Supporting patients to get the best from their osteoporosis treatment: a rapid realist review of what works, for whom, and in what circumstance.

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Acknowledgements

This Rapid Realist Review was commissioned by the Effectiveness Working Group of the Royal Osteoporosis Society Osteoporosis and Bone Research Academy, to inform the Society's 2020 Research Road Map and Cure Strategy. The authors acknowledge the assistance of Dr Lizzie Cottrell and Dr John Edwards in initial protocol writing and Sally Lawson, in protocol and early analysis. The authors are grateful to Caroline Sangan, Belinda Thompson and Francesca Thompson for their assistance in convening the Working Group, whose scientific membership comprises: Prof Eugene McCloskey (Chair); Dr Zoe Paskins (Vice-Chair); Prof David Armstrong; Dr Elizabeth Curtis; Dr John Edwards; Dr Kassim Javaid; Prof Thomas Hill; Prof Terry O'Neill; Prof Michael Stone; Dr Jennifer Walsh; Ms Janice McKinley; Ms Corinne Turnbull. In addition, we would like to acknowledge the support of other members of the Royal Osteoporosis Society Osteoporosis and Bone Research Academy: Professor Juliet Compston (Chair); Professor Nick Harvey (Vice-Chair); Professor David Reid (Senior Medical Advisor); Nic Vine (Patient Advocate); and Mary Bishop (Patient Advocate).

Abstract

Purpose: In people with osteoporosis, adherence to medicines is poorer than other diseases and patients report follow up is lacking, and multiple unmet information needs. We conducted a rapid realist review to understand what contextual conditions and mechanisms enable interventions to support osteoporosis medication optimisation.

Methods: A primary search identified observational or interventional studies which aimed to improve medicines adherence or optimisation; a supplementary second search identified research of any design to gain additional insights on emerging findings. Extracted data was interrogated for patterns of context-mechanism-outcome configurations, further discussed in team meetings, informed by background literature and the Practicalities and Perception Approach as an underpinning conceptual framework.

Results: We identified 5 contextual timepoints for the person with osteoporosis (identifying a problem; starting medicine; continuing medicine) and the practitioner and healthcare system (making a diagnosis and giving a treatment recommendation; reviewing medicine). Interventions which support patient informed decision making appear to influence long-term commitment to treatment. Supporting patients' practical ability to adhere (e.g., by lowering treatment burden and issuing reminders) only appears to be helpful, when combined with other approaches to address patient beliefs and concerns. However, few studies explicitly addressed patients' perceptions of illness and treatment. Supporting primary care clinician decision making and integration of primary and secondary care services also appears to be important, in improving rates of treatment initiation and adherence.

Conclusions: We identified a need for further research to identify a sustainable, integrated, patient-centred, cost and clinically effective model of long-term care for people with osteoporosis.

Mini abstract – Systematic reviews that examine effectiveness of interventions to improve medicines optimisation do not explain how or why they work. This realist review identified interventions which optimise medicines optimisation in osteoporosis include opportunities to address patients' perceptions of illness and treatment and/or support primary care clinician decision making.

Introduction

Osteoporosis, and consequent fragility fractures are an important cause of disability, impaired quality of life and mortality.[1-2] Effective treatments exist which lower fracture risk and are clinically and cost-effective. However, for the last two decades, clinicians and academics have been writing about the problem of poor persistence to medication (defined as the cumulative time duration from initiation to discontinuation of therapy) and adherence (the extent to which the patient's action matches the agreed recommendations,[3] among people with osteoporosis.[4-6] Long-term persistence rates with oral bisphosphonates, the mainstay of treatment for prevention of osteoporotic fractures, are reportedly worse than in other long-term conditions and estimated between 16% and 60% at one year.[6]

Medicines optimisation is defined as 'a patient-focused approach to getting the best from investment in and use of medicines that requires a holistic approach, an enhanced level of patient centred professionalism, and partnership between clinical professionals and a patient'.[7] Medicines optimisation addresses safety and effectiveness, while also encompassing adherence. Thus, the construct of medicines optimisation allows considerations of outcomes important to both patients and healthcare professionals such as patient satisfaction, knowledge, patient involvement in decision making; health status and adverse events.[8]

Previous systematic reviews exist which have examined the effectiveness of interventions to promote adherence in osteoporosis but not medicines optimisation; [9,10] furthermore, reviews which aim to summarise information about complex interventions are limited in their ability to examine how interventions work in different settings, for which patients, why they have certain effects, including on adherence, but also on a broader range of patient-centred outcomes.

