Interventions in primary care to reduce medication related adverse events and hospital admissions: systematic review and meta-analysis

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Objective: To identify and evaluate studies of interventions in primary care aimed at reducing medication related adverse events that result in morbidity, hospital admission, and/or mortality.

Methods: Fourteen electronic databases were systematically searched for published and unpublished data. Bibliographies of retrieved papers were searched and experts and first authors contacted in an attempt to locate additional studies. There were no restrictions on language of publication. All interventions applied in primary care settings which aimed to improve patient safety by reducing adverse events resulting from medication overuse or misuse were considered. Randomised controlled trials, controlled trials, controlled before and after studies, and interrupted time series studies were eligible for inclusion. Study quality assessment and data extraction were undertaken using the Cochrane Effective Practice and Organisation of Care data collection checklist and template. Meta-analysis was performed using a random effects model.

Results: 159 studies were initially identified, of which 38 satisfied our inclusion criteria. These were categorised as follows: 17 pharmacist-led interventions (of which 15 reported hospital admissions as an outcome); eight interventions led by other primary healthcare professionals that reported preventable drug related morbidity as an outcome; and 13 complex interventions that included a component of medication review aimed at reducing falls in the elderly (the outcome being falls). Meta-analysis found that pharmacist-led interventions are effective at reducing hospital admissions (OR 0.64 [95% CI 0.43 to 0.96]), but restricting analysis to the randomised controlled trials failed to demonstrate significant benefit (OR 0.92 [95% CI 0.81 to 1.05]). Pooling the results of studies in the other categories did not demonstrate any significant effect.

Conclusions: There is relatively weak evidence to indicate that pharmacist-led mediation reviews are effective in reducing hospital admissions. There is currently no evidence for the effectiveness of other interventions which aim at reducing admissions or preventable drug related morbidity. More randomised controlled trials of primary care based pharmacist-led interventions are needed to decide whether or not this intervention is effective in reducing hospital admissions.

Medication related adverse events in primary care represent an important common cause of morbidity. A recent prospective cohort study has shown that, within 4 weeks of receiving a primary care prescription, 25% of patients experience an adverse drug event, 11% of which are judged preventable. A systematic review and meta-analysis reported that a median 7.1% (interquartile range 5.7–16.2) of hospital admissions result from drug related problems, of which 59% were considered preventable (that is, attributable to error).

Clinical errors, escalating costs of negligence claims, and continuing public debate about the prevalence of drug related morbidities have raised the profile of safety considerations in delivery of health care. Improving patient safety is therefore now a government priority in many economically developed countries including the UK and USA. Reduction of prescribing errors is of particular interest, both as a result of the disease burden posed and the likelihood of finding effective interventions.

To date, however, there has been no systematic review to help inform the development of interventions aimed at reducing the incidence of preventable drug related morbidity. Furthermore, there has been little research seeking to evaluate interventions that might lead to safer prescribing. We therefore sought systematically to identify and evaluate studies of interventions delivered in primary care settings which aimed to reduce preventable drug related morbidity.

METHODS

Searching


A further four databases were searched to identify dissertations and unpublished work including: the UK National Research Register (Issue 4, 2001), Dissertation Abstracts (1994–2001), Index to Thesis (1970–2001), and the System for Information on the Grey Literature (SIGLE). Bibliographies of key background papers and studies included in the review were also searched to identify
addition, other unpublished studies. In an attempt to identify other
relevant unpublished studies, we wrote to subject experts and
the first authors of included studies.

Search strategies, customised for each database, did not employ
any language restriction and comprised four key concepts: study design, primary care setting, medication, and error. Search strategies were designed for each concept and then combined. Full details of the search strategy used are available from the first author.

Selection
In keeping with the Cochrane EPOC guidelines, we accepted
data from randomised controlled trials and high quality
controlled clinical trials, controlled before and after studies, and interrupted time series studies. Table 1 describes the
quality criteria used to assess each study design.

