

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Acceptability of bisphosphonates among patients, clinicians and managers: a systematic review and framework synthesis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040634
Article Type:	Original research
Date Submitted by the Author:	18-May-2020
Complete List of Authors:	<p>Paskins, Zoe; Keele University, School of Primary Community and Social Care; Haywood Hospital, Academic Rheumatology Centre Crawford-Manning, Fay; Keele University, School of Primary Community and Social Care; Haywood Hospital, Academic Rheumatology Centre Cottrell, Elizabeth ; Keele University, School of Primary, Community and Social Care Corp, Nadia; Keele University, School of Primary, Community and Social Care Wright, Jenny; Keele University, School of Primary Community and Social Care Jinks, Clare; Keele University, School of Primary, Community and Social Care Bishop, Simon; University of Nottingham, Centre for Health Innovation, Leadership and Learning Doyle, Alison; Royal Osteoporosis Society Ong, Terence; University of Malaya, Faculty of Medicine GITTOES, NEIL; University of Birmingham, Centre for Endocrinology Diabetes and Metabolism Leonardi-Bee, Jo; University of Nottingham, Faculty of Medicine & Health Sciences Langley, Tessa; University of Nottingham, Division of Epidemiology and Public Health Horne, Robert; University College London, School of Pharmacy Sahota, Opinder; Nottingham University Hospitals NHS Trust, Department of Geriatric Medicine</p>
Keywords:	Rheumatology < INTERNAL MEDICINE, Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Title: Acceptability of bisphosphonates among patients, clinicians and managers: a**
6 **systematic review and framework synthesis.**
7
8
9

10
11 Corresponding Author: Dr. Zoe Paskins, School of Primary Community and Social Care, Keele
12 University, David Weatherall Building, Newcastle-under-Lyme, UK, ST5 5BG and Haywood
13 Academic Rheumatology Centre, Haywood Hospital, High Lane, Burslem, Stoke-on-Trent ST6
14
15
16 7AG.

17
18
19 z.paskins@keele.ac.uk, 01782 733975
20

21 Author List:
22

23
24 Dr. Zoe Paskins, School of Primary, Community and Social Care, Keele University & Haywood
25 Academic Rheumatology Centre, Stoke-on-Trent, UK
26

27
28 Dr. Fay Crawford-Manning, School of Primary, Community and Social Care, Keele University
29 & Haywood Academic Rheumatology Centre, Stoke-on-Trent, UK
30

31
32 Dr. Elizabeth Cottrell, School of Primary, Community and Social Care, Keele University,
33 Newcastle-under-Lyme, UK
34

35
36 Dr. Nadia Corp, School of Primary, Community and Social Care, Keele University, Newcastle-
37 under-Lyme, UK
38

39
40 Dr. Jenny Wright, School of Primary, Community and Social Care, Keele University,
41 Newcastle-under-Lyme, UK
42

43
44 Prof. Clare Jinks, School of Primary, Community and Social Care, Keele University,
45 Newcastle-under-Lyme, UK
46

47
48 Dr. Simon Bishop, Centre for Health Innovation, Leadership and Learning, University of
49 Nottingham, Nottingham, UK
50

51
52 Alison Doyle, Royal Osteoporosis Society, Bath, UK
53

54
55 Dr. Terence Ong, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala
56 Lumpar, Malaysia
57
58
59
60

1
2
3 Prof. Neil Gittoes, Centre for Endocrinology Diabetes and Metabolism, University of
4 Birmingham, Birmingham, UK
5

6
7 Prof. Jo Leonardi-Bee, Faculty of Medicine & Health Sciences, University of Nottingham,
8 Nottingham, UK
9

10
11 Associate Prof. Tessa Langley, Division of Epidemiology and Public Health, University of
12 Nottingham, Nottingham, UK
13

14
15 Prof. Robert Horne, School of Pharmacy, University College London, London, UK
16

17
18 Prof. Opinder Sahota, Department of Geriatric Medicine, Nottingham University Hospitals
19 NHS Trust, Nottingham, UK
20
21

22
23
24
25 Author Statement:
26

27
28 Conceptualisation: ZP, SB, EC, AD, TO, NG, JLB, TL, OS. Protocol: ZP, EC, NC, SB, LLB, TL, TO,
29 OS, NG, AD. Search Implementation: ZP, EC, NC, JW, FCM. Data extraction and Quality: ZP,
30 EC, NC, JW, FCM, SB. Synthesis: ZB, SB, EC, FCM, RH, CJ. Writing- Original draft: ZP, FCM.
31 Writing- Review and Editing: ZP, SB, AD, TO, NG, JLB, CJ, TL, OS, FCM, JW, NC, NH, EC
32
33
34
35
36
37

