Optimal prescribing of drugs to prevent CVD and drugs that cause dependency: an evidence gap map

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Rationale

- The early detection of risk factors for cardiovascular disease (CVD) and initiation of preventative treatment is a key part of the NHS Long Term Plan[1]
- The prescribing of statins (and antihypertensives) is recommended as an effective measure to prevent CVD[2]
- However evidence suggests that both the prescribing of statins and the taking of prescribed statins, are not at optimal levels[3]
- It is essential to understand the factors influencing the prescription and taking of statins throughout the patient pathway in order to achieve optimisation
- Drugs that may cause dependency (DCD), such as benzodiazepines, z-drugs, gabapentinoids and opioids are prescribed to 1 in 4 adults in the UK
- Evidence suggests that many patients have been taking DCD beyond the short periods for which they are licensed
- Addiction to DCD is a priority area for reform, with a required focus on prescribing (and de-prescribing) practices[4]
- It is essential to understand the factors which may influence the prescription, review and withdrawal of DCD
- A systematic review is required which synthesises evidence about factors influencing the optimal prescribing and/or taking of DCD and drugs to prevent CVD. However, scoping of the literature in this area reveals an array of systematic reviews covering aspects of the overarching topic of interest.
- Prior to conducting a systematic review and synthesis of evidence to understand the factors that influence the prescription and/or taking of drugs to prevent CVD and DCD, there is a need to clarify the state of the systematic review evidence in the area by the production of an evidence gap map.

Aim

To map the quantitative and qualitative systematic review evidence available to inform the optimal prescribing of statins, antihypertensives and drugs which can cause dependency (DCD) and the point at which this evidence could be used to inform decision making in the patient care pathway for each type of medication.

Research question

What is known about how to achieve optimal prescribing of statins, antihypertensives and drugs which may cause dependency from the perspectives of patients and their families, prescribers, policy makers and other relevant professionals within the health care system?

Specific research objectives:

To map recent systematic review evidence regarding:

- effectiveness or experiences of interventions intended to improve prescribing practices or patient adherence regarding statins, antihypertensives and/or DCD
- effectiveness or experiences of interventions intended to improve implementation of interventions intended to improve prescribing practices or patient adherence regarding statins, antihypertensives and/or DCD
- practitioner views or perceptions of making prescribing decisions regarding statins, antihypertensives and/or DCD

To meet these research objectives, we plan to conduct the searching and mapping exercise in several stages:

1. Look for relevant systematic reviews,
2. Develop patient care pathways for each of the types of medications of interest, drawing upon existing guidelines and consultation with our stakeholders and PPI group,
3. Map these systematic reviews onto the key decision points within different care pathways for each type of medication,
4. Look for primary research which may inform key decision points on each care pathway where few high quality systematic reviews have been conducted.

This protocol provides detail on how we will conduct stages 1 to 3 of this work. Stage 4 will be informed by the work conducted in the previous stages and thus described in a separate protocol.

Identification of studies

The bibliographic database search strategies will be developed using MEDLINE (via Ovid) by an information specialist (SB) in consultation with the review team, key stakeholders and members of the public with experience of being prescribed one of the medications of interest. The search strategy for evidence relating to statins and antihypertensives will combine search terms for optimising prescribing with terms for statins/antihypertensives and terms for cardiovascular diseases. The search strategy for evidence relating to drugs which can cause dependency will combine search terms for optimising prescribing with terms for relevant drugs (Benzodiazepines, z-drugs, opioids and antidepressants). The search strategies will use both controlled headings (e.g. MeSH in MEDLINE) and free-text searching (i.e. title and abstract searching). Search terms will be derived from the titles, abstracts and indexing terms of pre-identified systematic reviews relevant to our research objectives and the primary studies included therein. Terms thus identified will be supplemented by an appropriate selection of synonyms. The search results will be date limited from 2010 to date and a systematic reviews study type search filter will be used to limit the results to systematic reviews.

