians remember information that they already know (or would be expected to know) by presenting the information in different, more accessible or relevant formats, or at a particularly appropriate time. Reminders can take different forms:

- cue sheets containing general knowledge or advice, with no patient information or patient-specific advice and not requiring a response

- checklists containing general knowledge or advice with no patient information or patient-specific advice but requiring response to specific questions
- patient profiles containing patient data and/or patient-specific knowledge or advice; these may also contain general knowledge or advice, but no response is required
- profile checklists containing patient data and/or patient-specific knowledge or advice; one or more of the statements or questions indicate that a response must be recorded.[11]

Reminders can be delivered manually (on paper) and electronically (on paper or on screen).[11]

2.2 Disease Management Interventions

Disease management programs are generally designed to improve the process of health care delivery and patients' outcomes. Appropriate management of a particular chronic condition may reduce the overall treatment costs through reducing emergency room visits, fewer hospitalization, and better choice of drugs.[12]

2.3 Policy-related Interventions

Drug plans have undertaken a variety of strategies in attempting to manage drug utilization and to curb rising prescription costs. Formulary-based interventions (prior authorization and reference pricing) and drug utilization interventions are all tested and used by drug plans in North America.

Prior authorization is widely used by most of the drug plans in Canada. Different terms have been used by Canadian provincial drug plans to describe prior authorization: limited use in Ontario; special authorization in British Columbia, Alberta, New Brunswick and Newfoundland; exceptional status in Manitoba, Saskatchewan, Nova Scotia and Prince Edward Island. Under prior authorization, the drug plan must authorize a prescription for a certain class of drugs before it can be filled. Prior authorization might be required in order to limit the use of drugs in a certain class to patients with particular medical conditions or complications. In other cases, prior authorization can be used as a means of reinforcing a preferred drug list, where the preferred drug is listed as a general benefit while other drugs in the class require prior authorization. Prior authorization may also be used in combination with a step-up therapy program, so the patient must try a less expensive drug before receiving the drug originally requested.[12]

Reference pricing has also been used to control drug utilization and drug cost. Under a reference-pricing system, a base price is established as a basis for reimbursement. The base price is usually based on the least expensive drug in a particular class. Any amount charged above the reference price is the responsibility of the patient.[12]

Drug utilization review (DUR) is another strategy that has been widely used in North America for monitoring and managing the appropriate use of drugs. Generally, DUR programs review claim data to identify inappropriate prescribing that may lead to adverse medical outcomes. In addition to monitoring adverse drug reaction, many programs used interventions based on DUR to influence physician prescribing behaviour.[12] For example, DUR may identify particular physicians who prescribe fewer or more drugs than their peers, or who do not adhere to the treatment guidelines (physician profiling). Once identified, education interventions can be designed and targeted to those physicians with inappropriate prescribing.[12] The DUR educational intervention includes a cover letter describing the purpose of the DUR program, an educational fact sheet describing the appropriate use of certain drugs, patient profiles with potential misprescribing examples, and a physician response form requesting feedback on whether the physician plans to act on the

intervention and what action is identified. In addition to the DUR education intervention, some DUR programs also use reminders to reinforce changes.

2.4 Patient Interventions

Patient interventions include patient educational interventions and patient reminders. Patient educational interventions are defined as those that include formal and structured instruction on the disease and on ways to manage the symptoms.[13] Patient education interventions include self-management programs, counselling, leaflets, and small group meetings.

Patient reminders are used to improve patient adherence to medication, screening or vaccination. They can be delivered by a variety of methods (e.g., telephone or mail) and levels of intensity (e.g., single or multiple reminders).[14]

For the purpose of this report, interventions have been classified into five major categories: professional interventions, disease management interventions, interventions for dissemination of dyspepsia guidelines, regulatory interventions, and patient interventions.

3 OBJECTIVE

The objective of this review is to identify evidence-based interventions that have been used nationally and internationally to stimulate appropriate utilization of proton pump inhibitors (and/or acid suppressants).

4 METHODOLOGY

4.1 Literature Search Strategy

MEDLINE®, EMBASE®, BIOSIS®, Cochrane Library (Issue 4, 2006), and HEED (Health Economics Evaluations Database) were searched to find literature focusing on PPI prescribing and use. The search was not restricted by language or literature type. Date restrictions were not applied; searches were last updated November 28, 2006.

Given that the term "intervention" has multiple meanings in clinical literature, the search relied on key words and phrases associated with known intervention types, such as academic detailing. Some controlled vocabulary terms were used but, in general, these were too broad to be useful. For more detail on search terms, see Appendix 1.

An extensive gray literature search was conducted. This search included but was not limited to: CRD (Centre for Reviews and Dissemination) databases, National Prescribing Service Limited (Australia), DERP (Drug Effectiveness Review Project), AHRQ (Agency for Healthcare Research and Quality), the Centre for Clinical Effectiveness (Monash University), as well as national and international gastroenterological and pharmacy associations. A general internet search was used to identify local initiatives not found in databases and health technology assessment (HTA) web sites.

4.2 Inclusion Criteria

Studies addressing interventions used to target appropriate prescribing and use of proton pump inhibitors (or anti-ulcer drugs) which focused on:

- reducing over prescribing of PPIs, or switching PPIs to H_2RA, or to another preferred PPI
- properly managing of PUD, GERD or dyspepsia
- reducing therapeutic cost
- increasing patient compliance with drug therapy.

Studies addressing guideline implementation strategies for PUD, GERD or dyspepsia.

4.3 Exclusion criteria

- Narrative reviews, editorials or commentaries
- Studies only presenting observational data or trends in current practice
- Surveys

5 RESULTS

Twenty-four studies that met the inclusion criteria were identified. They were categorized as: professional interventions (five studies);[15-19] disease management interventions (three studies);[20-22] dissemination strategies for dyspepsia guidelines (three studies);[23-25] policy-related interventions (10 studies);[26-35] and patient interventions (three studies).[36-38] The majority of studies were small, non-randomized trials that included four controlled studies,[22,32-34] three time-series,[16,26,30] four before-and-after studies,[17-19,27] ; and observational studies that included two cohort studies[28,29] and one case-control study.[31]

5.1 Professional Interventions

Five studies were identified that targeted physician prescribing for anti-ulcer drugs.[15-19] Three studies targeted prescribing for PPIs,[15,17,18] one study targeted *H. pylori* eradication therapy,[19] and one study targeted cimetidine prescribing (switching from cimetidine to another, less expensive H_2RA).[16] The latter study was included in this report because the intervention could be also applied where different PPIs with similar effectiveness have very different costs. The details of information extracted from each study are presented in Appendix 2.