38 Key Words:
39

40 Acceptability; Theoretical Framework of Acceptability, Bisphosphonates;
41 Osteoporosis
42
43

44 **Current word count 3875**
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Abstract** (299/300 words):
4

5 *OBJECTIVE:* To explore the acceptability of different bisphosphonate regimens for
6 the treatment of osteoporosis among patients, clinicians and managers, payers and
7 academics.
8
9

10 *DESIGN:* A systematic review of primary qualitative studies. Seven databases were
11 searched from inception to July 2019. Screening, data extraction and quality
12 assessment of full-articles selected for inclusion were performed independently by
13 two authors. A framework synthesis was applied to extracted data based on the
14 Theoretical Framework of Acceptability (TFA). The TFA includes seven domains
15 relating to sense-making, emotions, opportunity costs, burden, perceived
16 effectiveness, ethicality and self-efficacy. Confidence in synthesis findings was
17 assessed.
18
19

20 *SETTING:* Any developed country healthcare setting
21
22

23 *PARTICIPANTS:* Patients, healthcare professionals, managers, payers and
24 academics
25
26

27 *INTERVENTION:* Experiences and views of oral and intravenous bisphosphonates.
28
29

30 *RESULTS:* Twenty-five studies were included, mostly describing perceptions of oral
31 bisphosphonates. We identified, with high confidence, how patients and HCPs make
32 sense (coherence) of bisphosphonates by balancing perceptions of need against
33 concerns, how uncertainty prevails about bisphosphonate perceived effectiveness
34 and a number of individual and service factors that have potential to increase self-
35 efficacy in recommending and adhering to bisphosphonates. We identified, with
36 moderate confidence, that bisphosphonate taking induces concern, but has the
37 potential to engender reassurance, and that both side effects and special
38 instructions for taking oral bisphosphonates can result in treatment burden. Finally,
39 we identified with low confidence that multi-morbidity plays a role in people's
40 perception of bisphosphonate acceptability.
41
42

43 *CONCLUSION:* By using the lens of acceptability, our findings demonstrate with
44 high confidence that a theoretically informed, whole-system approach is necessary
45 to both understand and improve adherence. Clinicians and patients need supporting
46 to understand the need for bisphosphonates, and clinicians need to clarify to
47 patients what constitutes bisphosphonate treatment success. Further research is
48
49
50
51
52
53
54
55
56
57
58
59
60

needed to explore perspectives of male patients and those with multi-morbidity receiving bisphosphonates, and patients receiving intravenous treatment.

Strengths and Limitations

- Comprehensive search underpinned by theoretical framework
- Inclusion of clinician views in addition to patient perspectives.
- Use of GRADE-CERQual to give confidence in findings
- Lack of clarity on bisphosphonate regimens patients were taking in some included studies.

INTRODUCTION/BACKGROUND

Osteoporosis is a disease that is characterised by skeletal fragility and changes in bone microarchitecture resulting in increased risk of fractures with no or low trauma.[1] The management and care of people with low trauma or fragility fractures results in considerable societal economic burden, annual cost in the UK alone is £4.4 billion.[2] Furthermore, the personal impact of fragility fractures is considerable, with potential deleterious effects on physical and psychological health, ability to live independently and increased risk of death. Many of these fractures are potentially preventable with appropriate cost- and clinically-effective drug treatments such as bisphosphonates, the mainstay of osteoporosis treatment. However, the success of treatment depends on patients initiating (starting), executing (or implementing - taking correctly) and persisting (continuing) medication; collectively these processes are described as adherence. Adherence with osteoporosis medications is notoriously poor and reported to be poorer than other disease areas. Oral bisphosphonate persistence rates at 1 year are commonly estimated between 16 and 60%. [3] Worldwide, many people who would benefit from osteoporosis drugs are not receiving them, and this treatment gap has been described as an 'osteoporosis crisis'. [4] The treatment gap is compounded by poor adherence which results in potentially preventable fragility fractures with their associated burden for patients and their carers, difficulties in professional-patient relationships, and wasted healthcare resources. [5]