Realist reviews provide an alternative approach to a traditional systematic review by considering 'what works for whom, in what contexts, to what extent, and how and why?', with specific attention to context (C), mechanisms of effect (M) and outcomes (O), so-called C-M-O configurations.[11] Recurrent patterns of C-M-O configurations, also called 'programme theories' can identify broad rules of how and why certain outcomes occur, and why interventions are effective, or not. Rapid realist reviews have emerged as a practical approach to inform policy making when time is limited, with a focus on engaging stakeholders and identifying context-specific explanations for what works, and why.[12]

This review focuses on the interventions, contextual factors and mechanisms that support medicines optimisation in people with osteoporosis, by answering the following questions:

i. What mechanisms enable components of interventions to support osteoporosis medication optimisation?
ii. What were the underlying contextual conditions that enabled these mechanisms?

Our purpose was to make recommendations for healthcare professionals and patients on key approaches that have potential to be effective and/or ineffective and identify where further research is needed.

Methods

The methods for this review are informed by the 10 steps for a Rapid Realist Review proposed by Saul et al [12] and our study protocol, registered with PROSPERO (2021 CRD42021240357).

The project scope, questions for review and purpose statement (Steps 1, 2 and 3) were determined through discussion with the Royal Osteoporosis Society (ROS) Bone Research Academy Effectiveness Working Group (EWG), an expert in medicines adherence (RH), and clinical academic with experience of realist methods (IM). The EWG includes experts and stakeholders in the field of osteoporosis, including clinicians, researchers, and patient advocates.

Developing initial programme theories

Drawing on the project team's expertise, this review is informed by previous qualitative research syntheses relating to osteoporosis,[13,14] and a recent realist synthesis about medicines management in older people which helped us develop an understanding of the context and problem [15]. We used a conceptual framework about levels of interventions to address determinants of non-adherence, which we felt would also have relevance for medicines optimisation: the 'adherence lollipop' (Supplementary Figure 1) [16-7]. The three levels are the patient; the patient-provider interaction; and, the healthcare and social environment. Interventions targeted at the patient or patient-clinician interaction need to take into account perceptions (treatment beliefs related to necessity and concern) and practicalities (Supplementary Figure 2). Using our background literature, we developed a typology of determinants of non-adherence using this conceptual framework and initial candidate Programme Theories (Supplementary Data 1).

Search strategy and study selection

We conducted two searches. Our primary search identified interventional and observational studies which evaluated the effects of interventions, in people with osteoporosis, to optimise medicines or improve adherence. We used a search strategy already used by a previous systematic review in this field (Supplementary Data 2).[9] We searched four databases: MEDLINE, Psychinfo, CINAHL and EMBASE. Papers were identified from July 2012 to the date of 19th March 2021. Our key inclusion criteria were to include studies (interventional or observational) which concerned supporting people with osteoporosis in medicines optimisation. After de-duplication of identified records, initial screening of titles and abstracts was undertaken by one reviewer. Selection of included studies was undertaken by reviewers in pairs and disagreement regarding eligibility was resolved by discussion. We assessed study quality using a modified quality appraisal tool adapted from the Quality In Prognosis Studies tool (QUIPs) in order to appraise the weight of contribution of individual studies to programme theory.[18]

Our second search was iterative in nature and aimed at gaining additional insight on included key papers and emerging mechanisms. This included a broader range of study designs and was achieved through citation tracking and reference checking of key papers, discussion with experts and further searches of Google Scholar (Step 6).