Studies were eligible for inclusion if they involved health
care professionals providing community based family medical
services. Community settings included family and general practice, community pharmacies, and nursing and residential homes. Studies of interventions in clinics attached
to a hospital were excluded unless they were described as a
primary care clinic.

We included interventions applied in primary care which
aimed to reduce drug-related morbidity, hospitalisation or
death resulting from medication overdose or misuse. We did not include studies that contained data solely relating to
errors of underuse.

Two reviewers independently screened the titles and
abstracts retrieved to assess studies against the inclusion
criteria. Full text copies of all papers considered to be of
potential relevance were obtained and first authors of studies
were contacted for clarification where necessary. Any
disagreement about relevance was resolved by discussion
between the reviewers.

Validity assessment
The quality of all included studies was assessed indepen-
dently by two reviewers, using the criteria developed by the
EPOC group. Parameters including baseline measurements,
concealment of allocation, blinding of outcome assessors, and
losses to follow up were assessed.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>EPOC inclusion criteria for study design</th>
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<tbody>
<tr>
<td>Randomised controlled trial:</td>
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| Participants (or other units) definitely assigned prospectively to one or
| more alternative forms of health care using a process of random
| allocation (e.g. random number generation, coin flips). |
| Controlled clinical trial: |
| Participants (or other units) were: |
| (a) Definitely assigned prospectively to one or more alternative forms of
| health care using a quasi-random allocation method (e.g. alternation, date of
| birth, patient identifier) or |
| (b) Possibly assigned prospectively to one or more alternative forms of
| health care using a process of random or quasi-random allocation. |
| Controlled before and after study: |
| Involvement of intervention and control groups other than by random
| process and inclusion of baseline period of assessment of main outcomes. |
| There are two minimum criteria for inclusion of controlled before and
| after studies in EPOC reviews: |
| (a) Contemporaneous data collection |
| (b) Appropriate choice of control site |
| Interrupted time series: |
| A change in trend attributable to the intervention. There are two minimum
| criteria for inclusion of interrupted time series designs in EPOC reviews: |
| (a) A clearly defined point in time when the intervention occurred |
| (b) At least three data points before and three after the intervention. |

Data abstraction and synthesis
Data extraction was completed by one reviewer and checked
by a co-reviewer using a data collection template. Discrepancies were resolved by discussion between reviewers.
Studies were grouped together according to similarity of
interventions and common outcomes. STATA 8 software was
used to pool data; random effects models were used to allow
for the anticipated statistical heterogeneity between studies.
Unadjusted data from studies in which participants were
recruited in clusters were adjusted for the clustering effect
assuming an intraclass correlation coefficient (ICC) of 0.02.

RESULTS
Description of studies
159 studies were identified, of which 38 satisfied our
inclusion criteria. The main reasons for excluding studies
are summarised in the QUOROM flow diagram (fig 1). Our
searches also identified 10 systematic reviews in related
areas5-9 that provided additional references.

The characteristics of included studies are described in
table 2. Eighteen studies were set in the USA, 16 in Europe,
three in Australia, and one in New Zealand. Most studies
examined a number of patient outcomes (for example, mortality rates, morbidity assessments and quality of life
scores), while others examined data on processes of care (for
example, completed medication reviews and drug utilisation
data). Few studies, however, used patient outcomes as an a
priori defined primary end point and none were designed to
link patient outcomes causally to drug related adverse events.

Methodological quality of included studies
Comments on the important methodological features of each
study are presented in table 2. None of the studies made any
adjustment for a clustering effect in the data presented, and
none that used randomisation described this in sufficient
detail for us to comment on the adequacy of concealment.
We were, through discussion, able to classify studies according to
the main features of the intervention.