1
2
3 There are a number of different bisphosphonates, some are administered orally
4 others intravenously. A variety of regimes in terms of dose frequency also exists.
5 Alendronic acid, an oral once-weekly bisphosphonate, is considered first-line and
6 most commonly used.[6] Bisphosphonates work to reduce fracture risk. A recent
7 network meta-analysis demonstrated that bisphosphonate treatment reduces the risk
8 of fragility fracture (depending on site) by 33-54%.[6] Oesophageal or
9 gastrointestinal related side effects are the most common adverse effects of oral
10 bisphosphonate use. To counter these, patients taking oral bisphosphonates are
11 required to remain upright and fast for half an hour after ingestion. Rare side effects
12 of bisphosphonates include osteonecrosis of the jaw and atypical femur fractures,
13 both of which have received significant media attention. Such media reports are
14 temporally related to declining bisphosphonate use.[7] Due to the gastrointestinal
15 side effects and special instructions for taking oral treatment, it has been suggested
16 that alternative bisphosphonate regimens, for example annual intravenous
17 zoledronic acid, may promote long-term adherence.[8-11] Studies to date which
18 have examined patient preferences for osteoporosis treatment, suggest that patients
19 prefer injections given less frequently;[12-14] however, research in other chronic
20 diseases shows that although adherence is improved with less frequent medications
21 and that patients prefer oral to injection treatment.[15] In osteoporosis, the majority
22 of studies that explore patient preferences employ quantitative methods, for
23 example, discrete choice experiments where patients are asked to choose between
24 hypothetical treatments in regards to various attributes (e.g. efficacy, side effects,
25 route and frequency of administration).[13] Such studies cannot provide
26 comprehensive insight into patient views, experiences or the explanations for these
27 preferences.

28
29 In order to fully understand the osteoporosis treatment gap, and ultimately improve
30 adherence, it is important to understand perspectives of all relevant stakeholders:
31 patients, healthcare professionals (HCPs), managers, payors and academics.[16,17]
32 This can be achieved using the lens of 'acceptability', defined as "a multi-faceted
33 construct that reflects the extent to which people delivering, or, receiving a
34 healthcare intervention consider it to be appropriate, based on anticipated or
35 experienced cognitive and emotional responses to the intervention".[18,19] In the
36 context of a research program designed to determine the research agenda for
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 optimising bisphosphonate treatment, the primary aim of this systematic review is to
4 explore the acceptability of different bisphosphonates regimens among patients, and
5 clinicians and managers.
6
7
8
9

10 11 **METHODS**

12
13 We conducted a systematic review and framework synthesis of qualitative studies
14 exploring patient and clinician views and experiences of bisphosphonates. The
15 conduct and reporting of this review followed the Preferred Reporting Items for
16 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see supplementary
17 material Table 1 for PRISMA checklist). The protocol of the systematic review is
18 registered in PROSPERO [CRD42019143526].
19
20
21
22
23

24 **Eligibility**

25
26 To be eligible for inclusion, studies needed to report on patients', clinicians',
27 academics', and/or manager/payers' experiences and preferences regarding
28 bisphosphonate regimens for adults (≥ 18 years) with osteoporosis. Bisphosphonates
29 needed to be mentioned by name, or there needed to be sufficient information that
30 was specific to bisphosphonate (e.g. reference to the special instructions for use of
31 oral bisphosphonates), to deduce that study findings related to bisphosphonates, as
32 agreed by two clinically experienced authors independently. Papers describing
33 experiences of osteoporosis more generally were included if there were findings
34 relating to bisphosphonate treatment in the study abstract. Studies were only
35 included if they were qualitative in design, or mixed methods with a qualitative
36 component, relevant to a developed country setting and written in English language.
37 Studies were excluded that involved paediatric patients; patients and clinicians
38 receiving/recommending other treatments for osteoporosis; and studies in which
39 bisphosphonates were being used for other indications (e.g. malignancy or Paget's
40 disease).
41
42
43
44
45
46
47
48
49
50
51

52 **Search Methods**

53
54 Systematic searches were conducted in 7 bibliographic databases (MEDLINE,
55 EMBASE, AMED, CINAHLPlus, PsycINFO, ASSIA, and Web of Science [Social
56 Science Citation Index (SSCI) and Conference Proceedings Citation Index- Social
57
58
59
60