Data Extraction

Data was extracted on: context (C), including patient context, nature of the patient-clinician interactions, and health-care setting; mechanisms (M), identifying any targeted determinants; and outcomes (O), informed by our initial programme theories (Step 7). The data extraction proforma (Supplementary Data 3) was initially pretested and piloted independently by reviewers on 3 studies.

Analysis

Extracted data was interrogated by five (ZP, IM, AS, LST, OB) authors independently for patterns of C-M-O configurations, using an IF-THEN approach to statements. Weekly team meetings were held to critically appraise, analyse, and synthesise the data. As we found we could not adequately refine our CMOs within our given timeframe and resource, in line with other published rapid realist reviews,[19] we decided to instead focus on identifying the key mechanisms that were observed across multiple interventions *with potential* to be effective; these were mechanisms within each (complex) intervention that either had evidence of effectiveness within interventional studies or within supporting literature, such as our supporting background reviews. We also focussed on identifying contextual factors that were associated with specific mechanisms.

Validation of the identified Contexts and Mechanisms occurred in two meetings of the EWG (Step 8). Within this workshop, recommendations for research and practice were co-developed (Step 9, 10).

Patient and public involvement

The idea for the study was informed by a priority setting exercise with people with osteoporosis.[20-21] The initial protocol and scope were discussed within a dedicated meeting of ROS patient advocates who advised on the title, search strategy and scope. Patient advocates were involved in the EWG meetings.

Results

The primary search identified 26 full-text articles of existing interventions (11 from the primary search, supplemented with 15 from Cornelisson et al, [9]) (Table 1, and further details in Supplementary Table 1). The iterative secondary search further identified 17 records that either provided further insight into these interventions or our emerging mechanisms of interest (Supplementary data 4).

Context

18 studies identified in the primary search were situated within specialised outpatient clinics,[22-31] or Fracture Liaison Services (FLSs - services in which a co-ordinator identifies patients with fragility fractures, carries out risk assessments, initiates evidence-based interventions for bone health and falls),[32-39] with 8 studies in community pharmacy services or primary care, or a combination.[40-47] The setting for one study was unclear.[46] In studies reporting patient-professional interventions, the clinician was most often a nurse, but also pharmacist, specialist doctor, Primary Care Practitioner (PCP) or non-clinician. Patient participants were all female in 10 studies, mostly taking oral medication (with one exception relating to daily teriparatide injections [47]) and the mean age, where reported, ranged from 62.4 to 75.6 years.

The most important contextual factors appeared to be related to timing of the intervention from the first identification of a problem to medicine reviews. We used the five stages of medicine management adapted from the MEMORABLE study to describe these time points of interest from the perspective of the person with osteoporosis and the clinician and health-care system (Figure 1).[19]

Mechanisms and Outcomes

We identified six key groups of mechanisms as illustrated in Figure 2, aligned to the three 'lollipop' levels of intervention and crossing over various contextual stages (timepoints) of medicines management (Figure 1).[17] Patient mechanisms were typically targeted at unintentional non-adherence, to increase patient capability and overcome practical difficulties. Patient-clinician mechanisms aimed to address intentional non-adherence, and healthcare mechanisms had potential for multiple effects. We discuss the main mechanisms in relation to the five contextual stages, below, with CMO configurations summarised in Supplementary Table 2.

Person with osteoporosis: Identifying the problem (Step 1)

Mechanisms to support patient informed decision making

From our background literature, we identified that patients may find it hard to 'identify the problem' and believe that osteoporosis is a normal condition of ageing for which treatment is futile, or, fail to believe that they are at risk.[13] We identified interventions which are specifically targeted at helping patients understand osteoporosis and make informed decisions, including a decision aid to promote shared decision making about medicines in clinical consultations, and educational brochures or videos, to provide information. For example, a within-consultation decision aid, compared to usual primary care was effective at increasing patient engagement, knowledge and understanding of fracture risk but did not change adherence, although a trend towards higher initiation rates were seen.[42] [48]

Group interaction with peers in group consultation may be a further factor to support informed decision making although two comparison study identified adherence rates were similar following traditional or group consultations. [25,49]

Two large trials which evaluated information, which was personalised and designed with behaviour change in mind, compared with usual care, showed no difference in clinical outcomes, such as persistence or process outcomes such as prescriptions and testing.[23,40] One explanation for the failure of these interventions to lead to changes in prescribing or medicine taking, despite increasing patient's acceptance of the problem, may be that the intervention was targeted at patients only, and clinician actions are needed to prescribe and establish patients on medication.