Figure 1 QUOROM flow diagram.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Study design</th>
<th>Interventions</th>
<th>Relevant outcomes</th>
<th>Baseline measurements</th>
<th>Concealment of allocation</th>
<th>Attrition bias</th>
<th>Blind outcome assessment</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkins</td>
<td>US</td>
<td>1148 patients with diabetes and/or hypertension attending primary care clinic</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions and emergency department visits</td>
<td>Done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not done</td>
<td>Hospital admissions: 0.16 patients/year v 0.17 patients/year (NS)</td>
</tr>
<tr>
<td>Cummings</td>
<td>US</td>
<td>160 ambulatory adults</td>
<td>CBA</td>
<td>Pharmacist-led</td>
<td>Hospital admissions</td>
<td>Done</td>
<td>N/A</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Hospital admissions: 28/61 v 46/68 (p = 0.06)</td>
</tr>
<tr>
<td>Thompson</td>
<td>US</td>
<td>152 elderly patients in a skilled nursing facility</td>
<td>CBA</td>
<td>Pharmacist-led</td>
<td>Hospital admissions and number of deaths</td>
<td>Done</td>
<td>N/A</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Hospital admissions: 2.9% v 11.1% (p = 0.06)</td>
</tr>
<tr>
<td>Kane</td>
<td>US</td>
<td>9738 nursing home residents</td>
<td>CBA</td>
<td>Health care professional/educational</td>
<td>Hospital admissions and emergency department visits</td>
<td>Done</td>
<td>N/A</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Deaths: 3/67 v 10/72 (p = 0.05)</td>
</tr>
<tr>
<td>Avorn</td>
<td>US</td>
<td>823 patients from six stratified pairs of nursing homes</td>
<td>RCT</td>
<td>Health care professional/educational</td>
<td>Formal assessments of mental status, memory, anxiety, depression, behaviour and sleep</td>
<td>Done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Done</td>
<td>Reduction in function in those taking antipsychotics: Mental status 38% vs 56% (NS), memory 31% v 54% (p = 0.05), anxiety 46% v 35% (NS), depression 56% vs 27% (p = 0.05), behaviour 45% v 38% (NS), sleep 35% v 25% (NS) Reduction in function in those taking benzodiazepines: Mental status 46% v 27% (NS), memory 62% v 29% (p = 0.05), anxiety 23% v 52% (p = 0.05), depression 40% v 38% (NS), behaviour 36% v 41% (NS), sleep 56% v 32% (NS) Falls with fractures: 5% v 4% (NS)</td>
</tr>
<tr>
<td>Vetter</td>
<td>UK</td>
<td>674 elderly patients of a single general practice</td>
<td>RCT</td>
<td>Intervention to reduce falls to reduce falls</td>
<td>Fall with fracture</td>
<td>Done</td>
<td>Done</td>
<td>Not done</td>
<td>Not clear</td>
<td>Population risk ratio for falls 0.63 (NS)</td>
</tr>
<tr>
<td>Zullich</td>
<td>US</td>
<td>155 elderly patients taking benzodiazepines from 10 long term care facilities</td>
<td>ITS</td>
<td>Health care professional/educational</td>
<td>Fall, hospital admission</td>
<td>N/A</td>
<td>N/A</td>
<td>Not done</td>
<td>Not clear</td>