1
2
3 Science & Humanities (CPCI-SSH)] from inception to 15th July 2019. The search
4 strategy utilised database subject headings and text word searching in title, abstract
5 or keywords, combining terms for: 1) bisphosphonates; 2) experiences and
6 preferences; and 3) qualitative research, based on DeJean et al.'s search filter (see
7 supplementary material 2 for full MEDLINE search strategy).[21] Search terms were
8 adapted as appropriate for each database platform.
9
10
11
12

13
14 In addition, grey literature was searched (DART Europe, Open Grey, and NDLTD
15 (National Digital Library of Theses and Dissertations)); the reference lists of all
16 included studies and relevant systematic reviews identified were checked and key
17 studies were citation tracked.
18
19
20

21 **Study Selection**

22
23 Two-stage screening of articles against eligibility criteria was undertaken. Firstly,
24 titles and abstracts were screened, then full texts. At both stages screening was
25 conducted by sets of two reviewers independently (NC, EC, ZP) and articles were
26 excluded by agreement. Disagreements were resolved through discussion or by third
27 reviewer adjudication.
28
29
30
31

32 **Data extraction**

33
34 For each paper data extraction was completed independently by two researchers
35 (ZP and JW or EC and FM). Key findings from the results sections of papers relating
36 to bisphosphonates were extracted; a 'key finding' was defined as any sentence or
37 statement relating to views or experiences of bisphosphonates from the results
38 section of the paper or abstract. Wherever possible, the key finding was extracted as
39 written by the author, with minimal edits only for clarification, description of context or
40 for consistency across papers. For each paper, two authors extracted key findings
41 independently, and subsequently agreed a final list of key findings for each paper.
42 Data were also extracted on participant numbers and demographics, data collection
43 technique, setting and country. Additionally, if available for patients, information was
44 extracted on their bisphosphonate use including type of drug and current status
45 (adherent, non-adherent, decliner).
46
47
48
49
50
51
52
53
54
55

56 **Quality appraisal**

57
58 The quality of each study was assessed using the CASP qualitative tool. This tool
59 consists of 10 items split into 3 sections (qualitative suitability, data analysis and
60

1
2
3 overall quality). The first two sections consist of items related to qualitative suitability
4 and data analysis, which were evaluated as “yes”, “no”, “unclear” or “partial”. The
5 final section was an assessment based on the overall quality of the paper including
6 the previous items and its relevance to the review objectives, this was rated as
7 “high”, “moderate” or “low”. All papers were quality appraised by two researchers
8 independently (FM, SB, JW). Disagreements were resolved through discussion with
9 a fourth reviewer (ZP).

16 **Synthesis**

17 We used a framework synthesis approach informed by the ‘Best Fit’ model described
18 by Carroll et al.[20] The “best fit” method offered a means to test, reinforce and build
19 on an existing published model, conceived for a different but relevant purpose. This
20 approach was chosen as a published theory was identified from the literature that
21 conceptualised acceptability - the Theoretical Framework of Acceptability (TFA).[18]
22 The TFA is a relatively new framework which was developed to inform the
23 understanding of acceptability of complex interventions, and consists of seven
24 constructs: affective attitudes - the emotions elicited by an intervention; intervention
25 coherence - the extent to which an intervention makes sense; perceived
26 effectiveness - the perceived extent to which intervention will achieve purpose;
27 burden – the amount of effort required to participate in an intervention; self-efficacy –
28 individual’s confidence that they can perform the behaviour(s) required to participate
29 in the intervention; opportunity-costs - the extent to which benefits, profits, or values
30 must be given up to engage in an intervention; and ethicality – the extent to which an
31 intervention has a good fit with an individual’s values. The framework also
32 incorporates temporal perspectives on *anticipated* and *experienced* acceptability at
33 three time points before (prospective), during (experienced) and after (retrospective)
34 experience of an intervention.

35 The TFA has not previously been used to evaluate drug acceptability. We anticipated
36 the seven constructs of the TFA would be relevant to engagement with drug
37 treatment; for example, burden could relate to treatment burden associated with
38 administering the drug or side effects. However, one aspect which did not appear to
39 be explicitly conceptualised within the framework was patient beliefs about
40 medicines. Studies across a range of long term conditions, healthcare systems and
41 cultures have consistently shown that engagement with treatment is influenced by
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 patients' personal evaluation of the medicine in question.[21] Particularly important is
4 how they judge their personal need for treatment relative to their concerns about it.
5 For this reason, we therefore included the Necessity Concerns Framework (NCF)
6 [21], to further explore the TFA domain relating to intervention coherence.
7
8
9