The results of the bibliographic database searches will be exported to Endnote X8 (Clarivate Analytics, Philadelphia, PA, USA) and de-duplicated using the automated de-duplication feature and manual checking.

We anticipate searching the following bibliographic databases, alphabetically ordered by provider:

Cochrane Database of Systematic Reviews (via the Cochrane Library)

CINAHL (via EBSCO)

Epistemonikos (via https://www.epistemonikos.org/en/)

medRxiv (via https://www.medrxiv.org/)

EMBASE (via Ovid)

Health Management Information Consortium (HMIC) (via Ovid)

MEDLINE ALL (via Ovid)

PsycInfo (via Ovid)

Conference Proceedings Citation Index – Science (via Web of Science, Clarivate Analytics)

Science Citation Index (via Web of Science, Clarivate Analytics)

Provisional Ovid MEDLINE search strategies for identifying systematic reviews of (1) statins/antihypertensives and (2) drugs that cause dependency can be seen in Appendix A.

The reference lists of all systematic reviews that meet our inclusion criteria will be checked for additional systematic reviews.

We will also search a selection of topically relevant websites including:

- Royal Pharmaceutical Society https://www.rpharms.com/
- British Cardiovascular Society https://www.britishcardiovascularsociety.org/
- European Society of Cardiology https://www.escardio.org/
- British and Irish Hypertension Society https://bihsoc.org/
- British Heart Foundation https://www.bhf.org.uk/
- Heart Research UK https://heartresearch.org.uk/
- Royal College of Physicians https://www.rcplondon.ac.uk/
- Royal College of Psychiatrists https://www.rcpsych.ac.uk/
- Mind https://www.mind.org.uk/
- Mental Health UK https://mentalhealth-uk.org/
- Priory Group https://www.priorygroup.com/

Inclusion Criteria

The inclusion criteria and exclusion criteria to be applied to the studies identified through the search strategy are detailed below. We have organised the criteria for quantitative studies according to the PICO format (Population, Intervention, Comparator and Outcome) and the criteria for qualitative studies according to the PICo format (population, phenomenon of Interest, Context):

Quantitative studies (PICO)

Population

Include:

Focus of the paper must be relating to the care and/or treatment of adults (mean/median age ≥ 16 years) where a prescription for one or more of the following classes of medications is being considered/already being received:

- Statins
- Antihypertensive
- Benzodiazepines

- Non-benzodiazepine hypnotics (i.e. Z-drugs)
- Opiates
- Antidepressants
- Gabapentinoids

Exclude:

- Child/Paediatric populations (mean/median age $\leq$ 15 years)
- Patient groups where medication type not explicitly mentioned
- Patients receiving services for use of illicit substances (e.g. heroin, cocaine)
- Patients receiving treatment for cancer pain
- Patients receiving end-of-life care

Intervention

Include:

For systematic reviews of quantitative evidence, interventions must aim to optimise one or more of the following:

- Patient adherence
- Prescriber (e.g. Doctor, nurse, pharmacist) adherence to clinical guidelines re: prescribing
- Prescriber practices
- Implementation of an intervention to enhance patient adherence or prescriber practices

These aims may also be an implicit focus of the review i.e. included as an outcome measure but not stated as an explicit aim. In which case, these outcomes must be clearly stated within the abstract of the article.

Interventions may be conducted at a system-level or be targeted at the patient and/or prescriber.

Comparator(s)/Control

For any comparative study evaluating the effectiveness of an intervention to optimise adherence and/or prescribing practise, any comparator is eligible for inclusion. Examples may include: wait-list control, treatment as usual, education.

Outcome

For systematic reviews of quantitative evidence all outcomes are of interest.

Qualitative studies (PICo)

Population

Same as quantitative studies (see above).