<td>Population risk ratio for hospital admission 1.38 (NS)</td>
</tr>
<tr>
<td>Kimberlin</td>
<td>US</td>
<td>762 patients using community pharmacies</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not done</td>
<td>Odds of admission not significantly different between groups (numbers not reported)</td>
</tr>
<tr>
<td>Wilkinson</td>
<td>UK</td>
<td>61 patients with depression attending three general practices</td>
<td>RCT</td>
<td>Health care professional/educational</td>
<td>Adverse events</td>
<td>Done</td>
<td>Done</td>
<td>Not done</td>
<td>Not done</td>
<td>Adverse events/number of patients: 46/14 v 37/19 (NS)</td>
</tr>
<tr>
<td>Knowlton</td>
<td>US</td>
<td>18 pharmacies</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions</td>
<td>Not done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not done</td>
<td>Hospital admission rates per month: 3.95% v 3.93% (NS)</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Study design</td>
<td>Interventions</td>
<td>Relevant outcomes</td>
<td>Baseline measurements</td>
<td>Concealment of allocation</td>
<td>Attrition bias</td>
<td>Blind outcome assessment</td>
<td>Main results</td>
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</tr>
<tr>
<td>Tinetti²⁶</td>
<td>US</td>
<td>301 elderly primary care patients</td>
<td>RCT</td>
<td>Intervention to reduce falls</td>
<td>Falls, hospital admissions, deaths</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Done</td>
<td>Falls: 35% v 47% (p = 0.04) Hospital admissions: 21% v 24% (NS) Deaths: 5% v 3% (NS) Falls resulting in injury: 13.4% v 10.1% (NS) Falls resulting in hospital admission: 0.6% v 0.9% (NS)</td>
</tr>
<tr>
<td>Wagner²³</td>
<td>US</td>
<td>1559 elderly primary care patients</td>
<td>RCT</td>
<td>Intervention to reduce falls</td>
<td>Falls resulting in injury, falls resulting in hospital admission</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Not done</td>
<td>Admissions with physical problems: 14.2% v 16.1% (NS)</td>
</tr>
<tr>
<td>Kendrick²⁴</td>
<td>UK</td>
<td>440 patients with long term mental health problems from 16 general practices</td>
<td>RCT</td>
<td>Health care professional/educational</td>
<td>Admissions</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Not clear</td>
<td>Falls resulting in injury: 13.4% v 10.1% (NS) Falls resulting in hospital admission: 0.6% v 0.9% (NS)</td>
</tr>
<tr>
<td>Hanlon²⁵</td>
<td>US</td>
<td>208 primary care patients on five or more regular medications</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Adverse drug events</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Done</td>
<td>Adverse drug events: 30.2% v 40.0% (NS)</td>
</tr>
<tr>
<td>Carter²⁶</td>
<td>Australia</td>
<td>658 elderly primary care patients</td>
<td>RCT</td>
<td>Intervention to reduce falls</td>
<td>Fall resulting in injury</td>
<td>Done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not clear</td>