One study was a cluster-randomized trial,[15] another was a one-time series,[16] and there were three before-and-after studies.[17-19] Three studies were based in the USA,[16,17,19] one in Sweden[15] and one in Hong Kong.[18] Four out of five studies took place in ambulatory settings.[15-17,19]

Four studies reported multifaceted interventions[15-18] with the common components of written education material, lectures, and physician feedback. Only one study, a consensus conference, addressed a single intervention.[19]

All studies used drug utilization (defined daily dose (DDD), number of prescriptions, rate of drug use or market share) as an outcome measure. Two studies also included drug expenditures (drug cost and cost savings) as an outcome measure.[17,18] Only one study estimated the cost of the intervention.[16]

The four multifaceted intervention studies reported improvement in physician prescribing for anti-ulcer drugs. None of the studies examined the long-term effect of the interventions; intervention effect was measured for periods ranging from three[17] to 12 months.[15,16,18]

Nilsson *et al.*[15] performed a cluster randomized study that compared a multifaceted intervention (including physician feedback, educational outreach visits "detailing", educational material, and local opinion leaders) to no intervention. They found that the prescribing rate of PPIs were reduced by 8.4% in the intervention group and increased by 7.9% in the control group, but the difference between the two groups was not statistically significant.

Lucas *et al.*[17] and Kumana *et al.*[18] used before-and-after designs to evaluate the impact of multifaceted interventions on reducing the rate of PPI prescribing. Lucas *et al.*[17] showed that there was a 12% decrease in the number of PPI prescriptions per enrolee in the nine-month post-intervention period when compared to the nine-month pre-intervention period. They also concluded that the timing for interventions is important for getting the desired effect of changing prescribing behaviour, especially if the intervention might increase the workload of the busy physicians. Kumana *et al.*[18] examined the impact of immediate concurrent feedback intervention in a hospital setting. They showed that immediate concurrent feedback intervention resulted in decreasing the average overall anti-ulcer drug (omeprazole and ranitidine) expenditures by 44% and 45% in inpatient and outpatient pharmacy, respectively.

Brufsky *et al.*[16] used an interrupted time-series design to examine the impact of a two-phase multifaceted intervention (Phase 1: printed education materials; Phase 2: physician re-evaluation of patients receiving H_2RA therapy and physician feedback) on switching patients from ranitidine, famotidine and nizatidine to cimetidine (a less expensive H_2RA) in both staff and group models. Shifting the market share to cimetidine was accelerated by the distribution of education material in the staff model but not in the group model. On the other hand, physician feedback and patient re-evaluation had no significant impact on continuous shifting from H_2RAs to cimetidine in the staff model, and the opposite was found in the group model.

Thamer *et al.*[19] evaluated the impact of the National Institutes of Health (NIH) consensus conference on *H. pylori* eradication therapy using the before-and-after study design. He found that the consensus conference had no impact on influencing physician prescribing behaviour.

5.2 Disease Management Interventions

Two trials examined the impact of acid-related disease management programs on improving health care and drug utilization (*H. pylori* test and treat, refer to endoscopy, or PPI discontinuation). A cluster randomized trial by Ofman *et al.*[20] found that, compared with usual care, acid-related disease management interventions (guidelines, educational meeting with local opinion leaders, three academic detailing visits, and patient education and counselling) were significantly effective in increasing *H. pylori* testing and treatment (61% versus 9%) and PPI discontinuation after one to12 weeks (70% versus 36%). A controlled trial by Majumdar *et al.* [22] compared high-intensity disease management interventions (guideline, patient lists, toolkit and academic detailing) and low-intensity intervention (guideline, patient lists, toolkit) with usual care. They found that providing guidelines, patient lists and toolkits was no better than usual care, while adding academic detailing led to a significant increase in *H. pylori* test ordering (29% in the intervention group versus 9% in the usual care group) and a significant decrease in PPI use by 9% per year.

A cluster randomized trial by Dennett *et al.* [21] comparing an *H. pylori* eradication program (distribution of education materials and peer comparison feedback) with usual care showed that the intervention program led to a statically significant increase in the rate of use of eradication therapy overall, in the post-intervention period (1.7% in the intervention group versus 0.9% in the

control group), but not in newly diagnosed patients (2.7% versus 1.9%). Details for the three studies in this section are included in Appendix 3.

5.3 Interventions for Disseminating Dyspepsia Guidelines

Three cluster randomized trials performed in the United Kingdom compared the implementation strategies for dyspepsia guidelines using postal distribution of guidelines plus educational outreach visits,[23,25] or interactive workshop,[24] versus postal distribution of guidelines alone. Details are provided in Appendix 4.

Chan *et al.*[23] studied the effectiveness of distributing dyspepsia guidelines combined with two outreach visits by nurse facilitators in an effort to implement an evidence-based dyspepsia guideline. They reported that the intervention was significantly effective in reducing ulcer healing prescribing costs by 5% when compared to postal distribution of guidelines alone. Another study by Hall *et al.*[25] reported that outreach visits by a community pharmacist, in an effort to implement dyspepsia guidelines, resulted in a non-significant change in the prescribing of drugs used in *H. pylori* eradication therapy (omeprazole and metronidazole). They concluded that routine use of untargeted outreach visits was not an effective strategy for implementing a dyspepsia guideline.

Banait *et al.*[24] studied the effectiveness of interactive workshops chaired by local hospital specialists, plus postal distribution of guidelines, versus postal distribution of guidelines alone. They found that the intervention was significantly more effective than passive guideline dissemination. However, it also produced a significant increase in the overall prescribing expenditures on anti-ulcer drugs in the intervention group as compared with the control group (8% versus 2%).

5.4 Policy-related Interventions

Ten studies examined the impact and effectiveness of three policy interventions aimed at improving physician prescribing for anti-ulcer drugs and control costs: five prior authorization studies,[26-29,35] two preferred drug list studies[30,31] and three drug utilization review studies.[32-34] Details are provided in Appendix 5.

Two studies evaluated the impact of a PPI prior authorization policy on drug costs and utilization.[26,27] Delate *et al.*,[26] using an interrupted time series analysis, found that prior authorization for PPIs in one state's Medicaid program resulted in a 90.9% decrease in PPIs expenditure per member, per month (particularly among patients without at least one diagnosis of gastrointestinal condition). It also resulted in a 223% increase in H_2RAs expenditure per member, per month, in the month immediately following the implementation of the policy, with no effect on health care utilization or expenditure. Before-and-after analysis by Marshall *et al.* [27] found that the PPI special authorization policy for British Colombia's PharmaCare program did not appear to alter the rate of PPI growth, but it reduced the overall therapeutic cost. This resulted in cost savings of $18.8 million in the 3.4 years following the special authorization policy.

A before-and-after study by Bursey *et al.*[35] analyzed the cost impact of a Newfoundland provincial drug program that has been designed to guide the treatment of upper gastrointestinal disorders. The program consisted of distributing locally-developed educational materials about the algorithms for the management of dyspepsia and GERD to all physicians and pharmacists in the province; it was followed by restricting payment to PPIs through the Newfoundland provincial drug program to situations defined by the algorithm. Implementation of such a program resulted in a cost saving to

the drug program of $1.6 million, $1.7 million and $1.0 million for H_2RAs, prokinetics and PPIs respectively in the subsequent three years.

Two open cohort studies measured compliance with the prior authorization strategy. Mamdani *et al.*[28] showed that a mandated step-up policy in the Ontario Drug Benefit Program had a small positive impact (9%) in compliance with using H_2RA before starting PPI therapy. On the other hand, McManus *et al.*[29] showed that restricting PPI coverage in Australia's Pharmaceutical Benefits Scheme is not effective in encouraging a step-up approach.

