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Impact of issuing longer- versus shorter-duration prescriptions:

a systematic review

Abstract

Background
Long-term conditions place a substantial burden on primary care services, with drug therapy being a core aspect of clinical management. However, the ideal frequency for issuing repeat prescriptions for these medications is unknown.

Aim
To examine the impact of longer-duration (2–4 months) versus shorter-duration (28-day) prescriptions.

Design and setting
Systematic review of primary care studies.

Method
Scientific and grey literature databases were searched from inception until 21 October 2015. Eligible studies were randomised controlled trials and observational studies that examined longer prescriptions (2–4 months) compared with shorter prescriptions (28 days) in patients with stable, chronic conditions being treated in primary care. Outcomes of interest were: health outcomes, adverse events, medication adherence, medication wastage, professional administration time, pharmacists' time and/or costs, patient experience, and patient out-of-pocket costs.

Results
From a search total of 24 876 records across all databases, 13 studies were eligible for review. Evidence of moderate quality from nine studies suggested that longer prescriptions are associated with increased medication adherence. Evidence from six studies suggested that longer prescriptions may increase medication waste, but results were not always statistically significant and were of very low quality. No eligible studies were identified that measured any of the other outcomes of interest, including health outcomes and adverse events.

Conclusion
There is insufficient evidence relating to the overall impact of differing prescription lengths on clinical and health service outcomes, although studies do suggest medication adherence may improve with longer prescriptions. UK recommendations to provide shorter prescriptions are not substantiated by the current evidence base.

Keywords
medication adherence; medication waste; prescription length; primary care; repeat prescribing; stable, chronic conditions; systematic review.

INTRODUCTION

Long-term conditions place a substantial burden on health services, particularly in the primary care setting where they are commonly managed.[1] For those patients with relatively stable conditions, drug therapy is usually managed using repeat prescriptions, which allow patients to request an additional prescription for a long-term medication without requiring a further consultation with a clinician.

The UK Department of Health advises that the frequency of repeat prescriptions should *'... balance patient convenience with clinical appropriateness, cost-effectiveness and patient safety.'*, but does not specify a recommended time period.[2] However, local guidance from many health service commissioners, as well as the UK's Pharmaceutical Services Negotiating Committee, encourages GPs to issue shorter prescriptions, typically 28 days in length.[3–6] This guidance is based on non-systematic review evidence of reductions in medicines waste and consequent cost savings.[7,8] One study has reported that shorter prescription lengths may benefit patients by providing better signalling to GPs for treatment discontinuations due to adverse events.[9] However, other work does not support the use of shorter prescriptions, with some studies suggesting they may increase health service costs by:

- increasing GP administrative workload and pharmacy dispensing costs;[10,11]
- increasing patient-incurred costs through more frequent trips to the pharmacist;[11] and
- adversely affecting medication adherence and patient satisfaction.[12–14]

Prescription lengths also vary considerably between, and within, countries. For example, the duration of thyroid prescriptions has been found to range from 28 days in France to 6 months in Australia,[15] and prescription durations across all therapeutic areas in the Canadian province of Quebec were approximately half the length of those in the rest of Canada.[16]

Given the disparity in evidence and practice, a systematic review was undertaken to examine the impact of primary care physicians issuing longer- (2–4 months) versus shorter- (28-day) duration prescriptions in patients with stable chronic conditions. The results of a cost analysis and decision analysis model are reported separately.[17,18]

METHOD

A systematic review was conducted following a standardised methodology and consistent with PRISMA guidance.[19,20] The protocol is published on the PROSPERO database (registration number CRD42015027042).

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How this fits in

Local guidance from many health service commissioners, as well as the UK's Pharmaceutical Services Negotiating Committee, encourages GPs to issue shorter-duration prescriptions, typically 28 days in length. This guidance is based on non-systematic review evidence, which was not substantiated by this systematic review. Longer prescription lengths for people with stable, chronic conditions could be potentially important to GPs by reducing their workload. It also has the potential to have a positive impact for patients, by improving adherence and thus medication effectiveness, and reducing time, cost, and inconvenience of frequently collecting prescriptions.

The protocol and choice of outcomes was drawn up in consultation with lay patient representatives.[21]

Data sources

The authors searched 12 major scientific and grey literature databases for entries dated from inception until 21 October 2015, with no country or language restrictions. Search terms included combinations of the terms 'prescription', 'length', and 'duration', as well as specific time periods. Backward and forward citation searches were conducted. Details of the databases searched and the full search terms are available from the authors.