<td>Falls resulting in injury: 10.4% v 14.3% (NS) Episodes of hypoglycaemia/patient/year: 0.014 v 0.0 (NS)</td>
</tr>
<tr>
<td>DeSonnerville²⁶</td>
<td>Netherlands</td>
<td>505 primary care patients with type II diabetes</td>
<td>CBA</td>
<td>Health care professional/educational</td>
<td>Episodes of hypoglycaemia</td>
<td>Not done</td>
<td>N/A</td>
<td>Not done</td>
<td>Not clear</td>
<td>Incidence rate of injurious falls (per 100 person years): 13.7 v 19.9 (NS) Mortality rate (per 100 person years): 23.0 v 17.3 (NS) Hospital admission rate: 6% v 6% (NS) Emergency department visits: 2% v 6% (NS) Severe low blood glucose events (increase from baseline): 3.1% v 2.9% (NS)</td>
</tr>
<tr>
<td>Ray²⁶</td>
<td>US</td>
<td>499 residents of seven matched pairs of nursing homes</td>
<td>RCT</td>
<td>Intervention to reduce falls</td>
<td>Falls, mortality</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td></td>
</tr>
<tr>
<td>Aubert²⁷</td>
<td>US</td>
<td>138 primary care patients with diabetes</td>
<td>RCT</td>
<td>Health care professional/educational</td>
<td>Hospital admissions, emergency department visits, severe low blood glucose events</td>
<td>Done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not clear</td>
<td></td>
</tr>
<tr>
<td>Lai²⁷</td>
<td>US</td>
<td>874 primary care patients</td>
<td>CBA</td>
<td>Pharmacist-led</td>
<td>Hospital admissions, emergency department visits</td>
<td>Done</td>
<td>N/A</td>
<td>Done</td>
<td>Done</td>
<td>Mean number of hospital admissions: 0.1 v 0.2 (NS) Mean number of emergency room visits: 0.06 v 0.05 (NS)</td>
</tr>
<tr>
<td>McCums²⁷</td>
<td>US</td>
<td>6000 patients using nine Kaiser Permanente pharmacies</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Done</td>
<td>Kaiser Permanente model associated with 3.3% lower likelihood of hospital admission Falls per person years: 0.52 v 1.16 (p = 0.05)</td>
</tr>
<tr>
<td>Campbell²⁷</td>
<td>NZ</td>
<td>93 elderly primary care patients using hypnotics</td>
<td>RCT</td>
<td>Intervention to reduce falls</td>
<td>Falls</td>
<td>Done</td>
<td>Done</td>
<td>Not done</td>
<td>Done</td>
<td>Falls in last 12 months: 43.3% v 35.6% (NS)</td>
</tr>
<tr>
<td>Coleman²⁷</td>
<td>US</td>
<td>169 elderly primary care patients</td>
<td>RCT</td>
<td>Health care professional/educational</td>
<td>Falls, hospital admissions, emergency department visits</td>
<td>Done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not clear</td>
<td>Mean hospital admissions/ year: 0.58 v 0.59 (NS) Mean emergency department visits/year: 0.23 v 0.27 (NS) Adverse drug reactions: 8.3% v 6.7% (NS) Hospital admissions: 6.0% v 2.7% (NS) Mortality rate: 3.6% v 3.8% (NS)</td>
</tr>
<tr>
<td>Bond²⁷</td>
<td>UK</td>
<td>3074 primary care patients</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Adverse drug reactions, hospital admissions, mortality</td>
<td>Not done</td>
<td>Done</td>
<td>Not clear</td>
<td>Not clear</td>
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</tbody>
</table>