Two studies assessed the effect of a PPI preferred drug list.[30,31] A recent interrupted time series by Schneeweiss *et al.*[30] examined the effect of restricting PPI coverage to rabeprazole, a less costly PPI, in British Colombia's PharmaCare Program on the utilization of drugs and heath care services. The impact of the preferential listing of rabeprazole was determined using longitudinal-linked claim data on all BC residents 66 years and older who had previously used one of the restricted drugs (omeprazole, pantoprazole and lansoprazole) in the six-month period before the policy implementation. Results from this study showed that the coverage restriction led to substantial switching to the rabeprazole. (Among the 38,426 prevalent users of restricted PPIs, 17,424 patients or 45% switched to rabeprazole, and 3442 patients or 9% later resumed using a restricted PPI after a treatment trial with rabeprazole.) This rapid switching to rabeprazole was accompanied by no shift in the total PPI utilization (p=0.82), but there was a slight reduction in the rate of increase (-383 daily doses per 10,000 residents per month), which did not reach statistical significance (p=0.08). It was also reported in this study that there was no increase in the monthly hospitalization rates for GI hemorrhage (0.15, p=0.35) or in major PUD complications (-0.64, p=0.16) after the PPI coverage restriction compared with the time before the intervention. It was estimated British Colombia's PharmaCare Program saved $2.9 million within the first six months of policy implementation.

Raisch *et al.*[31] examined the effect of preferred drug policy on patient outcomes (heartburn severity and acid regurgitation) using a case-control study (51 cases failed a switch from omeprazole to lansoprazole as preferred drugs versus 51 success patients). Results from this case-control study indicated that failure patients had significantly poorer health outcomes during the lansoprazole trial but the total health care utilization cost did not differ significantly between the two groups.

Three controlled clinical trials examined the effect of DUR educational intervention on changing physician prescribing behaviour for anti-ulcer drugs. All three trials were carried out in North American Medicaid programs: two in the USA[33,34] and one in Mexico.[32] Okano *et al.*[33] showed that DUR interventions aimed at reducing the over-prescribing of sucralfate concurrent therapy with anti-ulcer drugs by physicians significantly reduces sucralfate concurrent therapy. Another control trial by Raisch *et al.*[32] found that DUR intervention resulted in a significant decrease in inappropriate prescribing of anti-ulcer drugs (long-term use, high acute daily dose, and improper diagnosis). A third study by Culbertson *et al.*[34] suggested that involving both pharmacists and physicians in DUR intervention with additional reminders (follow-up phone calls to pharmacists) enhances the effectiveness of DUR intervention.

5.5 Patient Interventions

Three studies were identified that targeted patient behaviour (details are provided in Appendix 6). A cluster randomized study by Krol *et al.*[36] suggested that a simple patient-directed intervention (a mailed information leaflet from physicians that included updated clinical recommendations for the management of dyspepsia, and advice on when to reduce or to stop PPIs and when to seek help

from a physician) significantly reduced the long-term prescriptions for PPIs in patients with dyspepsia.

A randomized controlled trial by Al-Eidan *et al.*[37] compared the effect of hospital pharmacy counselling versus standard active advice on *H. pylori* eradication therapy compliance rates in 76 patients. They found that structured patient counselling and follow up have a significant effect on compliance and *H. pylori* eradication rates. Another randomized trial by Stevens *et al.*[38] found that there was no difference in the compliance rate between the intervention group (patients who received long-term counselling by a pharmacist, followed by a phone call) and the control group (usual care).

6 DISCUSSION AND CONCLUSIONS

There are few studies which examine interventions that tend to promote the appropriate use of PPIs. Therefore, studies focusing on dyspepsia guideline implementation and dyspepsia management programs were also included. The majority of interventions were multifaceted interventions, regardless of whether the goal was appropriate PPI prescribing, guideline implementation or disease management. The components for these multifaceted interventions vary among studies, leading to difficulty in attributing the effectiveness to particular components. All studies involving multifaceted interventions showed positive impact on outcomes. This was especially evident where passive distribution of educational material was reinforced by interactive educational components such as meetings, educational outreach visits or physician feedback. These findings are compatible with other reviews that multifaceted interventions are more likely to succeed than a single intervention.[39,40]

Formulary-related interventions such as prior authorization and reference-based pricing have been found to be useful in controlling PPI drug expenditure, but long-term impact on health outcomes and drug cost has not been addressed. These findings are supported by a systematic review by Aaserud *et al.*[41] who concluded that reference-base pricing can reduce drug plan expenditures by inducing a shift in drug use towards less expensive drugs without causing adverse effects on health or increasing health care utilization.

The three studies that examined the impact of DUR interventions found that interventions based on drug utilization reviews were effective in changing physician-prescribing behaviour for acid suppressants or PPIs, especially when DUR interventions involve both physicians and pharmacists.

Educating patients about their conditions and when and how to use their medications has been found to be useful in controlling long-term use of PPIs in one study.[36]

In studies where cost saving was a measured outcome, the cost of the interventions was not calculated or subtracted from the apparent cost saving. This may overestimate the value of the cost saving. None of the studies explored the cost effectiveness of the intervention.

Barriers to implementation were not carefully addressed in most studies included in this review. Only one study described physicians' busy workloads as barriers to intervention implementation.[17] Another study showed that outreach visits that are not targeted to physicians with specific difficulties or barriers had no effect on changing physicians' behaviours.[25] Identifying barriers to implementation and tailoring interventions to address these barriers may enhance the success of the intervention and improve health care and patient outcomes.[42] Barriers may include lack of hard

evidence or lack of communication about evidence-based health care, fear of using the evidence, poor knowledge about the result of their current behaviour, increased workload, lack of time, lack of money and resources, and persistence of the status quo (i.e., the natural tendency to return to previous practice patterns).[43,44]

The majority of the included studies are small; non-randomized studies (controlled trials, time series and before-and-after) with weak study designs. It is therefore not possible to exclude the effect of other activities that occur at the same time as the intervention. This makes it difficult to attribute the observed changes to the intervention so that caution should be taken in interpreting the effectiveness of interventions.[45] In addition, randomized controlled trials included in this review used professionals as a unit of allocation (cluster randomization), but analyzed the results by patients (using drug utilization or drug cost as indicators), which tends to inflate the intervention effect.[46] It is also difficult to compare effectiveness of interventions given the diverse objectives, measurement methods and outcomes among studies.

In conclusion, the evidence on the best intervention for enhancing appropriate prescribing of PPIs is limited, but this review suggests that combining educational multifaceted interventions with evidence-based formulary intervention may appropriately affect the prescribing of PPIs.