Although inferential, studies in the review suggested other factors might influence patient perception of their own susceptibility, and therefore decision making. Specifically, findings of two studies suggest BMD results may inform perception of risk and decision making about taking medicines and adherence over the longer term [38,44]. Communication of individual fracture risk results (using the FRAX tool) was identified a possible factor which could inform decision making. However, studies which evaluated the impact of FRAX on clinical outcomes (in primary care) did not describe how this was communicated to the patient,[42,44] and an included qualitative study identified non-adherent women frequently questioned or appeared not to understand their fracture risk.[50]

Practitioner and Health system: Establishing diagnosis and recommending medication (Step 2)

Mechanisms to support primary care clinician decision making

Our background literature identified that primary care clinicians experienced a number of uncertainties around osteoporosis management.[13] In our findings, interventions, in outpatient or FLS settings, which included support for primary care clinical decision making at treatment initiation, eg. additional investigations and individualised counselling, were associated with improvements in initiation rates [27]. Similarly, within the SCOOP trial in primary care,[44, 51] identification, investigation and treatment recommendations were enacted by the study team in the intervention arm, suggesting clinician decision making support may have been an important mechanism in achieving observed higher initiation rates.

Person with osteoporosis: Starting medication (Step 3)

Mechanisms to reduce treatment burden and patient workload

Interventions targeted at making the first prescription easier or more convenient for patients were associated with improved initiation rates and included automated phone calls with an option to press a number to be transferred to pharmacy,[52] and specialists FLSs which issued prescriptions directly meaning the patient did not have to visit their Primary Care Provider (PCP).[38]

Mechanisms to support patient informed decision making

The use of an additional community pharmacy consultation in new starters was used to reiterate treatment benefits, the importance of adherence, lifestyle management, practical issues about requesting repeat prescriptions but also to elicit patient concerns and identify patient-specific solutions.[53] This intervention had a small impact on adherence at 1 year in new starters of osteoporosis medications. Similarly, Ganda et al identified patients attending FLS, who had early primary care appointments after starting were more likely to adhere over 6 months.[34]

Person with osteoporosis – continuing medication (Step 4)

Mechanisms to support reinforcement, routinisation and memory

Follow up calls or appointments have also been used to reinforce messages or remind patients, however, where the purpose of the call only to give information e.g. to remind about educational sessions,[46] there was no increase in long-term adherence identified.

Other interventions to remind people to take their medicine included automated phone calls, education materials, text message reminders, alarm clocks, or calendar stickers. A study examining the feasibility and acceptability of personalised text messages found that less than half of participants wanted text reminders.[28] A package of resources including education booklets, memo stickers (for calendars) and alarm clocks did not alter persistence over 12 months in a RCT of 334 patients.[22] The only support for alarm clock reminders improving adherence, comes from a non-randomised study, which may suggest that patient selection may be important.[54]

Mechanisms to support patient-informed decision making

Our background literature identified several qualitative studies that involved people with osteoporosis reappraising the relevance and purpose of medication, including searching for evidence of treatment effectiveness and considering concerns about side effects and/or safety.[7] These are described as ‘disruption loops’ in Figure 1.