10 The first author initially conducted inductive open coding on the data extracted,
11 before mapping the codes to a draft framework derived from a priori themes (the
12 domains of the TFA). Authors then met to first discuss the themes and compare
13 findings for each study and the 'fit' to the draft framework. A preliminary synthesis
14 was achieved using tabulation of studies, organising the studies into groups relating
15 to temporal perspectives and research question, and exploring relationships between
16 studies and between groups.
17
18
19
20
21
22

23 A final coding framework was agreed at a second meeting of authors. A second
24 author (FM) recoded the original key findings, where necessary, to the new
25 framework to ensure all findings were represented. Finally, relationships between
26 themes and TFA and NCF domains were explored by further group discussion. We
27 used the Grades of Recommendation, Assessment, Development, and Evaluation
28 Confidence in the Evidence from Qualitative Reviews (GRADE-CERQual) approach
29 to determine confidence in our synthesised findings.[22]
30
31
32
33
34
35
36
37
38

39 RESULTS

40 The literature search identified 2040 unique articles, of which 25 met eligibility criteria
41 (Figure 1), a summary of the studies is shown in Table 1.
42
43
44

45 The included studies were categorised into three groups: perceptions of
46 osteoporosis generally; [23,24,26,27,31,38,39] healthcare service delivery issues
47 unrelated to osteoporosis (de-prescribing) [35] and inter-professional communication
48 in primary care[34]) and studies specific to osteoporosis treatments. The latter group
49 was further subdivided into: those examining treatment barriers;[16,28,36,37,42,43]
50 adherence;[29–30,44] decision-making;[32–33,40,41,46] or bisphosphonate-related
51 side effects.[25,45] Only one study examining adherence and one examining
52 decision making had research questions which specifically related to
53 bisphosphonates.[30,41]
54
55
56
57
58
59
60

1
2
3 The majority (23) of studies were conducted in North America or Europe. Eleven
4 studies explored patient views,[23–33] six explored HCPs' views,[34–39] seven had
5 a mixed sample[16,40–45] and two studies interviewed managers.[16,37] No studies
6 included academic or payor participants. Of the 18 papers that included patients, 10
7 studies described how many of the patients were on anti-osteoporotic medication,
8 however, only two reported the specific type of medication. Only one study reporting
9 patient experience of receiving intravenous bisphosphonate.[31]
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1: Summary of included studies

Studies in Group 1: Views of Osteoporosis						
First author and year	Participantsⁱ	Participant No. (male:female)	Bisphosphonate use and adherenceⁱⁱ	Data collection methods	Recruitment setting	Country
Besser 2012[23]	Pts	14 (0:14)	AOD unspecified	Interview	One hospital	UK
Jaglal 2003[39]	HCPs Family Physicians (n=32)	32 (12:20)	N/A	Focus group	Primary Care	Canada
Otmar 2012[38]	HCPs GP (n = 14), Practice nurse (n = 2)	16 (11:5)	N/A	Focus group	Primary care	Australia
Sale 2015[24]	Pts	28 (2:26)	19/28 pts on AOD adherent (n=19) declined (n= 4)	Interview	National osteoporosis patient group	Canada
Sale 2010[26]	Pts	24 (6:18)	9/24 pts on AOD, risedronate (n=8), etidronate (n=1)	Focus group	Fracture Clinic	Canada
Weston 2011[27]	Pts	10 (0:10)	AOD unspecified	Interview	Primary Care	UK
Hansen 2017[31]	Pts	15 (0:15)	AOD unspecified adherent (n=12) declined/stopped AOD (n=3)	Interview	Women attending DXA at 2 hospitals	Denmark
Studies in Group 2: Views of Osteoporosis Treatment (treatment barriers)						
Alami 2016[42]	Mixed	Pts: 37 (0:37) HCPs: 18 (8:10)	23/47 pts on AOD, adherent (n=19) declined/stopped AOD (n=18)	Focus group	Hospital/community over 5 regions	France
Drew 2016[37]	HCPs Nurse (n = 14), GP (n= 2), Specialists (n =17), Orthopaedic Surgeon (n = 4) Managers (n = 5), DXA technician (n=1)	43 (not given)	N/A	Interview	11 hospitals in one region	UK
Feldstein 2008[16]	Mixed	Pts: 10 (0:10) HCPs: 57 (not given)	AOD unspecified	Interview and focus group	Primary and secondary care	USA
Guzman-Clarke 2007[43]	Mixed	100 (94:6)	24/100 pts on AOD	Focus group	Urban academic Medical Centre	USA
Merle 2019(a)[28]	HCPs (GP)	16 (11:5)	N/A	Interview	Primary Care	France
Merle 2019(b)[36]	Pts	98 (53:45)	AOD Unspecified	Focus group	Recruited from 2 existing research studies and community (medical insurance company)	France
Studies in Group 2: Views of Osteoporosis Treatment (adherence)						
Iversen 2011[44]	Mixed	Pts: 32 (2:30) HCPs: 12 (5:7)	AOD unspecified	Focus group	Secondary care	USA
Lau 2008[29]	Pts	37 (0:37)	33/37 pts on AOD, alendronate (n=9), etidronate (n=5),	Focus group	Primary care, secondary care and community pharmacies	Canada

