Systematic Review protocol

Developing and evaluating a measure of inappropriate polypharmacy in primary care

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Contents

Inappropriate Polypharmacy
Background and Rationale

The size of the problem
Medication use is greatest in primary care, and steadily growing with 1.1 billion items dispensed in 2014 in the UK [1]. Multimorbidity [2] and a culture of single-condition guideline-driven prescribing [3] are important factors contributing to widespread polypharmacy (defined as the use of multiple medications in a single individual). In the UK, the proportion of individuals receiving ≥5 drugs has doubled between 1995 and 2010 [4]. Work by the current programme research team has found polypharmacy to be common, particularly in the elderly with multiple, relatively unrelated conditions [5].

Adverse consequences of polypharmacy
Polypharmacy is associated with several undesirable consequences, including medication errors [6], adverse drug reactions [7], reduced quality of life [8], impaired medication adherence [9] and death [10]. However, recent evidence suggests the association between polypharmacy and unplanned hospitalisation to be considerably attenuated in the most multi-morbid individuals [11]. Additionally, cardiovascular polypharmacy has been found to not be associated with an increase in hospitalisation for non-cardiovascular problems [12]. This clearly demonstrates that overly simplistic analyses of polypharmacy relating simple medication counts to adverse outcome may be misleading [11,12], and more sophisticated approaches accounting for clinical context are therefore required.

Measuring polypharmacy
In a recent report for the King's Fund, members of the current research team highlighted the need to consider the appropriateness of polypharmacy [13]. Brook defined appropriateness of an intervention as "the expected health benefit … exceeds the expected negative consequences … by a sufficiently wide margin that the procedure is worth doing, exclusive of cost" [14]. The term polypharmacy does not in itself imply inappropriate prescribing, yet most measures fail to differentiate appropriate and inappropriate polypharmacy.

Polypharmacy is usually measured using arbitrary numeric thresholds, but these have been criticised [15]: adverse outcomes vary with degree of polypharmacy [11,16], and thresholds cannot capture medication appropriateness. Many prescribing indicators exist which assess medication appropriateness [17], including explicit measures (e.g. Royal College of General Practitioners [18]) and implicit measures (e.g. Medication Appropriateness Index [19]). Explicit criteria comprise lists of drug-specific issues (e.g. beta-blockade in a person with asthma [18]) which can be implemented in an automated fashion but do not apply to all patients. Implicit criteria comprise generic aspects of prescribing applicable to any drug (e.g. appropriateness of dose, drug-drug interactions, contraindications), and are thus patient specific but generally require evaluation by a clinician. Medication appropriateness measures are widely available, with face validity, but generally do not account for multiple drug use and do not measure polypharmacy per se.

What is required?
There is therefore a need to develop a valid and reliable means of measuring inappropriate polypharmacy, encompassing both the amount of medication use and its clinical appropriateness. To be usable in clinical practice, a metric should ideally focus on generic prescribing issues (to ensure relevance to all patients) whilst still permitting automation as part of a computerised clinical system. Although such a strategy would be unable to account for qualitative aspects of prescribing appropriateness [20], it benefits from transparency and reproducibility. It would have a valuable risk-stratification role identifying those at greatest risk of harm due to inappropriate polypharmacy, with the potential to therefore reduce alert fatigue in clinicians who are otherwise bombarded with unfocused safety warnings. A measure of inappropriate polypharmacy would allow medication optimisation interventions to be effectively targeted, and the impact of such interventions to be reliably evaluated.

Systematic Review protocol v1 03 Oct 16

Objectives

This review aims to identify a comprehensive list of assessment tools and indicators of potentially inappropriate prescribing to assess polypharmacy. This review is being undertaken as part of a wider study aiming to develop a measure of polypharmacy for use in primary care. The findings of this review will be used to inform the development of this measure.

Outcomes

The primary outcome of the review is to identify published generic prescribing indicators relevant to inappropriate polypharmacy.

Methods

Search Strategy

To locate and derive indicators of potentially inappropriate polypharmacy for expert review, an initial systematic review will be undertaken, building on previous literature reviews [17,18,19]. In particular, we note that on reviewing Kaufman [19] we concluded that the search used only included PubMed, and in particular excluded Embase so it is possible that important pharmacy papers may have been missed. We will search Embase, MEDLINE (Ovid), PsycINFO, CINAHL, Health Management Information Consortium, Cochrane Library, Web of Science, the Trip and NHS Evidence databases, from 1992 (the year the Medication Appropriateness Index was first published) until the present day. We will use exploded MeSH terms (e.g. Inappropriate Prescribing; Potentially Inappropriate Medication List; Polypharmacy; Drug Utilization Review; Medication Therapy Management) and combinations of relevant keywords and their variants (for example, groupings will include (a) polypharmacy, potentially inappropriate prescribing/medication; or (b) medication, drug therapy, drug utilisation, drug utilisation review, prescribing, combined with (c) suboptimal, appropriate, underuse, misuse). Additional publications will be identified by a manual search of references of relevant papers. Detailed search terms are described in below. The review will be registered with PROSPERO.