Phenomenon of interest

With respect to systematic reviews of qualitative evidence, the focus should be on one or more of the following:

- Guidelines intended to optimise patient adherence or prescribing practices

- Patient, family member or carer views/perceptions/experiences of healthcare consultations to discuss initiation, reviewing or discontinuing a prescription
- Patient, family member or carer views/perception/experiences of interventions aiming to improve adherence/prescribing practice
- Patient, family, carer views/perceptions/experiences on reasons for adherence or non-adherence
- Practitioner views/perceptions/experiences of interventions aiming to improve patient adherence and/or prescribing practice
- Practitioner views/perceptions of making prescribing decisions

Context

Any setting.

Additional inclusion/exclusion categories (study design, date limit geographical location)

Study design:

Systematic reviews are defined according to the criteria outlined by Martinic et al (2019) in that each systematic review must:

1) Have a clearly stated research question
2) Indicate which sources were searched, with a reproducible/complete search strategy an search date
3) Define inclusion and exclusion criteria
4) Clearly outline screening/study selection methods
5) Critically appraise and report the quality/risk of bias of the included studies
6) Provide information about data analysis and synthesis that allows the reproducibility of the results

Include:

- Systematic reviews of quantitative and/or qualitative literature
- Systematic reviews of guidelines relating to prescribing of medications listed in 'Population' section above
- Systematic review of reviews
- Scoping reviews
- Rapid reviews

Exclude:

- Reviews which were not undertaken systematically
- Narrative summaries of literature base
- Primary studies

Date limit:

Systematic reviews published from 2010 onwards

Geographical limit:

Stage 1: None

Process of applying inclusion criteria

As an initial calibration exercise of inclusion judgments and the clarity of our inclusion criteria, all reviewers will apply inclusion and exclusion criteria to the same sample (n=100) of search results. Decisions will be discussed in a group meeting to ensure consistent application of criteria. Where necessary, inclusion and exclusion criteria will be revised to enable more consistent reviewer interpretation and judgement.

The revised inclusion and exclusion criteria will then be applied to the title and abstract of each identified citation independently by two reviewers, with disagreements resolved through discussion or referral to a third reviewer as required. The full text of each record will be assessed for inclusion in the same way.

Endnote X8 software will be used to support study selection (Clarivate Analytics, Philadelphia, PA, USA). A PRISMA-style flowchart will be produced to detail the study selection process and reason for exclusion of each record retrieved at full text will be reported.[5]

Data extraction

A standardised data extraction coding set will be developed and piloted by the review team on a selection of included studies. It will be used to collect the following information from each included full text.

Examples of data which will be extracted include:

- Author
- Date of publication
- Title
- Study focus
- Study aim
- Type of review
- Type of studies included
- Type of synthesis
- Type of medication being prescribed
- Medical condition(s) being treated
- Mean age of population
- Ethnicity of sample
- Socio-economic status of sample
- Intervention name
- Perspectives obtained (Qualitative studies only)
- Service/part of care pathway
- Outcomes evaluated

Data extraction will be performed by one reviewer and checked by a second, with disagreements being settled through discussion, recruiting a third person as arbiter, if required.

Study quality assessment strategy

The quality of all systematic reviews identified as eligible following full-text screening will be appraised using the AMSTAR-2 quality appraisal tool for systematic reviews of primary studies of randomised and non-randomised study designs.[6] We plan to adapt the AMSTAR-2 by adding items

from the reporting standards for qualitative evidence synthesis (e.g. Tong et al., 2012[7]) to enhance the tools applicability to reviews of qualitative evidence. Quality appraisal will be undertaken by one reviewer and checked by a second, with disagreements being resolved through discussion.

Data analysis and presentation

We will map systematic reviews which meet our inclusion criteria onto the relevant patient care pathway for the medication of interest. These care pathways will be developed by drawing on stakeholder and patient expertise and integrating knowledge/recommendations from existing care pathways, such as the NICE pathway for optimising prescribing.[8] Systematic reviews will be grouped according to the research objectives they relate to within each pathway.

This approach will enable us to identify where clusters of high quality recent systematic reviews exist at key decision making points within the patient care pathways for statins, antihypertensives and DCD. It will also highlights where there is little systematic review evidence to support decision making on these pathways and thus areas in which we need to seek primary research.