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APPENDIX 1: Search Strategy and Process

Identification of Search Terms

In the context of this search, the term "intervention" is used to denote programs, activities, or policies which seek to change behavior associated with the prescribing and use of PPIs. Examples of such interventions include academic detailing, educational outreach, or audit and feedback. While we can identify interventions when we see them, we cannot necessarily find the words to describe them. In a 2002 literature review on changing clinical behavior, Hu and Patterson observed that while "[t]he term intervention is commonly used...there is no universally accepted definition in the behavior change literature."[47] For the purposes of their review, they defined interventions as "a consciously applied action with the aim of producing change in a desired manner."[47]

Given the elusive nature of the concept of interventions, this search relied on keyword phrases and selected MeSH and EMTREE controlled vocabulary. To determine keywords and subject headings, we reviewed a search constructed, run and tested in 2004 by Grimshaw *et al.*[48] After combining the Grimshaw strategy with a highly sensitive search strategy for PPIs, we retrieved approximately 2600 records from MEDLINE ® alone. A scan of the results showed that due to the highly sensitive nature of the Grimshaw search, precision—that is, the percentage of relevant articles, was low. To increase precision, we removed a number of search terms which we found too broad; for example, "Program Evaluation" and "Outcome and Process Assessment (Health Care)" – both MeSH headings. The resulting search strategy was a combination of the Grimshaw search and additional keywords and phrases identified in consultation with this study's author.

Databases Searched

MEDLINE®, EMBASE®, BIOSIS®, Cochrane Library (Issue 4, 2006), and HEED (Health Economics Evaluations Database).

Search Strategy

The following strategy shows the search run in Ovid MEDLINE; this search was adapted for EMBASE, BIOSIS, Cochrane and HEED. No limits or filters were applied.

Key	
term/	Subject heading (MeSH or Emtree)
*	Major MeSH or Emtree term
ti,ab	Terms are searched in title and abstract fields
ai	Antagonists and inhibitors subheading
rn	CAS Registry/EC Number/Name of Substance
?	Single character truncation
$	Unlimited truncation
adj	requires search terms to be next to each other, in any order
adj2	Requires search terms to be within 2 words of each other, in any order

	Proton Pump Inhibitors
1	proton pumps/ai
2	rabeprazole/ or (rabeprazol? or pantoprazol? or lansoprazol? or esomeprazol?).ti,ab,rn. or omeprazole/ or omeprazol?.ti,ab.
3	proton pump inhibitor?.ti,ab.
4	(antgra or audazol or aulcer or belmazol or ceprandal or danlox or demepraxol or desec or dizprazol or dudencer or elgam or emeproton or epirazole or erbolin or exter or gasec or gastrimut or gastroloc or gibancer or indurgan or inhibitron or inhipump or lensor or logastric).ti,ab,rn.
5	(lomac or losec or mepral or miol or miracid or mopral or morecon or nilsec or nopramin or amep or omp or omz or ocid or olexin or omapren or omed or omegast or omepral or omeprazol or omeprazole or omeprazolum or omeprazon or omeprol or omesek or omezol or omezolan or omid or omisec).ti,ab,rn.
6	dakar.rn.
7	(omizac or ompanyt or ortanol or osiren or ozoken or paprazol or parizac or pepticum or pepticus or peptilcer or prazentol or prazidec or prazolit or prilosec or procelac or proclor or prysma or ramezol or regulacid or sanamidol or secrepina or tedec ulceral or ulceral or ulcesep or ulcometion or ulcozol or ulcsep or ulsen or ultop or ulzol).ti,ab,rn.
8	(victrix or zefxon or zegerid or zepral or zimor or zoltum or zanprol or ufiprazole or ufiprazol or ufiprazolum).ti,ab,rn.
9	(nexium or perprazole or nexiam or inexium or sompraz or axagon or esopral or lucen or axiago or agopton or alexin or amarin or aprazol or bamalite or blason or compraz or estomil or fudermex or gastrex or gastride or gastroliber or ilsatec or ketian or keval or lancid).ti,ab,rn.
10	(lanfast or lanproton or lansopep or lansoprazolum or lansox or lanston or lanz or lanzo or lanzogastro or lanzol or lanzopral or lanzor or lasoprol or limpidex or lizul or mesactol).ti,ab,rn.
11	(monolitum or ogast or ogasto or ogastro or opiren or pampe or peptomil or prevacid or prezal or promp or prosogan or suprecid or takepron or ulcertec or uldapril or ulpax or unival or zoprol or zoton).ti,ab,rn.
12	(pantoprazole or pantoprazol or pantoprazole or pantoprazolum or controloc or pantoloc or protonix or angastra or apton or eupantol or inipomp or gastromax or noprop or pamgest or pantecta or panto or pantoc).ti,ab,rn.
13	(pantocal or pantocarm or pantodac or pantop or pantopan or pantopaz or pantorc or pantozol or (pantozol adj rifun) or pantus or peptazol or protium or rifun or singastril or somac or supracam or ulcemex or ulcotenal or ulserch or ziprol or zurcal or zurcale or zurcazol).ti,ab,rn.
14	(aciphex or gastrodine or pariet or rabec or rabeloc).ti,ab,rn.
15	or/1-14
	Intervention Terms
16	Intervention studies/ or intervention$ stud$.ti,ab.
17	((optimi?e or optimal or reduce or reducing or improve? or improving or improvement? or effect? or impact? or change? or appropriate or appropriately or appropriateness or feedback) adj (formular$ or prescribing or utili?ation or dose or dosing or doses or dosage?)).ti,ab.
18	(opinion adj leader?).ti,ab.
19	((group or academic) adj detailing).ti,ab.
20	((guideline? or cpg or cpgs) adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).ti,ab.
21	((effect? or impact or evaluat$ or introduc$ or compar$) adj2 program$).ti,ab.
22	(audit adj feedback).ti,ab.
23	(tailored adj intervention?).ti,ab.
24	((standard or usual or routine or regular or traditional or conventional or pattern) adj care).ti,ab.
25	((impact or effect$) adj2 (legislation or regulations or policy)).ti,ab.
26	((cost or economic or payment) adj (incentive? or impact or effect or affector change$)).ti,ab.
27	"Outcome Assessment (Health Care)"/
28	*utilization review/
29	*physician's practice patterns/

30	evaluation studies/
31	comparative studies/
32	*pamphlets/ or pamphlet$.ti,ab.
33	pilot projects/ or pilot project$.ti,ab.
34	quality assurance health care/
35	(cost adj (share or sharing or containment or reduction or reduce or reducing or reduces or containment or contains or improvement or improves or improved)).ti,ab.
36	(workshop? or feedback or active dissemination or written material? or computer based support or email reminder? or printed material? or active dissemination or eductional outreach or cme credit or opinion leader? or grand round lecture? or tailored program? or reminder?).ti,ab.
37	Or/16-36
38	15 and 37 [PPIs and Intervention terms]

Gray Literature Search

An extensive gray literature search was conducted. This search included but was not limited to: CRD (Centre for Reviews and Dissemination) Databases, National Prescribing Service (Australia), DERP (Drug Effectiveness Review Project), AHRQ (Agency for Healthcare Research and Quality), Centre for Clinical Effectiveness (Monash University) as well as national and international gastroenterological and pharmacy associations. A general internet search was used to identify local initiatives not found in databases and HTA web sites.