			risedronate (n=19)			
1	Salter 2014[30]	Pts	30 (0:30)	20/30 pts on AOD adherent (n=19) declined (n=1) stopped AOD (n=10)	Interview	Primary Care UK
2						
3						
4						
5	Studies in Group 2: Views of Osteoporosis Treatment (Decision Making)					
6	Mazor 2016[32]	Pts	36 (0:36)	15/36 pts on AOD adherent (n=15) declined (n=10) stopped (n=11)	Telephone Interview	Primary Care USA
7						
8						
9						
10	Sale 2011[46]	Pts	24 (6:15)	14/21 pts on AOD	Telephone Interview	Hospital based fracture screening programme Canada
11						
12	Swart 2018[40]	Mixed	Pts: 26 (4:22) HCPs: 13 (not given)	10/26 pts on AOD adherent (n=10) declined (n=16)	Interview	Recruited from a fracture prevention study Netherlands
13						
14	Scoville 2011[41]	Mixed	Pt: 18 (0:18) HCP: 19 (12:7)	N/A	Videographic	Primary care (osteoporosis choice trial) USA
15						
16	Wozniak 2017[33]	Pts	12 (3:9)	7/12 pts on AOD, adherent (n=7) stopped (n=5)	Interview	Recruited from a fracture prevention trial nested in secondary care Canada
17						
18						
19	Studies in Group 2: Views of Osteoporosis Treatment (Bisphosphonate side effects)					
20	Sturrock 2019[45]	Mixed	24 (4:19)	13/23 pts on AOD	Interview	Three regions including from secondary care UK
21						
22	Sturrock 2017[25]	Pts	17 (7:10)	N/A	Interview	Primary Care UK
23						
24	Studies in Group 3: Non-Specific Osteoporosis Issues					
25	Ailabouni 2016[35]	HCPs	10 GPs	N/A	Interview	Primary Care New Zealand
26	Sippli 2017[34]	HCPs	28 (6:22)	N/A	Interview	Primary Care Germany
27						
28						
29						

ⁱ Pts – patients; HCPs – healthcare professionals

ⁱⁱ Where specified. AOD – anti-osteoporosis drug. N/A not applicable

1
2
3 The findings related to quality appraisal are summarised in Table 2. The most
4 common limitations of the included studies were lack of description of author
5 reflexivity, lack of depth of analysis, use of normative statements and relatively small
6 samples or studies conducted in a single site which may limit transferability of the
7 findings. Furthermore, although the characteristics of the sample were generally
8 reasonably described, in order to address our research question, we required
9 information about medication use of participants which was frequently not described.
10
11

12
13 Using the CASP tool, 12 (48%) studies were scored as high value and the remaining
14 13 (52%) studies as moderate value. For 8/13 (62%) studies scored as moderate in
15 value, this was because the focus of the paper was less relevant to our research
16 question rather than because of methodological issues.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 2. Quality Appraisal