Table 2 Continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Study design</th>
<th>Interventions</th>
<th>Relevant outcomes</th>
<th>Baseline measurements</th>
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<th>Attrition bias</th>
<th>Blind outcome assessment</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furniss</td>
<td>UK</td>
<td>330 residents of seven matched pairs of nursing homes</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Formal assessments of cognitive function, depression and behaviour and deaths</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Not clear</td>
<td>Mean difference in cognitive function score: 1.6 in favour of control (NS)</td>
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<td>Mean difference in depression score: −0.75 in favour of intervention (NS)</td>
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<td>Mean difference in behaviour score: −2.2 in favour of control (p = 0.02)</td>
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<td>Deaths: 4 v 14 (p = 0.03)</td>
</tr>
<tr>
<td>Kempton</td>
<td>Australia</td>
<td>3600 elderly primary care patients</td>
<td>CBA</td>
<td>Intervention to</td>
<td>Falls leading to hospital admission</td>
<td>Done</td>
<td>N/A</td>
<td>Not done</td>
<td>Done</td>
<td>Fall related hospital admission rate ratio: 0.8 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Malone</td>
<td>US</td>
<td>1054 primary care patients</td>
<td>RCT</td>
<td>reduce falls</td>
<td>Hospital admissions</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Mean increase in hospital admission rates over study period: 0.13 v 0.19 (NS)</td>
</tr>
<tr>
<td>McMurdo</td>
<td>UK</td>
<td>133 elderly patients from nine residential homes</td>
<td>RCT</td>
<td>Intervention to</td>
<td>Falls</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not done</td>
<td>Done</td>
<td>Falls per person per week: 0.06 v 0.07 (NS)</td>
</tr>
<tr>
<td>Piette</td>
<td>US</td>
<td>280 primary care patients with diabetes</td>
<td>RCT</td>
<td>reduce falls</td>
<td>Hospital admissions, emergency department visits</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Hospital admissions: 24% v 23% (NS)</td>
</tr>
<tr>
<td>Poulsstrup</td>
<td>Denmark</td>
<td>26221 elderly primary care patients</td>
<td>CBA</td>
<td>Intervention to</td>
<td>Fractures</td>
<td>Done</td>
<td>N/A</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Emergency department visits: 48% v 40% (NS)</td>
</tr>
<tr>
<td>Van Haastregt</td>
<td>Netherlands</td>
<td>316 elderly primary care patients</td>
<td>RCT</td>
<td>reduce falls</td>
<td>Falls</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Not clear</td>
<td>Reduction in fractures in intervention group compared to control: 1.4% (NS)</td>
</tr>
<tr>
<td>Bernsten</td>
<td>Multi-centre (Europe)</td>
<td>2454 elderly primary care patients</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions</td>
<td>Not done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not clear</td>
<td>Injuries falls: 28% v 22% (NS)</td>
</tr>
<tr>
<td>Henborg</td>
<td>Denmark</td>
<td>500 patients obtaining asthma medication from community pharmacists</td>
<td>CBA</td>
<td>Pharmacist-led</td>
<td>Hospital admissions, emergency department visits</td>
<td>Done</td>
<td>N/A</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Falls resulting in medical care: 18% v 12% (NS)</td>
</tr>
<tr>
<td>Kraska</td>
<td>UK</td>
<td>332 elderly primary care patients from six general practices</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions, pharmaceutical care issues</td>
<td>Done</td>
<td>Not clear</td>
<td>Done</td>
<td>Not clear</td>
<td>Hospital admissions: 35.6% v 40.4% (NS)</td>
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<td>Hospital admissions per patient: 0.019 v 0.058 (not tested)</td>
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<td>Emergency department visits: 12 v 13 (not tested)</td>
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<td>Potential or suspected adverse drug reactions resolved: 84.3% v 57.8% (p = 0.0001)</td>
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<td></td>
<td>Median number of hospital admissions since diagnosis: 1 v 1 (NS)</td>
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<td></td>
<td>Proportion of participants with an episode of severe hypoglycaemia since diagnosis: 4% v 4% (NS)</td>
</tr>
<tr>
<td>Olivarius</td>
<td>Denmark</td>
<td>1316 primary care patients with diabetes</td>
<td>RCT</td>
<td>Health care professional/educational</td>
<td>Hospital admissions, severe hypoglycaemic episodes</td>
<td>Done</td>
<td>Not clear</td>
<td>Not done</td>
<td>Not done</td>
<td>Difference in mean percentage hospital admission rate pre/post study: 1.3 v 0.9 (NS)</td>
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<td></td>
<td></td>
<td></td>
<td>Adjusted mortality rates per 100 person years: 27.2 v 31.7 (NS)</td>
</tr>
<tr>
<td>Roberts</td>
<td>Australia</td>
<td>3230 residents of 55 nursing homes</td>
<td>RCT</td>
<td>Pharmacist-led</td>
<td>Hospital admissions, mortality</td>
<td>Not clear</td>
<td>Done</td>
<td>Not done</td>
<td>Not clear</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacist-led interventions