An updated search of PubMed in July 2017 identified no further articles.

Eligibility criteria

To be eligible, studies had to be randomised controlled trials (RCTs) or observational studies that compared longer-duration prescriptions (2–4 months) with 28-day prescriptions (or those lasting around 1 month) in specific patients. Participants had chronic conditions (such as hypothyroidism, diabetes, cardiovascular disease, and depression) that were relatively stable. Studies were restricted to primary care settings in middle- and high-income countries; those conducted exclusively in secondary or tertiary care settings were excluded. The studies had to report on one or more of the following outcomes:

- health outcomes;
- adverse events;
- medication adherence;
- medication wastage;
- professional administration time;
- pharmacists' time and/or costs;
- patient experience; and
- patient out-of-pocket costs.

Data extraction and synthesis

Two independent reviewers screened titles and abstracts identified by the searches, and screened full papers of potentially relevant studies. A third reviewer resolved disagreements. Relevant studies' characteristics were independently extracted by two reviewers, with a third reviewer checking and comparing the data extraction. An attempt was made to contact study authors for data missing from the identified papers.

Studies were analysed by outcome and by therapeutic area (for example, lipid-lowering medication or diabetic medication) as most of the included studies reported their results in this way. Studies varied in the nature and detail of the drug classification used; where necessary, medication categories (for example, statins) were grouped into the corresponding therapeutic area (for example, lipid lowering) to improve consistency across studies.

Within each study, effect sizes were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes, and the mean difference (MD) with 95% CIs for continuous outcomes. Where appropriate, standard deviations (SDs) were imputed based on *P*-values.[19] Forest plots were generated using RevMan version 5.3. Meta-analyses were not conducted due to clinical heterogeneity between studies. The review was not designed to consider differences between therapeutic areas.

Risk of bias and quality of evidence

As only observational studies were identified, the authors assessed risk of bias using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, although additional sources of bias (for example, sample size) were also considered.[22] Risk of bias was assessed by two reviewers independently, with discrepancies resolved through discussion.

The GRADE criteria were used to assess the quality of evidence for each outcome.[23]

RESULTS

The initial search identified 24 876 records across all databases. After duplicate removal, screening of titles and abstracts,

and searching citations, 53 references were considered for full-text evaluation. Thirteen references representing 13 studies met the inclusion criteria; four were only reported in abstract form but were included because they presented clear outcome data.[24–27] Study characteristics are available from the authors.

All 13 studies were conducted in the US; they comprised nine retrospective cohorts,[24–32] three cross-sectional analyses,[33–35] and one retrospective before-and-after study.[36] Three provided details of the healthcare setting, which included:

- a primary care clinic;[28]
- patients seen in primary care, mental health clinic, inpatient services, and primary care mental health;[30] and
- an internal medicine practice.[33]

Other studies did not explicitly report being conducted in primary care although the authors considered them unlikely to have been conducted exclusively in secondary or tertiary care settings (for example, because they included claims data from community pharmacies).

When reported, study populations included patients new to treatment,[25–27,30] patients receiving ongoing care,[28,29,31] or both.[35] Comparisons between prescription lengths were assessed for various therapeutic medication groups, including, most commonly, medications to lower lipids, and those for hypertension, diabetes, and depression.[25–30,32–36] Most studies compared a 30-day medication supply with that for a longer period, as follows:

- a 90-day supply;[24–26,29,32,35]
- a 60-day supply;[28] or
- both 31-to-89-day or >90-day supplies.[27,31,34]

Other studies compared 100-day versus 34-day supplies,[36] <90-day supplies versus a 90-day supply,[30] and a range of prescription lengths ≤90 days.[33]

No eligible studies were identified that measured health outcomes or adverse events. Only one retrospective cohort study measured a risk factor for a health outcome: serum cholesterol was lower in the 60-day prescription group compared with its 30-day counterpart at 3 years (mean 4.8 mmol/l [SD 1.2 mmol/l] versus 5.0 mmol/l [SD 1.4 mmol/l] respectively; $P = 0.003$).[28]

No eligible studies reported professional administration time, pharmacists' time and/or costs, patient experience, or out-of-pocket costs other than prescription costs. The most common reported outcomes were medication adherence and wastage.

Medication adherence

Nine studies reported medication adherence, indirectly estimated using pharmacy claims refill data (available from the authors).[25,26,28,30–34,36] Commonly used measures of adherence were the:

- proportion of days covered (PDC) — number of days in a given time period 'covered' by prescription claims for a particular drug, divided by the number of days in the time period; or
- medication possession ratio (MPR) — total number of days supplied for all refills of a particular drug in a given time period, divided by the number of days in the time period.