First author and year	CASP tool Question										Comments ⁱ
	1	2	3	4	5	6	7	8	9	10	
Group 1: Views of Osteoporosis											
Besser 2012[23]	✓	✓	✓	p	✓		✓	p	✓	Moderate	Small sample, no mention of data saturation, limited to 'psychological' factors affecting adherence (discounting other factors by omission) and some use of normative statements
Jaglal 2003[39]	✓	✓	✓	✓	✓	u	✓	✓	✓	Moderate	Few findings relevant to our research question
Otmar 2012[38]	✓	✓	✓	✓	✓		✓	✓	✓	Moderate	Well conducted study, but limited findings relating to bisphosphonates
Sale 2015[24]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
Sale 2010[26]	✓	✓	✓	p	✓	u	✓	p	✓	Moderate	Small single site study, although data saturation reached. Language does not always appear to match approach (e.g. reporting patient 'inability' to link fractures to osteoporosis suggests prior normative assumptions)
Weston 2011[27]	✓	✓	✓	✓	✓	✓	✓	✓	✓	High	
Group 2: Views of Osteoporosis Treatment											
Alami 2016[42]	✓	✓	✓	✓	✓		✓	✓	✓	High	
Drew 2016[37]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
Feldstein 2008[16]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
Guzman- Clarke 2007[43]	✓	✓	✓	✓	✓	u	✓	u	✓	Moderate	Only partially relevant for our review given the focus on a specific population (Glucocorticoid-Induced Osteoporosis)
Merle 2019[28]	✓	✓	✓	p	✓	u	✓	u	✓	Moderate	Small sample (although data saturation reached) without attempt to structure to population and analysis lacks depth to answer our objective relating to bisphosphonate acceptability
Merle 2019[36]	✓	✓	✓	✓	✓	u	✓	✓	✓	Moderate	Limited information relevant to our research question in view of general focus on osteoporosis
Iversen 2011[44]	✓	✓	✓	p	✓		✓	p	✓	Moderate	Single centre study, although data saturation reached, limited information on coding/analysis and no discussion of findings with relevance to wider literature
Lau 2008[29]	✓	✓	✓	✓	✓		✓	✓	✓	High	
Salter 2014[30]	✓	✓	✓	✓	✓		✓	✓	✓	High	

1	Hansen 2017[31]	✓	✓	✓	✓	✓	✓	✓	✓	✓	High	
2												
3	Mazor 2016[32]	✓	✓	✓	✓	✓	u	✓	u	✓	Moderate	Good relevance, single site. Descriptive approach without critical reflexivity or discussion of prior assumptions
4												
5	Sale 2011[46]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
6												
7	Swart 2018[40]	✓	✓	✓	✓	✓	✓	✓	✓	✓	High	
8												
9	Scoville 2011[41]	✓	✓	✓	✓	✓	u	✓	✓	✓	Moderate	Well conducted videographic study, but data coded against deductive categories of reasons to reject treatment, so limited potential to inform our objective about acceptability
10												
11	Wozniak 2017[33]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
12												
13	Sturrock 2019[45]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
14												
15	Sturrock 2017[25]	✓	✓	✓	✓	✓		✓	✓	✓	Moderate	Aim only partially relevant to study question
16												
17	Group 3: Non-specific Osteoporosis Issues											
18												
19	Ailabouni 2016[35]	✓	✓	✓	p	✓	✓	✓	✓	✓	Moderate	Relatively small (10 respondents) study, although data saturation reached. Only partial relevant for current review with brief coverage of GPs views on discontinuing bisphosphonates in light of multimorbidities
20												
21	Sippli 2017[34]	✓	✓	✓	✓	✓		✓	✓	✓	Moderate	Limited findings related to our research question
22												
23												
24												
25												
26												
27												
28												
29	i CASP Quality assessment questions; 1, Was there a clear statement of the aims of the research? 2, Is a qualitative methodology appropriate? 3, Was the research design appropriate to address the aims of the research? 4, Was the recruitment strategy appropriate to the aims of the research? 5, Was the data collected in a way that addressed the research issue? 6, Has the relationship between researcher and participants been adequately considered? 7, Have ethical issues been taken into consideration? 8, Was the data analysis sufficiently rigorous? 9, Is there a clear statement of findings? 10, Value of study and relevance to review objectives. ✓ = Yes, u = Unsure, p = partial, blank = No.											
30												
31												
32												
33												
34	ii Comments only made for those ranked Moderate or Low.											
35												
36												
37												
38												
39												
40												
41												
42												
43												
44												
45												
46												

1
2
3 Fifteen individual sub-themes were identified which mapped to the seven domains of
4 the TFA. Key findings relating to ethicality related to conflict between
5 bisphosphonates and participants' values and were usually discussed as part of
6 sense making. For this reason, issues relating to 'ethicality' were considered as part
7 of 'intervention coherence', leaving six main themes, as shown schematically in
8 Figure 2. Although it was possible to distinguish between two temporal perspectives,
9 related to anticipated and experienced acceptability within most domains (with the
10 exception of self-efficacy) the majority of anticipated acceptability findings related to
11 intervention coherence.
12
13
14
15
16
17
18