Seventeen studies included a medication review component in the intervention arm that was performed by a pharmacist.20–36 Thirteen of these studies20–32 included hospital admission data in a form that allowed the calculation of an odds ratio to summarise the findings; the remaining four did not, however, present data in this form and were excluded from the meta-analysis.33–36 We found significant heterogeneity between studies ($\chi^2 = 126.71, df = 12, p < 0.001$). Random effects meta-analysis showed a significant positive effect of these interventions on hospital admissions (OR 0.64 (95% CI 0.43 to 0.96), fig 2).

A sensitivity analysis restricting the included studies to randomised controlled trials removed the heterogeneity ($\chi^2 = 5.62, df = 7, p = 0.58$) but no longer found a positive effect (OR 0.92 (95% CI 0.81 to 1.05), fig 3). A sensitivity analysis using an ICC of 0.01 when adjusting the results of clustered studies did not affect the above results.

A funnel plot was prepared and this suggested the presence of publication bias (fig 4). This was supported by Begg’s rank correlation p value for bias of 0.04, but not by Egger’s weighted regression method (p value for bias 0.88).

Interventions led by other primary healthcare professionals

Eight studies reported interventions led by other primary healthcare professionals. Nurses used protocols to manage diabetes, heart failure, depression, and asthma in six of these37–42 and the remaining two involved education programmes for primary care physicians.43 44 Four of the nurse

| Study | Participants | Main results | Relevant outcomes
|-------|--------------|--------------|----------------------|
| Zermansky 32 | UK 1188 elderly primary care patients | Proportion admitted to hospital: 19% v 17% (NS) | -
| Jensen 47 | Sweden 439 elderly patients from nine residential care facilities | Falls: 44% v 56% (p = 0.05) | -
| Bouvy 22 | Netherlands 152 patients with heart failure | Hospital admissions: 32/74 v 42/78 (p = 0.4) | -
| Bemsten 2001 | - | - | -
| Roberts 2001 | - | - | -
| Zermansky 2001 | - | - | -
| Bouvy 2003 | - | - | -

Overall (95% CI) 0.91 (0.80, 1.04)

Figure 2 Forest plot of pharmacist-led intervention studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkins 1979</td>
<td>0.92 (0.49, 1.71)</td>
<td>7.8</td>
</tr>
<tr>
<td>Cummings 1984</td>
<td>0.41 (0.20, 0.83)</td>
<td>7.4</td>
</tr>
<tr>
<td>Thompson 1984</td>
<td>0.23 (0.05, 1.20)</td>
<td>3.8</td>
</tr>
<tr>
<td>Lee 1998</td>
<td>0.71 (0.50, 1.02)</td>
<td>9.0</td>
</tr>
<tr>
<td>McCornick 1998</td>
<td>0.18 (0.13, 0.23)</td>
<td>9.3</td>
</tr>
<tr>
<td>Bond 2000</td>
<td>1.09 (0.56, 2.10)</td>
<td>7.7</td>
</tr>
<tr>
<td>Malone 2000</td>
<td>1.01 (0.77, 1.31)</td>
<td>9.3</td>
</tr>
<tr>
<td>Bemsten 2001</td>
<td>0.81 (0.64, 1.04)</td>
<td>9.4</td>
</tr>
<tr>
<td>Herberg 2001</td>
<td>0.31 (0.08, 1.18)</td>
<td>4.6</td>
</tr>
<tr>
<td>Kriska 2001</td>
<td>0.72 (0.24, 2.13)</td>
<td>5.6</td>
</tr>
<tr>
<td>Roberts 2001</td>
<td>0.83 (0.59, 1.17)</td>
<td>9.1</td>
</tr>
<tr>
<td>Zermansky 2001</td>
<td>1.17 (0.86, 1.58)</td>
<td>9.2</td>
</tr>
<tr>
<td>Bouvy 2003</td>
<td>0.65 (0.34, 1.24)</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Overall (95% CI) 0.64 (0.43, 0.96)

Figure 3 Forest plot of pharmacist-led intervention randomised controlled trials.
led interventions reported the incidence of adverse drug events which satisfied our inclusion criteria and allowed the calculation of an odds ratio. These were combined in a meta-analysis but no significant effect was found (OR 1.05 (95% CI 0.57 to 1.94)); there was no significant heterogeneity ($\chi^2 = 1.95, \text{df} = 3, p = 0.58$).

**Complex interventions to reduce falls in the elderly**
Thirteen studies described interventions with a number of components that aimed to reduce the incidence of falls in the elderly. To be included in this review, one of the components had to be a medication review undertaken by a primary healthcare professional, the presumption being made that any reduction in the incidence of falls was at least in part a reduction in drug related morbidity. Nine of the studies presented data in a way which allowed the calculation of an odds ratio and these were pooled in a meta-analysis. No significant effect was demonstrated (OR 0.91 (95% CI 0.68 to 1.21)) and there was no significant heterogeneity ($\chi^2 = 14.59, \text{df} = 8, p = 0.07$).

**Studies not included in the meta-analysis**
Table 2 presents the key features of all studies that satisfied our inclusion criteria, including those that could not be included in the meta-analysis.