APPENDIX 2: Studies of Professional Interventions

Study Design	Participant	Intervention	Setting	Outcome	Results	Authors' Conclusion
Multifaceted Interventions						
Nilsson *et al.*[15] 2001 Cluster randomized control trial	Intervention: 8 general practitioners (GPs) Control: 32 GPs	Intent: reduce over-prescribing in general and to increase prescribing of H_2RA at the expense of PPIs Intervention model: feedback on individual prescribing rate; interactive, problem-oriented, educational outreach visits; educational material and local opinion leaders	6 health care centres and 3 continuing medical education groups in Stockholm	Drug utilization (DDD)	Mean change in percentage of DDDs a year before and after intervention (PPIs): intervention: -8.4 versus control: 7.9, CI for the difference in the mean change (-36.3, 3.7) Mean change in percentage of DDDs a year before-and-after intervention (H_2RAs): intervention: 7.1 versus control: -6.8, CI for the difference in the mean change (-7.8, 35.5)	Although the difference is not significant due to the small sample size in the intervention group, this study suggested that feedback of individual prescribing rates, combined with problem-oriented educational outreach visits, is a promising model for improving prescribing behaviour
Brufsky *et al.*[16] 1997 Interrupted time series	Staff model: physicians employed by group-practice HMO Group model: independent physicians contracted by HMO	Intent: Convert patients from other H_2RA to cimetidine on the basis of equal effectiveness to reduce cost. Intervention model: printed education materials, physician re-evaluation of patients receiving H_2RA therapy, physician feedback. In staff model: physician participation was voluntary with no incentives. In group model: operational aspect of intervention was managed by pharmacy benefit management contractor who coordinated all physician and patient mailings, patient counselling, assisted in developing clinical material, tracked conversion in database	Harvard Community Health Plan	Drug utilization	Market share: *In-staff model:* Baseline period: ranitidine (84%), cimetidine (4%), famotidine (12%) and nizatidine (0%). Formulary announcement period: market share of cimetidine increased by 1.1% per month for the following 12 months ($P < 0.0001$) and ranitidine continued to decline by 1.2% per month ($P < 0.0001$). Distribution of education material period: shifting the market share to cimetidine was accelerated by distribution of educational material. Physician feedback and second therapeutic evaluation period: no significant impact on continuing shifting from ranitidine to cimetidine	Annual saving exceeds the implementation cost with no discernible effect on number of hospitalizations. The magnitude of savings was much greater in the staff model than in the group model. Because cost was an important factor, this intervention can be generalized to situations in which similar agents with equal effectiveness have very different costs.

					In-group model: Baseline period: ranitidine (70%), cimetidine (12%), famotidine (12%) and nizatidine (5%). Formulary announcement and distribution of educational material periods: no significant impact on shifting trend. Therapeutic re-evaluation increased cimetidine market share (+9.7%; P <0.0001) and decreased prescribing of both ranitidine (-11.6%; P <0.0001) and famotidine (-1.2%; P<0.02)	
				Health outcome	No impact on hospitalization rate in both models	
				Cost of intervention	In-staff model: $35,450 In-group model:$24,250	
Lucas *et al.*[17] 2001 Before-and-after study	Physicians who had a patient with an active PPI prescription	Intent: convert patients from PPIs to H_2RAs on the basis of guideline to reduce cost. Intervention model: distribution of locally developed guidelines for PPI use; group meeting lead by local gastroenterologist to discuss the cost-effective treatment of GERD; patient lists; physician reminder and feedback on institutional performance	Portland Veterans Affairs Primary Care Clinics	Drug utilization	PPI Rx/ enrolee: (9 months before versus 9 months after) 0.39 versus 0.27 H_2RA Rx/ enrolee: (9 months before versus 9 months after) 0.33 versus 0.39	This low-intensity intervention that incorporated a population-based approach into clinician practice appears to be effective and may serve as a model for other health care systems. Timing for this intervention is important. It should not be used at a time when GPs are asked to make other changes that might increase their workload.
				Drug cost	% of PPI prescription of all PPIs plus H_2RA prescriptions: (9 months before versus 9 months after) 55% versus 40% PPI outpatient pharmacy cost/ enrolee: (9 months before versus 9 months after) $43 versus $28. H_2RA outpatient pharmacy cost/enrolee: (9 months before versus 9 months after) $6 versus $2 % of PPI cost of the total outpatient pharmacy cost: before	

					(3 quarters) versus after (3 quarters) intervention was 9.9% versus 6.7%	
Kumana *et al.*[18] 1998 Before-and-after study	All hospital physicians	Intent: reduce over-prescribing of omeprazole and increase appropriate prescribing of intravenous omeprazole Intervention model: distribution of locally developed guidelines; departmental seminars; and immediate concurrent feedback (providing immediate feedback to physicians with inappropriate prescribing)	Queen Mary Hospital (Hong Kong)	Drug utilization Drug cost	Average monthly omeprazole and ranitidine usage: in-patients decreased by 44% and outpatients decreased by 45% with the increase use of less expensive alternatives (cimetidine, famotidine and nizatidine) during the intervention period Average monthly cost saving: compared to pre-intervention period monthly saving during the intervention period, about HK$156,000	Regarding hospital antiulcer drugs, this "immediate concurrent feedback" strategy was associated with more rational prescribing and usage, and an important saving of resources
Single Intervention						
Thamer *et al.*[19] 1998 Before-and-after study	13,382 patients who received a care for PUD	Intent: increase appropriate prescribing of *H. pylori* eradication therapy for PUD Intervention: NIH consensus conference *on H. pylori* eradication therapy	Pennsylvania Medicaid Program	Drug utilization	Prescription rate of anti-microbial for PUD and omeprazole significantly increases across the study period but trend analysis showed that it is not attributed to NIH conference	Two years after the highly publicized NIH conference on *H. pylori* eradication, anti-microbial agents were not widely prescribed among the Pennsylvania Medicaid population, physicians do not appear to be using the recommendation developed by NIH expert panel based on recent scientific advances

CI=Confidence Interval; DDD=defined daily dose; GERD=gastrointestinal reflux diseases; GP=General Practitioner; HMO=health maintenance organization; PPI=proton pump inhibitor; PUD=peptic ulcer disease

APPENDIX 3: Studies of Disease Management Interventions

Study Design	Participant	Intervention	Setting	Outcome	Results	Authors' Conclusion
Ofman *et al.*[20] 2003 Cluster randomized control trial	8 clinic sites (406 non-NSAID chronic acid suppressant users) grouped into intervention group and control (usual care)	Intent: improve the management acid-related disorders in chronic acid suppressant users Disease management intervention: - Physician intervention: development of evidence-based practice guideline, single group meeting with local physician leaders, followed by face-to-face academic detailing by staff pharmacist with 3 follow-up meetings - Patient intervention: patient education by pharmacist followed by a follow-up phone call by nurse	Orlando Health Care Group	Health care utilization Drug utilization	*H. pylori* testing: control versus intervention; 9% versus 61%; p=0.001 Referral for endoscopy in no responders; control versus Intervention; 40% versus 62%; p=0.50 Use of *H. pylori* eradication regimen: control versus Intervention; 10% versus 96%; p=0.001 PPI trial in *H. pylori* negative patients: control versus Intervention; 65% versus 77%; p=0.36 No follow-up therapy in responders to *H. pylori* therapy: control versus Intervention; 80% versus 84%; p=0.99 PPI discontinue after 1 to 12 weeks: control versus Intervention; 36% versus 70%; p=0.04	This disease management program for patients with acid-related disorders led to improved process of care. The effectiveness of such a program in other settings requires further study
Dennett *et al.*[21] 2002 Cluster randomized control trial	537 GPs in 264 practices grouped into intervention group and control (usual care)	Intent: improve *H. pylori* management in patients with PUD Intervention: distribution of education material and peer comparison feedback	Managed care network	Drug utilization Drug cost	Rate of use of eradication therapy: *Overall:* intervention: 1.7% versus control; 0.9%; OR =2.0 (95% CI: 1.1, 3.4), p=0.02 *In newly diagnosed patients:* intervention: 2.7% versus control:1.9%; OR=1.4 (95% CI: 0.69, 2.9), p=0.34 Rate of use of eradication therapy in long-term anti-secretory users: intervention: 0.91 versus control: 0.0% Total change in cost of GI therapy per member from pre-intervention to post-intervention period: intervention: $6.38	After implementation of disease information program using peer comparison feedback, the intervention physicians prescribed eradication therapy significantly more often than the control physicians, but this was not accompanied by any significant increase in the total cost of drug therapy per patients