Search terms

The draft MEDLINE search strategy is shown below (Box 1) and will be used to identify potentially relevant papers. After the MEDLINE strategy is finalised, it will be adapted to the syntax and subject headings of the other databases aforementioned.

4

Inappropriate Polypharmacy

(exp Inappropriate prescribing/ or exp polypharmacy/ or exp medication errors/ or exp Potentially Inappropriate Medication List/ or (polypharmacy or underprescrib* or **under-prescrib* or over-prescrib* or mis-prescrib*** or overprescrib* or misprescrib* or (beer* adj criteri*) or (pim adj list*)).ti,ab. or ((**prescrib*** or prescript* or medicat* or medicin* or drug* or pharm*) adj2 (sub-optimal or suboptimal or optim* or appropriat* or inappropriat* or unaccept* or accept* or underus* or under-us* or over-us* or overus* or underutili* or under-utili* or malpractice* or safe* or unsafe* or danger* or error* or mistak* or (adverse* adj (event* or effect* or react*)) or harm* or omiss* or omit* or problem*)).ti,ab.) AND (((exp "Surveys and Questionnaires"/ or exp guideline/ or exp quality assurance, health care/) and **((updat*** or develop* or valid* or creat* or design* or **consensus*** or Delphi or rand* or reliab* **or interrat* or inter-rate*** or (inter adj rate*) or (appropriate* adj method*)).ti,ab.)) or (((score* or index* or scale* or survey* or questionnaire* or instrument* or outcome* or tool* or indicat* or measur* or screen* or criteri* or (quality adj2 assur*) or (patient adj2 experience*)) adj4 (**updat*** or develop* or valid* or creat* or design* or **consensus*** or Delphi or rand* or reliab**or interrat* or inter-rate*** or (inter adj rate*) or (appropriate* adj method*))).ti,ab.))

Box 1. Search strategy to be used in MEDLINE

We will also conduct a 'review of reviews' using a separate and broader search strategy, based on that described in Box 1.

Eligibility criteria

The term 'polypharmacy' refers to the prescribing of multiple medications to one person. However, the term polypharmacy has had both negative and positive connotations in the past [13], so we will, therefore, distinguish between appropriate polypharmacy and problematic or inappropriate polypharmacy [13]. For this review, we will use the following definitions of polypharmacy, as suggested by Duerden, Avery and Payne [13]:

> **Appropriate polypharmacy**: prescribing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimised and where the medicines are prescribed according to best evidence.

> **Problematic polypharmacy:** prescribing of multiple medications inappropriately, or where the intended benefit of the medication is not realised.

Articles will be eligible for inclusion if they report the use of a specific tool to assess polypharmacy or inappropriate prescribing. As we want to ensure we capture all relevant material to the review, we will include all settings in our search and we will include all ages of participants. We will also not distinguish between implicit and explicit indicators at this stage. However, for the RAND consensus panel, we will be presenting implicit indicators only. However, articles will be limited to English language only and will be limited by publication date (1992 onwards, as already discussed).

Articles using non-tool based medication review, educational interventions, validation studies of previously published tools, and general guidelines and recommendations relating to assessing inappropriate prescribing, and updated versions of tools which had not been subject to a new round of expert consensus, and articles not published in English will be excluded. Publications will be assessed for eligibility by title and abstract screening. Articles showing uncertainty regarding inclusion or exclusion criteria will be discussed between NE, JB and RP.

Data Extraction

Selection process

Initial search results obtained using the search strategy described above will be screened for eligibility and inclusion according to title and abstract using the following approach: we will take a random sample of 100 citations and double screen those, discuss discrepancies in inclusion and exclusion and refine how the criteria are being applied. If necessary we will repeat this step and check if the discrepancy rate has fallen. The remaining selection will be screened by a single reviewer (NE) with a further 10% selected for checking for inclusion by a second, more experienced reviewer (JB) for discrepancies in agreement. For any articles in which reviewers cannot agree, consensus will be reached through discussion with a third reviewer (RP). The full texts of articles identified as being potentially relevant for the review will be retrieved and reviewed by NE and JB independently.

Data collection process

Independent data extraction will take place using standardised, piloted data extraction forms developed for the study. Whilst this list is not exhaustive and subject to further refinement, we anticipate extracted information will include:

Overall Study details

- Study authors
- study setting (county, primary/secondary care)
- population target
- study methodology
- study design
- participants (if applicable)
- how indicators were developed including those excluded from final version(s)
- Acceptability of measure/tool to users (if applicable)

Individual indicator details

- Details of indicators themselves, including whether they are explicit or implicit
- Reporting of reliability/validity

Table 1. Data to be extracted from included papers

A single reviewer (NE) will extract the data according to the data extraction form. Again, a random sample of 10% will be selected for independent double data extraction by a second reviewer (JB). Discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will be requested from study authors. In the event indicators not being published within the paper identified, we will attempt to contact the author(s) of the study.