Eliciting and addressing patient concerns appears to be an important component of follow up interventions which were successful in improving medicines adherence in both outpatient and primary care settings.[27,45,47] Although most often, these interventions were delivered by training clinicians, in one FLS-located study, trained medical secretaries elicited problems, emphasized the importance of treatment, and provided practical suggestions or support in contacting their physician or person in charge or procuring the medicine (thereby reducing patient burden and/or increasing patient capacity).[33]

There is limited evidence to suggest bone density scans [43], but not bone turnover markers [55-6] improve adherence, possibly by informing patients’ and clinicians’ patient reappraisal about treatment effectiveness. 29% of women in one community-based trial highlighted that the bone turnover markers influenced their decision making.[57]

Mechanisms to reduce treatment burden and patient workload

Reduced drug frequency also has potential to reduce patient 'burden'. A number of studies found that persistence was higher in patients who were prescribed monthly or weekly oral drugs,[22,24] findings which are confirmed by a meta-analysis of 9 studies comparing once weekly with once daily dosing.[58]

Practitioner and health-systems: Reviewing medication – Step 5

Mechanisms to support clinician decision making

Regular follow up with patients enabled FLS or community pharmacy clinicians to glean information from patients to guide treatment decisions leading to changes in outcomes other than adherence. For example, having their treatment appropriately stopped because of side effects, or the indication for preventative treatment (glucocorticoids) being withdrawn.[39,45] Access to the full electronic health record and collaborative working with other clinicians involved in the patient care facilitated clinical decision making.[45] Treatment switching has also been shown to be more common in BMD-monitored patients,[43] and in the presence of continued support from specialist FLS to primary care.[27]

Mechanisms to offer targeted support

Targeting follow up interventions to non-adherent, high risk patients has been demonstrated to be a clinically and cost-effective strategy.[45,59] Strategies to identify these patients included using standardized search algorithms in a pharmacy database to identify patients not re-filling oral medication prescriptions or, an 'adherence scoring tool' patient questionnaire, asking if teriparatide treatment had been omitted, if people had 'lost interest' in their treatment and if people were clear on the benefits.[45,47] In both studies, the targeted intervention involved a clinician-patient consultation to explore problems, reiterate treatment importance. Self-reported adherence may not be an effective case finding strategy as one included study identified no correlation between self-reported compliance and persistence as assessed by pharmaceutical claims data.[34]

Mechanisms to offer integrated and sustainable support

Our background literature identified uncertainty about professional roles, between primary and secondary care as an important context to successful treatment.[7] Medication persistence with oral treatment was no different between primary and secondary or specialist (FLS) care interventions.[34,41] Collaboration between primary and secondary care may be more important than who actually delivers the intervention. [35] In one FLS study, the authors noted the FLS intervention increased work for the patient and PCP and postulated this was why the intervention was unsuccessful at altering long-term medication outcomes.[32]

We identified only one study which attempted to measure patient outcomes after FLS discharge, which had high rates of loss to follow up;[60] although self-reported adherence in the group contacted after FLS discharge (mean 19 months) was high (74%), unmet information needs were expressed by one third.

Discussion

Summary of findings

In this rapid realist review, we have identified important contexts and mechanisms key to optimising medicine use in people with osteoporosis. Using a 5-step model of medicines optimisation, we identified that for patients, interventions which support informed decision making are important during treatment initiation and may improve long-term commitment to treatment; potential mechanisms include improving their knowledge and understanding. However, supporting informed decision making, with follow up appointments is also important to manage 'disruption loops', where patients may question the effectiveness or safety of treatment. Targeting this follow up to those who most need it, also shows promise as a cost and clinically effective strategy. Supporting primary care clinician decision making and integration of primary and secondary care services also appears to be important, in improving rates of treatment initiation and adherence. Supporting patients' ability to adhere (e.g., by lowering treatment burden and issuing reminders) may be helpful to address practical difficulties, but there is little evidence for interventions which address practical treatment barriers without addressing patient beliefs and concerns.

Importantly, this review highlights a broad range of important outcomes of importance to our stakeholders and patient partners. Interventions which have been labelled as 'unsuccessful' for not significantly increasing adherence rates, have been identified as leading to changes in other important outcomes, such as identification of side effects and appropriate treatment switching or stopping. Paradoxically, previous research has neglected these outcomes by withdrawing patients from studies who had side effects and needed changes in treatment, in order to solely focus on adherence.[39]