Policy Relevance

Audience

Key stakeholders for this mapping review include representatives from NHS England and NHS Improvement, Health Education England, Public Health England and the National Institute for Clinical Excellence. These representatives include policy makers and clinicians who will be involved throughout this mapping review.

Required Impact

This mapping review seeks to inform the following policy questions/areas:

> *What are the system level behaviours, beliefs and assumptions that can affect change in optimising prescribing across a patient's care pathway?*
>
> *To further explore and validate the interventions from the findings of the review supporting optimal prescribing and potential primary research to generate, test and evaluate new intervention options.*

It is intended that the results of this review inform which interventions the NHS should implement or support in order to achieve optimised medicines use and identify areas in which further primary research is required.

Stakeholder and patient/public involvement

Key opportunities for integrating stakeholder feedback during the review process include:

- Defining our research question
- Developing the project protocol, specifically enabling us to identify key populations and outcome categories to include within our map
- Developing the patient care pathways, which highlights the key decision making opportunities, for patients who are prescribed statins, antihypertensives and DCD
- Checking what level of information will be useful to the intended users of our evidence map
- Ensuring our map of available evidence is accessible to our intended audience
- Providing feedback on preliminary findings and draft reports
- Identifying opportunities for dissemination of findings.

We will also work alongside people with experience of being prescribed statins, antihypertensives and/or DCD.

Key points where it will be useful to integrate feedback from patients and members of the public during this review include:

- Refining and/or sense checking research question/s
- Refining and/or sense checking search strategy
- Developing our inclusion criteria
- Developing an 'ideal' patient care pathways for statins, antihypertensives and DCD
- Gathering view on their experience of patient care pathway as suggested by clinical and policy maker stakeholders
- Ensuring the information contained in our evidence map is accessible to patients and members of the public
- Identifying research 'gaps' for further systematic review work or primary research
- Identifying opportunities to disseminate our findings
- Producing accessible summaries to support the dissemination of this work. This may include involvement with writing plain language summaries, producing podcasts.

Patient and Public Involvement within this mapping review will be coordinated by Kristin Liabo and Malcolm Turner, both of whom are members of Peninsula Public Involvement Group (PenPIG).

Meetings will be arranged by the core research team in consultation with the stakeholders and patient and public involvement (PPI) group to suit project progress and stakeholder availability.

Dissemination plans

Access to the evidence map will be shared with the stakeholders listed above. We will work alongside our stakeholders and PPI group to develop dissemination materials and pathway to ensure our work reaches our intended audiences the people it is intended to benefit.

We will produce a final project report which will be sent to the key stakeholders involved with this review. The results from this review will also be published within relevant academic journals. We will also produce plain language summaries with our PPI group, which can then be used as a basis for other dissemination materials the research and stakeholder team feel are appropriate. These dissemination materials may include a Briefing paper, podcast and blog post. Key outputs will be shared via the Exeter PRP ERF webpage, blog and Twitter feed.

The dissemination plan will be developed further as the findings of the review emerge to allow for the key messages and delivery mechanisms for each audience to be identified.

Resources

The estimated timeline for the mapping review as outlined within this protocol is 24 weeks. This will include input from all members of the Exeter Policy Research Programme Evidence Review Facility.

Weeks 1-9: We will request input via email exchanges to support the development of patient care pathways for each of the medication types of interest (statins, hypertensives, anti-depressants and DCD). A face-to-face (online) meeting to support this work may be requested in week 4 of the project.

Week 6: Meeting with PPI group to support development of patient care pathways

Week 18-20: Separate online meetings with PPI group and stakeholders to discuss preliminary findings of the mapping review.