Data synthesis

As the purpose of the review is to identify published indicators, we do not propose synthesising the data in a traditional way. However, we will be assessing both a) quality of the development of each indicator and b) quality of the evidence underpinning each indicator. This process is described below.

Quality Assessment

We plan to assess the quality of the development of each indicator using the Joanna Briggs Institute checklist for Narrative, Expert Opinion and text tool. The assessment of the quality of the evidence underpinning each indicator will be undertaken as part of the next stage of the study and therefore will not be discussed here.

Risk of bias in individual studies

Risk of bias assessment in individual studies is not applicable for this review.

Meta-Bias

We do not plan to assess publication bias across studies.

Dissemination

Findings from the systematic review will be used to inform and develop the indicators for review within a RAND appropriateness consensus panel. We aim to publish our findings from the overall programme of work (this systematic review is part of Phase 1) in both high quality peer-reviewed journals and policy-oriented publications. Results will additionally be presented at national and international conferences (e.g. SAPC, RCGP, NAPCRG). Copies of the final publication will be provided to members of the RAND Appropriateness panel.

Project timeline

This systematic review is being led from the University of Cambridge, with methodological expert input from the Universities of Bristol, Nottingham and Manchester. Regular monthly study team meetings will be held to review progress including project management concerns, methodological issues and provisional findings. The following key milestones have been identified as essential to ensuring successful and timely progression of the review (see Figure 1 for details):

Figure 1. Systematic review Gantt chart

	2016				2017
	Sept	**Oct**	**Nov**	**Dec**	**Jan**
Develop protocol for systematic review					
Conduct initial searches to refine protocol					
Register Systematic review on PROSPERO					
Complete searches and de-duplication					
Screening titles and abstracts reviewer 1					
Screening titles and abstracts reviewer 2 (test set only, plus 10%)					
Data extraction (Single reviewer, 10% double data extracted)			15th		
Synthesis - identification of initial indicators			15th		
Writing up methods and findings					

Data management

Data management will be undertaken by the local researcher (NE) with supervision from the local Principal Investigator (JB) and Chief investigator (RP). Electronic copies of data will be backed up though University network servers. Data will be stored and archived when appropriate in accordance with University policy and data protection legislation. The confidential handling, storage and disposal of data are compliant with the Data Protection Act of 1998.

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Conflicts of Interest

The team declare no potential conflict of interest.

Systematic Review protocol v1 03 Oct 16

References

1. Health and Social Care Information Centre (HSCIC). Prescription Cost Analysis, England 2014. 2015, Health and Social Care Information Centre, Leeds
2. Barnett K et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380:37-43
3. Boyd CM et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716-24
4. Guthrie B, Makubate B. The rising tide of polypharmacy and potentially serious drug interactions 1995–2010: repeated cross sectional analysis of dispensed prescribing in one region. Primary Health Care Res Devel. 2012;13(S1):45 2E.2
5. Payne RA et al. Prevalence of polypharmacy in a Scottish primary care population. Eur J Clin Pharmacol. 2014;70:575-81
6. Avery A et al. Investigating the Prevalence and Causes of Prescribing Errors in General Practice: The PRACtICe Study. 2012, General Medical Council, London
7. Dequito AB et al. Preventable and non-preventable adverse drug events in hospitalized patients: a prospective chart review in the Netherlands. Drug Saf. 2011;34:1089-100
8. Fincke BG et al. The interaction of patient perception of overmedication with drug compliance and side effects. J Gen Intern Med. 1998;13:182-5
9. Vik SA et al. Measurement, correlates, and health outcomes of medication adherence among seniors. Ann Pharmacother. 2004;38:303-12
10. Jyrkkä J et al. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging. 2009;26:1039-48
11. Payne RA et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014;77:1073-82
12. Appleton SC et al. Cardiovascular polypharmacy is not associated with unplanned hospitalisation: evidence from a retrospective cohort study. BMC Fam Pract. 2014;15:58
13. Duerden M et al. Polypharmacy and medicines optimisation: Making it safe and sound. 2013, King's Fund, London
14. Brook RH et al. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care. 1986;2:53-63
15. Viktil KK et al. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol. 2007;63:187–195
16. Guthrie B et al. High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. BMJ. 2011;342:d3514
17. Spinewine A et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370:173-84
18. Spencer R et al. Identification of an updated set of prescribing--safety indicators for GPs. Br J Gen Pract. 2014;64:e181-90
19. Kaufmann CP, et al. Inappropriate prescribing: a systematic overview of published assessment tools. Eur J Clin Pharmacol (2014) 70:1–11
20. Hanlon JT et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45:1045-51