Using a realist approach has enabled this review to move beyond a limited summary for what works and does not work, to understand what components of interventions work, for whom and why. Our findings suggest that follow up which aims purely to remind, persuade or reinforce treatment importance is insufficient to improve adherence and need to be combined with opportunities to address patients' perceptions of their condition and its treatment (necessity benefits and concerns). In realist terms, we consider that interventions which aim to 'push' information onto the patient are ineffective and interventions which 'interact', and are person-centred are needed[61]. This is in line with UK NICE guidance on Medicines Adherence (NICE),[3] informed by the Perceptions and Practicalities Approach,[18] which emphasizes that patients make decisions about medicines based on their understanding of their condition and the possible treatments, their view of their own need for the medicine and their concerns about the medicine. Although some interventions explicitly mentioned addressing patient concerns, no studies specifically reported eliciting or addressing patient perceptions about treatment need. Furthermore, understanding of 'the condition' may be problematic in the context of osteoporosis medicine which is recommended on the basis of high fracture risk, rather than for a diagnosis of osteoporosis. Osteoporosis 'treatment' is potentially a confusing concept when 'treatment' addresses fracture prevention rather than relief of symptoms.

Limited evidence from our review suggests that other interventions to remind and support routinisation are helpful, and may support persistence only, if patients want them, and they can be adapted to their needs. A significant literature evaluates the use of text reminders, although it has mainly focused on younger adults,[62] meaning that acceptability in people with osteoporosis is likely to be affected by health and/or digital literacy, or other barriers to communication such as

hearing, visual or cognitive impairment. Importantly, only one study within our review measured health literacy of participants and digital literacy and other barriers to communication were not generally considered or reported.[40] This is particularly important as people with low health literacy are more at risk of poor health outcomes and are less likely to engage with or adhere to recommended treatments.[63]

Strengths and limitations

Strengths of this review included the depth and breadth of the underpinning background literature, supporting theory and expertise of the study team. In addition, we had extensive stakeholder involvement, including with clinicians, academics, representatives from the ROS and patient advocates to validate our emerging programme theories. However, this review is subject to a number of limitations. First, our search may have missed studies as we used the term 'osteoporosis' to define the population but osteoporosis medicines may be given to people at high fracture risk, without this diagnosis. The quality of the included studies was mostly low, and the interventions within them often not described in detail. A number of the included studies were from specialist settings, although the findings still have relevance for non-specialist settings. Furthermore, authors rarely suggested mechanisms or underpinning theory supporting their interventions. This depth of description and study quality limited the available data to extract regarding context and mechanisms; however, our existing background qualitative literature, and the recent realist review in a similar area enabled us to theorize candidate C-M-O configurations. Our secondary searches were necessarily brief in view of the nature of this rapid realist review, and more attention to supporting literature may have enabled more exploration of possible mechanisms.

Implications for clinical practice

We suggest the findings of this review highlight the need for all healthcare professionals involved in the care of people with osteoporosis to consider opportunities to promote informed decision making, and a person-centred approach, in all patient contacts. Our stakeholder group felt strongly that outcomes other than adherence are important, and that the clinical community should recognise the value of long-term care and follow up, to not just monitor adherence but to address concerns, identify side effects, monitor effectiveness and discuss other issues such as lifestyle management. As both national and international audits which evaluate the success of FLS focus on adherence as a key performance indicator,[64] we suggest that services and national audit schemes might consider additional measures of 'success' including the extent of patient participation and involvement in shared decision making; however, choosing optimum outcome measures for shared decision making is also a question for research.[65] Finally, a particularly interesting finding is the importance and value of including elements of medicine optimisation interventions which address primary care healthcare professional needs in addition to the needs of patients; as such, specialist services might consider to what extent they already do this, or can enhance this aspect of their service.

Implications for research

We identified three key recommendations for researchers in this field. First, we suggest researchers consider how new interventions designed to improve medicines optimisation address the mechanisms we have described, and target both clinician and patient. Reporting of interventions would be improved by use of the TIDIER (template for intervention description and replication) checklist.[66] Second, we strongly suggest researchers target and measure outcomes other than adherence, including other clinical outcomes, patient experience measures and cost-effectiveness.

Finally, we ask researchers to consider how to engage and include populations who are under-represented in current work, including steroid users, and those most at risk of poor outcomes, including those with low health literacy and other barriers to communication.