				Health outcome QOL score	versus control: $5.56; p=0.82 Disease specific QOL (GSRS): No significant difference in the mean change in dyspeptic syndrome score from pre-intervention to post-intervention between members treated by intervention and control physicians (p=0.86)	
Majumadar *et al.*[22] 2005 Controlled clinical trial	14 multi-speciality practices (581 chronic PPI or H_2RA users) grouped into 3 groups: low- and high-intensity intervention groups and control (usual care)	Intent: improve *H. pylori* management in long-term acid suppressant. Low intensity intervention: guideline, patient list and toolkit (3 practices and 147 patients) High-intensity intervention: low-intensity intervention plus academic detailing and reinforcement by pharmacist (5 practices and 122 patients) Control: usual care (6 practices and 312 patients)	Harvard Vanguard Medical Associates	Health care utilization Drug utilization	*H. pylori* testing: Pre-post change: in low intensity versus change in control (IRR): 0.98 (95% CI: 0.22, 4.40) Pre-post change in high intensity versus change in control (IRR): 4.82 (95% CI: 1.34, 17.3). Treatment: Pre-post change in low intensity versus change in control (incidence rate ratio (IRR): 1.45 (95% CI: 0.18, 11.5). Pre-post change in high intensity versus change in control (IRR): 2.96 (95% CI: 0.45, 19.5) Rate of acid suppression use: high-intensity intervention: PPI: 0.75% decrease in PPI prescription per month; p=0.028. H_2RA: no change in the rate of H_2RA prescription per month. Low-intensity intervention and usual care (control): no change over time in the prescription rate of both H_2RA and PPI	Providing guidelines, patient lists and toolkits was no better than usual care. Adding group detailing and pharmacist reinforcements led to improvement in *H. pylori* management and decrease in use of proton pump inhibitors

CI=Confidence Interval; DDD=defined daily dose; GP=General Practitioner; GSRS=Gastrointestinal Symptom Rating Scale; IRR=incidence rate ratio; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor; QOL=Quality of life

APPENDIX 4: Studies of Dissemination Strategies for Dyspepsia Guidelines

Study Design	Participant	Intervention	Setting	Outcome	Results	Authors' Conclusion
Chan *et al.*[23] 2001 Study 1: Cluster randomized control trial	66 practices (279 GPs) randomized to either a control group or intervention group	Intent: impact of implementing dyspepsia guidelines on drug costs. Intervention (133 GPs): distribution of evidence-based dyspepsia guideline and two reinforcement visits (at 0 and 6 months) by a nurse academic detailer Control (146 GPs): distribution of evidence-based dyspepsia guideline alone	North & Mid-Hampshire Health Authority	Drug cost	Acid suppressants prescribing cost: before implementation: lower in control group versus intervention group (NS). After implementation: 5% (£222,000) less in the intervention group than in the control group; p=0.008 H_2RAs prescribing cost: fell significantly in intervention group (from £134,000 to £123,000; p=0.02) and remained unchanged in control group (from £150,000 to £168,000; p=0.56) PPIs prescribing cost: remained steady in the intervention group (from £200,000 to £220,000; p=0.08) and rose in the control group (£210,000 to £275,000; p=0.02)	There appeared to be a shift in prescribing practice as a result of distributing evidence-based guidelines with implementation support. A nurse facilitator is well received and can be effective in implementing evidence-based dyspepsia guideline in primary care. This data supports the strategy as a practical method of implementing guidelines, and resulted in significant savings in ulcer healing ost.
Chan *et Al.* [23] 2001 Study 2: before-and-after	260 out of 300 (87%) attend the presentation by the nurse facilitator	Intervention: distribution of locally tailored guidelines and had two visits (at 0 and 6 months) by a nurse academic detailer	Portsmouth & South East Hampshire Health Authority	Drug cost	Acid suppressants prescribing cost: Before implementation: increase by 8% (£345,000; p=0.008) between the 2 years prior to implementation. After implementation: 4% (-£255,000; p=0.04)	
Banait *et al.* [24] 2003 Cluster randomized control trial	113 GPs randomized to either a control group or intervention group	Intent: proper management of dyspepsia Intervention (57 GPs): distribution of guidelines and educational outreach programme (post graduate educational allowance-approved practice-based interactive workshops	Salford and Trafford Health Authority	Health care utilization	Median percentage of appropriate referral for open access endoscopy per practice (interquartile range): control versus intervention was 50.0 (22.1-72.4) versus 63.9 (50.0-100.0); p=0.025 Testing rate for *H. pylori* (median serological tests requested): control versus intervention was 4 versus 0; p<0.001	This study supports other research suggesting that educational outreach is more effective than passive guideline dissemination in promoting changes in clinical practice behaviour; however, the intervention also produced unintended outcomes, notably an

		chaired by local hospital specialists) Control (57 GPs): distribution of guidelines alone		Health outcomes Drug cost	Finding at open access endoscopy (pre/post-intervention period): no change in the relative proportion of major, minor and normal endoscopic finding for either control or intervention groups Differences in expenditure for acid suppressants (6 month post – 6 months before intervention): a significant increase in the intervention group than in control (p=0.020)	increase in prescribing costs.
Hall *et al.*[25] 2001 Cluster randomized control trial	76 eligible practices – 32 in North Tyneside and 44 in Newcastle – randomized to either a control group or intervention group	Intent: encourage GPs to undertake *H. pylori* eradication Intervention (38 GPs): distribution of guidelines followed by a single outreach visits by a community pharmacist Control (38 GPs): distribution of guidelines alone	Newcastle and North Tyneside Health Authority Clinical Effectiveness Unit	Drug utilization	The effect of intervention was a non-significant change in the use of omeprazole by -0.02 (95% CI -0.12 , +0.08) dose unit The effect of intervention was a non-significant change in the use of metronidazole by -0.005 (95% CI: -0.025, +0.038) dose unit	Routine use of untargeted outreach visiting is probably not a worthwhile strategy. Future evaluation could usefully focus on pragmatic evaluation of targeted visits and consider greater use of social marketing strategies.