References

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6. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008. https://doi.org/10.1136/bmj.j4008
7. Tong, A., Flemming, K., McInnes, E. et al. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol 12, 181 (2012). https://doi.org/10.1186/1471-2288-12-181
8. National Institute for Health and Clinical Excellence. Medicines Optimisations Overview [Internet]. 2019 Available from: https://pathways.nice.org.uk/pathways/medicines-optimisation

Appendix 1. Ovid MEDLINE draft search strategies

Statins/antihypertensives

1. ((appropriate* or discontinu* or enhance* or inappropriate* or incorrect* or "in correct*" or optim* or safe or suboptim* or "sub optim*" or tapering or withdrawal) adj4 (drug* or medicine* or medication* or prescri*)).tw.
2. Inappropriate Prescribing/
3. exp *Drug Prescriptions/
4. ((drug* or guideline* or guidance or medicine* or medication* or patient* or prescri*) adj4 (adhere* or compliance or concordance)).tw.
5. exp *Patient Compliance/
6. ((shared or sharing or informed) adj2 (decision* or choice*)).tw.
7. (decision adj2 (aid* or support*)).tw.
8. *Decision Making/
9. *decision support techniques/
10. ((consumer* or patient*) adj3 (involv* or participat*)).tw.
11. *patient participation/
12. ("patient cent*" adj2 (approach* or care or decision* or intervention* or treatment*)).tw.
13. Patient-Centered Care/
14. (behavi* adj2 chang*).tw.
15. (restriction adj2 (policy or policies)).tw.

16. or/1-15
17. statin*.tw.
18. ("HMG-CoA reductase inhibitor*" or "3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor*" or "3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor*" or "HMGCR inhibitor*" or "Hydroxymethylglutaryl-CoA Reductase Inhibitor*").tw.
19. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
20. (atorvastatin or Lipitor or Torvast).tw.
21. (fluvastatin or Lescol).tw.
22. (lovastatin or Mevacor or Altocor or Altoprev).tw.
23. (pitavastatin or Livalo or Pitava).tw.
24. (pravastatin or Pravachol or Selektine or Lipostat).tw.
25. (rosuvastatin or Crestor).tw.
26. (simvastatin or Zocor or Lipex).tw.
27. antihypertensive*.tw.
28. exp Antihypertensive Agents/
29. ("ACE inhibitor*" or antagonist or "angiotensin II receptor" or "beta blocker*" or "calcium channel blocker*" or "thiazide diuretic*").tw.
30. (acebutolol or adrenomedullin or alprenolol or amlodipine or atenolol or bendroflumethiazide or bepridil or betaxolol or bethanidine or bimatoprost or bisoprolol or bosentan or "bretylium tosylate" or brimonidine tartrate or bupranolol or captopril or carteolol or carvedilol or celiprolol or chlorisondamine or chlorothiazide or chlorthalidone or cilazapril or clonidine or cromakalim or cyclopenthiazide or debrisoquin or diazoxide or dihydralazine or dihydroalprenolol or diltiazem or doxazosin or enalapril or enalaprilat or eplerenone or epoprostenol or felodipine or fenoldopam or fosinopril or guanabenz or guanethidine or guanfacine or hexamethonium or "hexamethonium compound*" or hydralazine or hydrochlorothiazide or hydroflumethiazide or indapamide or indoramin or irbesartan or isradipine or kallidin or ketanserin or labetalol or latanoprost or lisinopril or losartan or mecamylamine or methyldopa or metipranolol or metolazone or metoprolol or mibefradil or minoxidil or muzolimine or nadolol or nebivolol or nicardipine or nicorandil or nimodipine or nisoldipine or nitrendipine or nitroprusside or olmesartan medoxomil or oxprenolol or pargyline or pempidine or penbutolol or "pentolinium tartrate" or perindopril or phenoxybenzamine or phentolamine or pinacidil or pindolol or piperoxan or polythiazide or prazosin or propranolol or

protoveratrines or quinapril or ramipril or reserpine or rilmenidine or telmisartan or teprotide or terlipressin or ticrynafen or timolol or todralazine or tolazoline or torsemide or travoprost or trichlormethiazide or trimethaphan or valsartan or "veratrum alkaloid*" or vincamine or xipamide).tw.