The review authors elected not to separate these measures in their analyses (although PDC has been found to provide a more conservative estimate of adherence than the MPR).[37] PDC and MPR were expressed either as the proportion of patients achieving a particular threshold (generally ≥80%) or the average (mean) value.

Consistent findings were found across all studies. Three cohort studies found that prescription lengths of <90 days were associated with poorer adherence across a range of therapeutic areas (including lipid-lowering therapy, antihypertensives, diabetes medication, and antidepressants) based on adherence using a <80% threshold (OR range: 0.21–0.65, Table 1).[25,28,30] A

Table 1. Patients with ≥80% medication adherence, by prescription length

Study or sub-group	30 days		90 days		Odds ratio, M–H, fixed (95% CI)
	Events[a]	Total, *N*	Events[a]	Total, *N*	
Lipid-lowering medication					
Batal *et al* (2007)[28]	303	833	1307	2553	0.55 (0.46 to 0.64)
Hermes *et al* (2010)[25]	20 820	31 982	5414	7219	0.62 (0.59 to 0.66)
Antihypertensive medication					
Hermes *et al* (2010)[25]	41 064	53 192	7928	9405	0.63 (0.59 to 0.67)
Diabetic medication					
Hermes *et al* (2010)[25]	6094	8844	1221	1578	0.65 (0.57 to 0.74)
Antidepressant medication					
Pfeiffer *et al* (2012)[30]	123 993	296 634	67 077	87 000	0.21 (0.21 to 0.22)

[a]*Events = refers to the number of patients with ≥80% medication adherence. M–H = Mantel–Haenszel.* N *= the total number of participants evaluated in each arm of the study.*

Table 2. Mean medication adherence, by prescription length

Study or sub-group	30 days Mean	30 days SD	30 days Total, *N*	90 days Mean	90 days SD	90 days Total, *N*	Mean difference IV, fixed (95% CI)
Lipid-lowering medication							
Taitel *et al* (2012)[32]	0.671	0.278	12 136	0.819	0.194	2162	–0.15 (–0.16 to –0.14)
Antihypertensive medication							
Taitel *et al* (2012)[32]	0.774	0.292	33 009	0.910	0.174	5835	–0.14 (–0.14 to –0.13)
Diabetic medication							
Taitel *et al* (2012)[32]	0.755	0.289	11 842	0.875	0.19	1511	–0.12 (–0.13 to –0.11)
Antidepressant medication							
Taitel *et al* (2012)[32]	0.611	0.295	7017	0.817	0.196	266	–0.21 (–0.23 to –0.18)
Digoxin							
Steiner *et al* (1993)[31]	0.897	0.349	27	1.130	0.214	46	–0.23 (–0.38 to –0.09)
Mixed medications							
Jiang *et al* (2007)[26]	0.399	2.868	955	0.703	2.868	730	–0.30 (–0.58 to –0.03)

IV = inverse variance. N *= the total number of participants evaluated in each arm of the study. SD = standard deviation.*

further three cohort studies found similar associations based on mean reduction in adherence (mean decrease range: 0.12–0.30, Table 2).[26,31,32]

A controlled before-and-after study[36] found that the shortening of antihypertensive, diabetic, and lipid-lowering prescription length from 100 days to 34 days was statistically significantly associated ($P<0.01$) with a 5.3–13.2% reduction in time periods where PDC was ≥80%, and a mean decrease in PDC of 0.034–0.080. No differences were observed for seizure medication or antipsychotics (data not shown).[36]

In a further cross-sectional study, prescriptions of >90 days were associated with greater medication adherence (PDC >80%) compared with prescriptions of ≤30 days for drugs affecting the renin-angiotensin system, statins, and oral diabetes medications (relative risk 1.61, $P<0.001$ for each).[34] A second cross-sectional study found each 30-day increment in prescription length (up to a maximum of 90 days) was associated with a 5.7% increase in mean adherence ($P<0.0001$) to diabetes, antihypertensive, and lipid-lowering medications (data not shown).[33]

Medication wastage

Medication wastage was reported in six of the included studies (available from the authors).[24,26,27,29,32,35] All measures of wastage were indirect, estimated based on pharmacy claims refill data. The majority of these studies defined wastage in a similar manner, such as a:

'... switch in medication within the same therapeutic class or to the same medication but different strength occurring before the expected refill date.'[29]

One study also included discontinuation within its definition.[24]

Waste was expressed as:

- percentage of days' supply wasted;
- mean number of days' supply wasted; or
- percentage of patients with wasted medication.