In discussion with our stakeholders, we identified a need for further research to identify a sustainable, integrated, patient-centred, cost and clinically effective model of long-term care for people with osteoporosis. Further realist evaluation is needed to explore the model and extend, confirm or refute the emergent C-M-O configurations we have identified. This might include consideration for

- clinical decision-making needs
- how informed and shared decision making can be optimised, with specific attention to eliciting and addressing beliefs and concerns
- the role of clinical tests to monitor drug effectiveness
- the role of personalised or stratified approaches to long term care

Conclusion

For the first time, this rapid realist review summarises the important contexts and mechanisms which appear to be important in optimising medicine use in people with osteoporosis. We suggest people taking osteoporosis medicines need more patient-centred interventions and support to help them make informed decisions and reduce treatment burden. Targeting additional support and follow up to those most in need may be a cost and clinically effective approach to achieving this. Specialist services should consider the extent to which they integrate with, and support primary care clinical decision making, to impact long-term clinical outcomes.

Statements and Declarations

Funding

This work was supporting by funding from the Effectiveness Working Group of the Royal Osteoporosis Society Osteoporosis and Bone Research Academy. ZP is funded by the National Institute for Health Research (NIHR) Clinician Scientist Award (CS-2018-18-ST2-010)/NIHR Academy).

Professor Rob Horne is supported by the National Institute for Health Research (NIHR, Collaboration for Leadership in Applied Health Research and Care (CLAHRC), North Thames at Bart's Health NHS Trust and Asthma UK (AUKCAR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests

RH reports speaker engagements with honoraria with the following companies: AbbVie, Abbott, Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Biogen, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp Dohme, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi, Shire Pharmaceuticals, TEVA, UCB. RH is Founding Director of a UCL-Business company (Spoonful of Sugar Ltd) providing consultancy on treatment engagement and patient support programmes to healthcare policy makers, providers and pharmaceutical industry. ZP reports unpaid consultancy for UCB Pharma. OB, AS. LST and IM report no conflicts of interest.

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Table 1 - Characteristics of included studies in primary search

First Author Publication year	Country	Brief study aim(s)	Study design	Study settings	Participants	Study Quality
Bianchi et al. 2015 [22]	Italy	To evaluate efficacy of interventions for improving adherence and persistence through greater patient involvement, compared with standard clinical practice.	RCT	Outpatient	344 females, first prescription for medication.	Concerns
Cram et al. 2016 [23]	USA	To test if usual care augmented by a tailored patient-activation DXA result letter accompanied by an educational brochure would improve guideline-concordant pharmacological treatment compared to usual care only.	Cluster RCT	Outpatient	7749. Mean age 66.6 years, 83.8 % were women, and 75.3 % were non-Hispanic whites.	Low
Gonnelli et al. 2016 [24]	Italy	(1) Analyse persistence and compliance with oral OP meds and (2) evaluate whether individualised information on fracture risk improves adherence	Mixed	Outpatient	3379. (816 in RCT) Mostly female, median age 68/69 years	High
Liu 2021 [25]	Canada	Comparison of shared medical appointments (SMA) Vs usual care in decision to initiate treatment	Others	Outpatient	208 Women, median age 63 years	Low
Oral et al. 2015 [26]	Turkey Poland	Examine the compliance, persistence and preference between a fixed or flexible dosing regimen of daily risedronate	Mixed	Outpatient	448 postmenopausal females. 55–85 year-old,	Low
Roux et al. 2013 [27]	Canada	Evaluate 2 types of education intervention designed to increase initiation of treatment	Cluster RCT	Outpatient	881 over 50 men and women	Concerns
Sagalla 2021 [28]	USA	To evaluate the extent of and reasons for non-adherence to oral bisphosphonates among veterans and to assess the acceptability and feasibility of a pilot text message reminder	Cross-sectional survey	Outpatient	105 veterans 50 years and older men and women	Concerns
Seuffert et al. 2016 [29]	USA	Assess whether education and referral by a nurse practitioner could improve treatment adherence in patients with low bone mineral density	Cluster RCT	Outpatient	794 men and women	Concerns
Tamechika et al. 2018 [30]	Japan	To compare the usefulness and efficacy of monthly minodronate and weekly alendronate/risedronate for GIOP	Quasi-experimental	Outpatient	145 (102 females) 57.2 yrs [28.0, 83.0]; 54.2yrs [24.0,82.0].	Concerns
Wilton-Clark 2020 [31]	Canada	Evaluating the impact of autonomous treatment decisions after group consultations on adherence	Cohort	Outpatient	101 Postmenopausal women, mean age 62.7	Low
Beaton et al. 2017 [32]	Canada	To evaluate the impact of the implementation of the Fracture Clinic Screening Program on bone mineral density (BMD) testing, medication initiation, and medication persistence in the year after a fragility fracture.	Quasi-experimental	FLS	147,071, >50% females, main sample over 50s.	Low
Ducoulombier et al. 2015 [33]	France	To evaluate the contribution of phone follow-up to improve adherence to antiosteoporosis treatment among post-menopausal women with fractures.	RCT	FLS	164 females, mean age: 70.4 years	Concerns