**DISCUSSION**
We have shown that there is some evidence that pharmacist-led interventions incorporating a medication review component are effective in reducing hospital admissions. However, when restricted to randomised controlled trials (which are less susceptible to bias than controlled before–after studies and interrupted time series analysis), the pooled odds ratio became non-significant. We found no evidence of any significant effect of primary care medication reviews aimed at reducing falls in the elderly on the primary outcome, or of nurse-led chronic disease management programmes in reducing drug related morbidity.

**Strengths of review**
We searched a very broad range of published and unpublished sources of information and coupled this with rigorous quality assessment and appraisal of studies. We deliberately narrowed the focus of the review to those studies which attempted to address errors resulting in actual patient harm as opposed to process outcomes only.

**Limitations of review**
Publication bias is an important potential source of bias in systematic reviews. Considerable effort was therefore made to locate unpublished studies. However, a small number may have been omitted from the review, as is suggested by the borderline assessment of evidence of publication bias.

The setting for this review was primary care and our findings are unlikely to be applicable to all healthcare systems. For example, studies undertaken in ambulatory patients based in general medical clinics in the USA met our inclusion criteria but their relevance to the primary care systems of Western Europe can be questioned. We deliberately chose “bottom line” patient outcome measures as the focus of this review in order to maximise its usefulness to healthcare policy makers and service commissioners. Some studies that were included showed significant improvements in upstream outcomes and their value in this respect is not acknowledged by our criteria.

**Implications for health policy, clinical care, and future research**
This systematic review has shown a paucity of high quality evaluations of interventions aimed specifically at preventing medication related adverse events in primary care. The clinical implications of these studies are therefore at present limited.

Given the high disease burden associated with prescribing errors in primary care, there is a pressing need for further studies in this field. In developing future interventions, researchers should focus on patient safety and should endeavour to select outcome measures that allow for ready comparisons with other studies. For example, criteria exist to classify hospital admissions as “medication related”; yet none of the studies identified in the review used these criteria. Future studies need to be powered adequately to be able to detect clinically important reductions in prescribing errors, and they should consider building in a cost-effectiveness analysis.

In the USA and several other countries, the use of information technology to support medication safety is well developed. We were therefore surprised not to find more evaluations of the role of computers in improving patient safety in primary care, given the benefits that have been shown to accrue from its use in hospital facilities. There is therefore a need to assess the effectiveness of these system interventions in preventing medication related adverse events, and to evaluate future developments in these systems.

**CONCLUSIONS**
There is some evidence that pharmacist-led interventions aimed at optimising medication regimens are effective in

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**Key messages**

- Medication related adverse events originating in primary care are an important cause of morbidity and mortality.
- There has been limited formal evaluation, using randomised controlled study designs, of interventions aiming to reduce medication related adverse events in primary care.
- Relatively weak evidence was found that pharmacist-led medication reviews are effective in reducing hospital admissions.
- There was no evidence for the effectiveness of other interventions aimed at reducing admissions or preventable drug related morbidity.
- More work is needed in the development and rigorous evaluation of interventions in this field.
reducing hospital admissions from primary care. Larger, rigorously designed intervention studies are now needed to evaluate whether the significantly increased body of understanding of the causes of medication errors can be translated into meaningful improvements in patient outcomes.

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Funding: BUPA Foundation.

Competing interests: None declared.

AA, AS and BH conceived, designed and secured funding for the study with SR assisting in study design. SR and LS undertook the literature searches and selected studies for inclusion and extracted and analysed data under the supervision of AS. All authors contributed to the analysis of the results with SR performing the meta-analysis. SR and LS led the drafting of this report, a process to which all the other authors contributed. AA and AS are guarantors.

**REFERENCES**


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The seminar is for editors, authors, and all those interested in increasing the standard of publication ethics. The seminar will include:

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Interventions in primary care to reduce medication related adverse events and hospital admissions: systematic review and meta-analysis
S Royal, L Smeaton, A J Avery, B Hurwitz and A Sheikh

*Qual Saf Health Care* 2006 15: 23-31
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