Two retrospective cohort studies assessed percentage of days' supply wasted and found only small differences (≤1.5%) between different prescription lengths.[24,27] However, neither study reported raw data or statistical comparisons, and additional information could not be obtained from the authors.

Three studies evaluated the percentage of patients who wasted medication.[27,32,35] ORs could be calculated for one retrospective cohort and one cross-sectional study.[32,35] In general, there was a non-statistically significant trend for longer prescriptions (90 days versus 30 days) to be associated with higher proportions of patients with wasted medication; this was statistically significant for lipid-lowering drugs in the study by Taitel *et al* only (OR 0.84, 95% CI = 0.72 to 0.98, Table 3).[32] A third cohort study reported varying patterns across therapeutic areas, but with no statistical analysis and insufficient data to calculate effect sizes.[27]

Four studies reported the mean number of days' supply wasted over 1 year.[26,29,32,35] Effect sizes could not be calculated for one study in which it was unclear whether days wasted was standardised between the

Table 3. Patients with wasted medication, by prescription length

Study or sub-group	30 days Events[a]	30 days Total, *N*	90 days Events[a]	90 days Total, *N*	Odds ratio M–H, fixed (95% CI)
Lipid-lowering medication					
Taitel *et al* (2012)[32]	1014	12 136	212	2162	0.84 (0.72 to 0.98)
Walton *et al* (2001)[35]	1909	13 355	545	3635	0.95 (0.85 to 1.05)
Antihypertensive medication					
Taitel *et al* (2012)[32]	3928	33 009	712	5835	0.97 (0.89 to 1.06)
Diabetic medication					
Taitel *et al* (2012)[32]	1255	11 842	175	1511	0.90 (0.76 to 1.07)
Antidepressant medication					
Taitel *et al* (2012)[32]	975	7017	39	266	0.94 (0.66 to 1.33)

[a]*Events = refers to the number of patients with ≥80% medication adherence. M–H = Mantel–Haenszel.* N *= the total number of participants evaluated in each arm of the study.*

two prescription groups.[35] The remaining studies found evidence that shorter (30-day versus 90-day) prescriptions were statistically significantly associated with a mean reduction in waste days. Across a range of therapeutic areas, Taitel *et al* reported a reduction of 3.51–6.92 days over a 1-year study period (Table 4),[32] and Murphy *et al* found a reduction of 0.03–0.13 days over a 30-day period (Table 5);[29] Jiang *et al* found a mean reduction of 0.10 days averaged for all therapeutic areas (Table 5).[26]

Risk of bias and quality of evidence

Lack of methodological detail prevented assessment of risk of bias for the four studies presented as abstracts.[24–27] One study was classified as having a serious risk of bias due to its small sample size[31] and another was similarly classified because a cut-off point of 84 days was used, with no justification provided for the decision.[32] The remaining seven studies were considered to have a moderate risk of bias (further details available from the authors).[28–30,33–36] In nine studies, the authors did not explicitly report taking measures to control for selection bias.[11,28–35]

In terms of GRADE assessment, the evidence was determined to be of very low quality for all outcomes except adherence; the evidence relating to adherence was considered to be of moderate quality.

DISCUSSION

Summary

This is the first systematic review of evidence comparing the impact of shorter and longer prescriptions on clinical and health service outcomes. The authors found some evidence from six studies that longer prescriptions are associated with increased medication waste, but the results were not always statistically significant and are of very low quality. Evidence of moderate quality was found that suggested that longer prescriptions are associated with better adherence.

If medication adherence is positively correlated with health outcomes, as seems to be suggested by the wider literature,[38,39] there may be benefits to increasing the length of repeat prescriptions for patients with chronic conditions. However, the authors found no direct evidence assessing the association between different prescription lengths and health outcomes (including adverse events). Furthermore, although it is important to minimise medication waste, this needs to be balanced against the needs of patients and clinicians' workloads; however, the authors found no direct evidence comparing different prescription lengths with differences in health professionals' administrative time, pharmacists' time, or patient experience.