Ganda et al. 2014 [34]	Australia	To determine whether management by a secondary fracture prevention (SFP) program results in better compliance and persistence to OP medication than follow-up by the primary care physician, after an SFP program.	RCT	FLS	94, >80% females; mean age 67.5 (11.3)/65.9 (9.9) yrs	Low
Makras 2020 [35]	Greece	Participation rates in FLS in Greece following fracture.	Other	FLS	1350	high
McAlister 2019 [36]	Canada	Compare patient/physician educational intervention Vs nurse led case manager	RCT	FLS	361, Mostly female, with history of fracture	Low
ScholtenDJ 2020 [37]	USA	To assess the effects of implementation of a FLS at a tertiary care academic medical centre on osteoporosis treatment adherence and secondary fracture rates.	Others	FLS	6178, 50 years above men and women	Concerns
Senay 2019 [38]	Canada	Aimed to assess patterns of drug use in a high-level intervention FLS.	Cohort	FLS	332, >40 years men and women	Concerns
van den Berg et al. 2018[39]	Netherlands	Compare the effect of phone calls vs no phone calls on adherence	RCT	FLS	93 female, mean age 67.9; 55–78 mean age 69.4; 53-86	Concerns
Danila et al. 2018 [40]	USA	To improve rates of osteoporosis treatment among a high-risk population who previously reported a fracture but currently were not using osteoporosis therapies	RCT	Primary care	2684 females. participants predominately Caucasian, mean age: 74.9.	Low
Hitz 2021 [41]	Denmark	(1) to compare treatment by GPs Vs OP specialists on adherence to OP meds	Cohort	Primary care	3685, Mostly female > 50 years, more men in GP grp	Concerns
LeBlanc et al. 2016 [42]	USA	Analyse effects of the osteoporosis choice decision aid compared to usual care with and without FRAX risk calculator on knowledge, involvement in decision making process, initiation and adherence to oral bisphosphonates	RCT	Primary care	79 women over age 50	Low
Leslie 2019 [43]	Canada	Comparison of regular BMD monitoring on adherence and fracture outcomes	Cohort	Primary care	9118 women, mean age of 68.0 and 68.1 years	Low
Parsons 2020 [44]	UK	Investigated effect of screening intervention (FRAX) on osteoporosis meds adherence	RCT	Primary care	12483 females, mean age 75.6	Concerns
Stuurman-Bieze et al. 2014 [45]	Netherlands	Provide proactive pharmaceutical care	Quasi-experimental	Community	495, 78.5% female mean age 67.0 (13.9)	High
Tüzün et al. 2013 [46]	Turkey	To assess the impact of active patient training on treatment compliance and persistence in patients with postmenopausal osteoporosis.	RCT	Others/ unclear	448 female, mean age 62.4±7.7 years	High
vanMaren 2019 [47]	Netherlands	Effect of educational and motivational support programme on adherence	Quasi-experimental	Community	1573, 87.5 % women, mean age 72	Low