CI=Confidence Interval; GP=General Practitioner; NS=not significant

APPENDIX 5: Studies of Policy-related Interventions

Study Design	Participant	Intervention	Setting	Outcome	Results	Authors' Conclusion
Formulary-related Interventions: Impact of Prior Authorization						
Delate *et al.*[26] 2005 Interrupted time series	5,965 continuously eligible potential anti-secretory users: 2664 PPI users, 1860 H_2RA users and 1441 non-users	Intent: to channel potential PPI users to less expensive H_2RA alternative when clinically appropriate Intervention: prior authorization for PPIs that used diagnosis and risk based criteria to establish medical necessity for approval of PPIs	Medicaid Program	Drug utilization Drug cost Health care utilization and expenditure	PPI Rx per member per month: decreased by 92% and the expenditure decreased by 90.0% following the implementation of the PPI policy, p<0.001 for all H_2RA Rx per member per month: increased by 98% and the expenditure increased by 223.2% following the implementation of the PPI policy, p<0.001 for all Mean expenditure per member per month for anti-secretory drugs decreased by 49.9% from $3.44 to $1.74 in the post period, net expenditure decrease of $23.4 million 80.7% of prior-authorization PPI users received >=1 diagnosis for GI condition vs. 64.1% of H_2RA users, p<0.001 No difference between PPI users and H_2RA users in the utilization of total medical care expenditure using a two-part, finite mixture regression analysis	Prior authorization of PPIs had the effect of reducing use of high-cost PPIs, while encouraging use of lower costing H_2RAs without evidence of adverse medical consequences
Marshall *et al.*[27] 2002 Before-and-after	All patients eligible for BC Pharmacare >=65 years	Intent: to control the cost of H_2RAs and PPIs Intervention: reference-based pricing for H_2RA: limit reimbursement of	British Colombia Pharmacare	Drug utilization	DDD per 100,000 senior citizens for H_2RA: baseline period: 137,855 versus first 12 months after policy change period: 167,184 versus 17 months follow-up period: 156,489. The mixture of H_2RA has been	This analysis suggests that the combination of reference-based pricing for H_2RAs and special authorization for PPIs reduced government

		H_2RA to the cost of generic cimetidine, the lowest-cost H_2RA then available. Special authorization for PPIs: restricted full reimbursement for PPIs to specific clinical conditions		Drug cost Cost saving	changed in the 12 months following the reference-based pricing policy, where cimetidine represents 70% of the total H_2RA. The ratio of cimetidine has declined in the follow-up period DDD per 100,000 senior citizens for PPI: baseline period: 85,531 versus first 12 months after policy change period: 62,708 versus follow-up period: 91,821 Mean monthly H_2RAs drug ingredient cost per 100,000 senior citizens: baseline period: $117,514 versus first 12 months after policy change period $67,595 versus follow-up period: $64,834 Mean monthly PPIs drug ingredient cost per 100,000 senior citizens: baseline period: $193,023 versus first 12 months after policy change period: $143,957 versus follow-up period: $206,920 Projected cost saving (3.5 years) for H_2RA reference-based pricing policy: Total of $6 million or 1.8 million/year Projected cost saving (3.5 years) for PPI special authorization policy: $18.8 million or $5.5 million/year	pharmacy expenditures to some extent. Further analyses of these trends, such as health outcomes, patient satisfaction and utilization of non-pharmaceutical resources, would shed light on other indirect effects of reference- based pricing.
Bursy *et al.* [35] 2000	All physician and pharmacists in Newfoundland	Intent: to guide the treatment for gastrointestinal disorders and control the cost of H_2RAs, prokinetics	Newfoundland and Labrador provincial drug program	Drug cost	The program was implemented in July, 1996.	A program designed by health care professionals, approved by health care associations and implemented by the

Before-and-after		and PPIs			The combined 6-month expenditure (for H_2RAs, PPIs and prokinetics) after implementation: decreased by 36% from $3.2 million (for the 6-month period ending March 1996) to $2.0 million (for the 6-month period ending March 1997) and then increased to $2.7 million (for the 6-month period ending March 1999) which is still 16% lower than before program implementation	government to guide the treatment of upper gastrointestinal disorders has been introduced in Newfoundland and Labrador and has achieved a substantial reduction in drug expenditures. The program has been well accepted by the health care community. Research is required to determine the impact of the program on health outcomes.
Formulary-related Interventions: Compliance with Prior Authorization						
Mamdani *et al.*[28] 2001 Retrospective, open cohort	25,870 patients > 65 years who started PPI therapy and met the inclusion criteria	Intent: to curtail the rising cost of PPIs Intervention: step care approach strategy within prior authorization: use H_2RA before PPI therapy	Ontario Drug Benefit	Drug utilization	Before policy implementation: 63% received a trial of H_2RA 12 months before starting PPI therapy After policy implementation: 72% received a trial of H_2RA 12 months before starting PPI therapy; 9% gain in compliance with using H_2RA 12 months before starting PPI therapy	Modest gain (9%) in compliance with using H_2RA therapy within 12 months before starting PPI therapy was seen following the introduction of this policy.
McManus *et al.*[29] 1998 Retrospective, open cohort	4,554 new PPI users (no PPI approval in the previous 18 months)	Intent: to curtail the rising cost of PPIs Intervention: prescribing of PPI was restricted on cost-effectiveness grounds to refractory PUD or severe esophageal disease	Pharmaceutical Benefit Scheme (Australia)	Drug utilization	Despite the current restriction, 26.5% of the patients are treated directly with a PPI without being prescribed less expensive agents in the preceding 12 months	Prior authorization is not effective in encouraging stepped approach. Educational and regulatory mechanism should be used to encourage the use of PPI only in situations where they can be shown to be appropriate on clinical, safety and effectiveness grounds.

Formulary-related Interventions: Impact of Preferred Drug List						
Schneeweiss *et al.*[30] 2006 Time series	38,426 patients >=65 who filled an Rx for a restricted PPI during 6 months before restriction policy	Intent: to control the cost of PPIs Intervention: restricted PPI coverage to rabeprazole only which continues to require treatment failure with H_2RA. Other PPIs require out-of-pocket payment, unless PharmaCare approved their use	British Colombia Pharmacare	Drug utilization Health care utilization Cost saving	PPI utilization: No shift in the level of total PPI utilization (p=0.82) with slight reduction in rate of increase (-383 daily dose per 10,000 residents per month; p=0.08). Utilization of omeprazole, pantoprazole and lansoprazole decreased sharply (p<0.0001) and monthly utilization stabilized in the following 9 months. The use of rabeprazole increased sharply by 19,300 $\pm$ 2200 daily dose (p<0.0001). After completion of entire switching process (10 months), 90% of PPI initiations were for rabeprazole No increase in monthly hospitalization rate for GI hemorrhage (0.15; p=0.35); PUD complication (-0.64; p=0.16) after PPI coverage restriction compared with the time before the intervention PharmaCare saving attributed to PPI coverage restriction is approximately $2.9 million over the first 6 months of the policy	Coverage restriction of 3 leading PPIs led to a substantial utilization changes and savings, without increased non-compliance or clinical complication.