31. or/17-30
32. cardiovascular.tw.
33. exp Cardiovascular Diseases/
34. ((cardiac or coronary or heart) adj3 (arrest* or attack* or disease* or failure*)).tw.
35. ((heart or myocard*) adj3 (infarc* or ischaemi* or ischemi*)).tw.
36. angina*.tw.
37. Angina Pectoris/
38. stroke*.tw.
39. exp Stroke/
40. or/32-39
41. 16 and 31 and 40
42. ((effectiveness or implementation or literature or map or mapping or qualitative or rapid or realist or systematic or scoping or "state of the art" or umbrella) adj2 (assessment* or overview* or review* or synthes*)).tw.
43. ("meta analy*" or metaanaly* or metasynthe* or "meta synthe*").tw.
44. ((systematic or evidence) adj1 assess*).tw.
45. (qualitative adj2 (evidence or synthes*)).tw.
46. (overarching adj2 model).tw.
47. "review* of reviews".tw.
48. systematic review.pt.
49. meta-analysis.pt.
50. or/58-65
51. 41 and 50
52. limit 51 to yr="2010 -Current"

Drugs that cause dependency

1. ((appropriate* or discontinu* or enhance* or inappropriate* or incorrect* or "in correct*" or optim* or safe or suboptim* or "sub optim*" or tapering or withdrawal) adj4 (drug* or medicine* or medication* or prescri*)).tw.

2. Inappropriate Prescribing/
3. exp *Drug Prescriptions/
4. ((drug* or guideline* or guidance or medicine* or medication* or patient* or prescri*) adj4 (adhere* or compliance or concordance)).tw.
5. exp *Patient Compliance/
6. ((shared or sharing or informed) adj2 (decision* or choice*)).tw.
7. (decision adj2 (aid* or support*)).tw.
8. *Decision Making/
9. *decision support techniques/
10. ((consumer* or patient*) adj3 (involv* or participat*)).tw.
11. *patient participation/
12. ("patient cent*" adj2 (approach* or care or decision* or intervention* or treatment*)).tw.
13. Patient-Centered Care/
14. (behavi* adj2 chang*).tw.
15. (restriction adj2 (policy or policies)).tw.
16. or/1-15
17. benzodiazepine*.tw.
18. (alprazolam or flunitrazepam or chlordiazepoxide or clobazam or clonazepam or diazepam or lorazepam or midazolam or nitrazepam or oxazepam or prazepam or temazepam).tw.
19. exp Benzodiazepines/
20. (antidepres* or "anti depres*").tw.
21. (serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin* or SSRI* or SNRI* or NARI* or SARI* or NDRI* or tricyclic* or tetracyclic*).tw.
22. exp Antidepressive Agents/
23. (opioid* or opiate*).tw.
24. (morphine or hydromorphone or levorphanol or meperidine or methadone or propoxyphene of codeine or pentazocine or hydrocodone or oxycodone or fentanyl or tramadol).tw.
25. exp Analgesics, Opioid/
26. "z drug*".tw.
27. (zopiclone or zolpidem or zaleplon or eszopiclone).tw.
28. exp "hypnotics and sedatives"/
29. (gabapentin* or mirogabalin or phenibut or pregabalin).tw.

30. Gabapentin/
31. or/17-30
32. 16 and 31
33. ((effectiveness or implementation or literature or map or mapping or qualitative or rapid or realist or systematic or scoping or "state of the art" or umbrella) adj2 (assessment* or overview* or review* or synthes*)).tw.
34. ("meta analy*" or metaanaly* or metasynthe* or "meta synthe*").tw.
35. ((systematic or evidence) adj1 assess*).tw.
36. (qualitative adj2 (evidence or synthes*)).tw.
37. (overarching adj2 model).tw.
38. "review* of reviews".tw.
39. systematic review.pt.
40. meta-analysis.pt.
41. or/33-40
42. 32 and 41
43. limit 42 to yr="2010 -Current"