Strengths and limitations

Although the authors followed rigorous

Table 4. Mean days with wasted medication over the study period, by prescription length

Study or sub-group	30 days Mean	30 days SD	30 days Total, *N*	90 days Mean	90 days SD	90 days Total, *N*	Mean difference IV, fixed (95% CI)
Lipid-lowering medication							
Taitel *et al* (2012)[32]	2.251	10.673	12 136	5.757	22.205	2162	–3.51 (–4.46 to –2.55)
Antihypertensive medication							
Taitel *et al* (2012)[32]	4.037	16.236	33 009	9.211	30.284	5835	–5.17 (–5.97 to –4.38)
Diabetic medication							
Taitel *et al* (2012)[32]	3.289	13.441	11 842	7.899	25.385	1511	–4.61 (–5.91 to –3.31)
Antidepressant medication							
Taitel *et al* (2012)[32]	3.501	12.941	7017	10.425	32.463	266	–6.92 (–10.84 to –3.01)

IV = inverse variance. N *= the total number of participants evaluated in each arm of the study. SD = standard deviation.*

Table 5. Mean days with wasted medication per 30 days (rate data), by prescription length

Study or sub-group	30 days Mean	30 days SD	30 days Total, *N*	90 days Mean	90 days SD	90 days Total, *N*	Mean difference IV, random (95% CI)
Lipid-lowering medication							
Murphy *et al* (2012)[29]	0.085	0.9456	12 120	0.114	0.9782	11 910	–0.03 (–0.05 to –0.00)
Antihypertensive medication							
Murphy *et al* (2012)[29]	0.0997	1.2346	22 977	0.1487	1.1231	17 497	–0.05 (–0.07 to –0.03)
Diabetic medication							
Murphy *et al* (2012)[29]	0.1438	1.7003	4974	0.2147	0.9758	2484	–0.07 (–0.13 to –0.01)
Antidepressant medication							
Murphy *et al* (2012)[29]	0.1539	1.3536	9060	0.1426	0.876	3793	0.01 (–0.03 to 0.05)
Thyroid medication							
Murphy *et al* (2012)[29]	0.252	3.2802	6725	0.383	2.7845	4846	–0.13 (–0.24 to –0.02)
Mixed medications							
Jiang *et al* (2007)[26]	2.3	1.02	955	2.4	1.02	730	–0.10 (–0.20 to –0.00)

IV = inverse variance. N *= the total number of participants evaluated in each arm of the study. SD = standard deviation.*

methodology, there are limitations to this systematic review. It is possible that some of the studies are not truly representative of primary care, although the findings are generally consistent, regardless of setting. Moreover, all of the eligible studies were conducted in the US and their applicability to UK settings could be limited given differences in healthcare systems.

The authors may also have missed evidence where prescription lengths were considerably different from the inclusion criteria for this review. Some of the studies differentiated patients receiving new, versus existing, prescriptions, but the authors did not consider this in the protocol and insufficient studies reported this information to allow a post-hoc subgroup analysis.

Finally, it was not possible to make comparisons of effect sizes between different therapeutic areas. One of the authors recently conducted an analysis within routine UK primary care health records, not included in this systematic review, which addresses some of these concerns.[17]

A key issue with all of the studies was their use of indirect, proxy measures for both adherence and waste, based on administrative prescription refill data. The two key adherence measures used were PDC and MPR, which may introduce bias in favour of longer prescriptions, as well as underestimating true adherence.[40,41] Similar concerns can be raised about the estimation of waste. Nevertheless, a review of such approaches has determined that indirect measures still have value.[42]

None of the studies explored why adherence may differ between prescription lengths. Reasons for medication non-adherence are often complex, and can be both intentional and unintentional.[43] Longer prescription lengths may overcome barriers to unintentional adherence, including enabling patients to follow a regular medicine regimen or reducing logistical barriers, such as visits to the pharmacy.[28,31,33] However, given the observational nature of the studies, there is a risk of systematic differences, with longer prescriptions issued to those patients considered to be more adherent by the prescriber, those thought to have greater stability of their illness,[30] or those of non-white ethnicity.[44]

The authors identified only one study that showed a beneficial association between longer prescriptions and improved clinical outcome.[28] There was a lack of research examining the association between prescription duration and other outcomes, although some non-comparative evidence exists for shorter prescriptions being considered inconvenient and disempowering, and causing patient dissatisfaction and anxiety.[13,14,45]

Implications for research and practice

This review has found that medication adherence may be associated with longer-duration prescriptions, which, in theory, may translate into clinical benefit. The evidence that such prescriptions also lead to increased waste is weak. Current UK policy recommending the provision of shorter prescriptions is not substantiated by the current evidence base, but further research is required to evaluate the clinical, health service, and economic impact of differing prescription lengths.

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Ethical approval

Ethical approval was not required for this research.

Provenance

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Competing interests

The authors have declared no competing interests.

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