Raisch *et al.*[31] 2001 Matched-case control study	Failure group: 51 prior omeprazole users who switched back to omeprazole after lansoprazole therapy failure Success group: 51 patients matched by age, gender and duration who successfully switched from omeprazole to lansoprazole	Intent: to control the cost of PPIs Intervention: restricted PPI coverage to lansoprazole only	Southern Arizona VA Health Care System	Patient outcomes Health care costs Drug cost	Severity of heartburn: during lansoprazole trial versus returning to omeprazole: 3.2 ± 1.2 vs. 1.2 ± 0.68; p<0.001 Frequency of heartburn: during lansoprazole trial versus returning to omeprazole: 1.8 ± 1.7 vs. 0.9 ± 3.8; p=0.172 Acid regurgitation: during lansoprazole trial vs. returning to omeprazole: 3.0 ± 1.3 vs. 1.2 ± 0.6; p<0.001 Frequency of acid regurgitation: during vs. returning: 0.43 ± 1.19 vs. 0.09 ± 0.33; p<0.001 Change in the average monthly cost for GI-related health care resources: Pre-post: success group versus failure group: -25.36 ± 128.62 versus -16.87 ± 59.04; p=0.687. Pre-during: success group versus failure group: -25.36 ± 128.62 versus -21.57 ± 77.37; p=0.815 Change in the average monthly cost for drug expenditure: Pre-post: success group versus failure group: -11.57 ± 65.01 versus -53.14 ± 94.41; p=0.109. Pre-during: success group versus failure group: -11.57 ± 65.01 versus -49.18 ± 109.75; p=0.241	The formulary change had a negative impact on health outcomes among failure patients but did not significantly affect the total health care utilization cost. Identification of failure patients early in their lansoprazole trail periods could improve their health outcomes and satisfaction with medical care.

Drug Utilization Review						
Raisch *et al.*[32] 1999 Controlled clinical trial	228 prescribers having 1 or 2 patient profiles not meeting guideline (84 prescribers had >=3 patient profiles not meeting guideline)	Intent: to reduce over-prescribing of anti-ulcer drugs (H_2RAs) DUR Intervention: - cover letter describing the purpose of DUR; - educational fact sheet regarding prescribing H_2RA and other anti-ulcer agents; - patients profile with potential misprescribing - physician response form requested feedback	Mexico Medicaid program	Drug utilization	Anti-ulcer agent dispensed: Intervention versus control: 33.3% versus 17.9%; OR 2.29 (1.35, 3.87) All improvement combined: Intervention versus control: 42.9% versus 27.6%; OR = 1.98 (1.23,3.18)	The intervention significantly decreased anti-ulcer agents dispensing to patients whose prescribers were mailed the patient-specific feedback intervention.
Okano *et al.*[33] 1995 Controlled clinical trial	190 physicians inappropriately prescribed concurrent therapy of either H_2RA or omeprazole with sucralfate were randomized to intervention (97) and control (93)	Intent: to reduce over-prescribing of concurrent therapy of H_2RAs or omeprazole with sucralfate DUR Intervention: - cover letter describing the purpose of DUR; - educational fact sheet including evidence from the literature that concurrent therapy of H_2RA or omeprazole with sucralfate is not justified; - patients profile with potential misprescribing - physician response form requested feedback	Texas Medicaid Program	Drug utilization	75% in the control group still receiving concurrent therapy versus 57% in the intervention group, p=0.011	This study suggested that an intervention letter could be an appropriate way to inform physicians of potentially inappropriate prescribing and may lead to positive feedback.

Culbertson *et al.*[34] 1999 Controlled clinical trial	Physicians and pharmacists taking care of 715 patients who were prescribed unjustifiable chronic, full therapeutic anti-ulcer medication	Intent: to reduce long-term use of anti-ulcer drugs in patients without an identifiable indication DUR Intervention: - introductory letter from DUR -education leaflet for proper prescribing of antiulcer drugs - patient profile and a response form. Group 1: only physicians received intervention (138 patients) Group 2: physicians and pharmacists received intervention (329 patients) Group 3: physicians and pharmacists received intervention and pharmacists received reminder from DUR (248 patients)	Idaho Medicaid Program	Drug cost	Decrease in AUM cost: Group 1: 7.7% versus Group 2: 6.8% versus Group 3: 20.5%; P<0.05 Group 3 versus either Group 1 or Group 2	A follow-up phone call to the pharmacists in a state-wide DUR intervention enhances the effectiveness of DUR interventions under the conditions studied. Enlisting the support of community pharmacists may improve the cost savings of these interventions.

DDD=defined daily dose; DUR=drug utilization review; GI=gastrointestinal; OR=odds ratio; PPI=proton pump inhibitors; PUD=peptic ulcer disease

APPENDIX 6: Patient Interventions

Study Design	Participant	Intervention	Setting	Outcome	Results	Authors' Conclusion
Patient Education						
Krol *et al.*[36] 2004 Cluster randomized control trial	20 GPs (recruited 160 patients who had PPI >=12 weeks) were randomized to intervention and control (usual care) groups	Intent: reduce over-prescribing of PPIs Intervention (88 patients): mailed information leaflet from GPs (included updated clinical recommendation for dyspepsia and advice on how to reduce or stop PPI and when to seek help from GP) Control (72 patients): usual care	3 regions of Netherlands	Drug utilization Patient outcomes	% patients stopped prescribed PPI : control versus intervention : 4% versus 14%; RR (95% CI) = 2.93 (0.656, 23.075) % patients stopped or reduced PPI dose: Control versus intervention: 7% versus 24%; RR (95% CI) = 3.56 (1.088, 11.642) Patients increased PPI dose: Control versus intervention: 16% versus 7%; RR (95% CI) = 0.44 (0.136, 1.398) Dyspepsia symptoms severity after 12 weeks: Control versus intervention: 44% vs. 32%; RR = 0.594 (95% CI: 0.266, 1.325)	This study suggested that a simple patient-directed intervention reduced the volume of long-term prescription of PPIs in patients with dyspepsia.
Patient Counselling						
Al-Eidan *et al.*[37] 2001 Randomized control trial	76 *H. pylori* positive dyspeptic patients who received eradication therapy	Intent: increase patient compliance with *H. pylori* therapy Intervention: Hospital pharmacy counselling and follow up Control: Standard advice sheet	Antrim Area Hospital	Patient self-reported compliance	Compliance rate: Intervention versus control was: 92% vs. 23%, CI of the difference: 52.3%-84.5%; p<0.001	Structured patient counselling and follow-up can have a significant effect on *H. pylori* eradication rate and should be a routine part of therapy.
Stevens *et al.*[38] 2002 Randomized control trial	325 *H. pylori* positive adult dyspeptic patients who received eradication therapy	Intent: increase patient compliance with *H. pylori* therapy Intervention: extended counselling session with pharmacist followed by a phone call from a pharmacist during drug treatment. Control: standard usual care	Non-profit group-practice health maintenance organization (HMO)	Patient self-reported compliance at 8 days	% of patients missing >=1 doses of each component of eradication regimen: omeprazole: intervention 4.9% versus control 7.7%; Bismuth: intervention 12.2% versus control 17.2%; Metronidazole: intervention 11.0% versus control 15.0%; Tetracycline: intervention 12.2% versus control 16.6%	Long counselling by pharmacist did not affect self-reported adherence to treatment, eradication rate, or dyspepsia symptoms but increased patient satisfaction