19 The findings of the review are discussed below with GRADE-CERQual ratings of
20 confidence in Table 3 and illustrative key findings for each theme/subtheme shown in
21 Supplementary material 3. Subthemes are identified in the text in italics.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 3: GRADE-CERQual Summary of qualitative findings table

Review Finding [and contributing studies]	Methodological limitations	Coherence	Adequacy	Relevance	CERQual Confidence assessment
	Concerns				
<p>Intervention coherence: Both before starting, and during treatment, patients considered the perceived need or necessity for bisphosphonates based on their views of osteoporosis, including its seriousness and controllability, symptoms and their perception of their own health. Perceived need was weighed up against concerns about medication, including suspicion of drugs in general and specific concerns about bisphosphonate safety by both patients and HCPs. HCPs sometimes used principles of ethicality to support perceptions of low necessity and their reluctance to prescribe. The decision process of balancing necessity against concerns, was influenced by the doctor-patient relationship and wider societal influences including friends, family and the general media. This process influenced whether HCPs reported recommending bisphosphonates. For patients, the decision process could be explicit or tacit, was revisited over time and influenced both whether they initiated treatment and subsequently adhered. [16,23,33,35,36,38–44,24,45,46,257,26,28–32]</p>	<p><i>Minor</i> 12/22 papers rated moderate value due to sample size, depth of analysis or lack of reflexivityⁱ</p>	<p><i>None or very minor</i> The finding reflects the complexity and variation of the data, and these influences on sense making are well supported by details in the underlying studies</p>	<p><i>None or very minor</i> 22 papers contributed to this finding, and although some gave little detail, in-depth insights were reported in 10 papers and information was consistent across studies</p>	<p><i>Minor</i> Spread of studies from primary and secondary care and range of countries. Uncertainties remain about sense making related patients taking intravenous bisphosphonates and influence of gender</p>	<p>HIGH</p>
<p>Perceived effectiveness Both patients and HCPs expressed doubt or uncertainty about the mechanism of effectiveness of bisphosphonates and expressed a range of treatment expectations including strengthening bone - improving bone density, preventing worsening of osteoporosis - maintaining bone density and/or total fracture prevention. Patients wanted proof or evidence of effectiveness through more structured monitoring and follow-up, and were disincentivised to continue treatment in the absence of evidence of perceived effectiveness. [16,23,24,30,32,37,39–42,44]</p>	<p><i>Minor</i> 7/15 papers rated moderate value, mostly (4/7) due to limited relevant content. Methodological concerns relate to depth of analysis or lack of reflexivityⁱ</p>	<p><i>None or very minor</i> The finding reflects the complexity and variation of the data, and these issues are supported by details in the underlying studies</p>	<p><i>None or very minor</i> 15 papers contributed to this finding. Some gave little detail, but in-depth insights were reported in 6 papers and information was consistent</p>	<p><i>Minor</i> Spread of studies from primary and secondary care and range of countries. Uncertainties remain about perceived effectiveness of intravenous bisphosphonates</p>	<p>HIGH</p>
<p>Self-efficacy Measures to help patients integrate medication taking into daily routines (supporting routinisation), and the provision of information and support, enhanced their feeling of having control over their health and confidence to adhere to bisphosphonates. Clinician reported barriers to supporting adherence related to perceptions of their knowledge and attitudes, with several knowledge gaps and uncertainties reported, and the perception that osteoporosis was not a priority. Finally, service level barriers which impaired clinicians' self-efficacy in recommending and managing patients on bisphosphonates, included uncertainty</p>	<p><i>Minor</i> 7/15 papers rated moderate value, mostly (4/7) due to limited relevant content. Methodological concerns relate to</p>	<p><i>None or very minor</i> The finding reflects the complexity and variation of the data, and these issues are supported by details in the underlying studies</p>	<p><i>None or very minor</i> 17 papers contributed to this finding. Some gave little detail, but in-depth insights were reported in 5 papers and</p>	<p><i>Minor</i> Spread of studies from primary and secondary care and range of countries. Uncertainties remain about self-efficacy relating to</p>	<p>HIGH</p>

<p>about professional roles and responsibilities, capacity, access to intravenous drugs and communication and IT systems. [16,24,37–39,42–45,25,27–31,34,35]</p>	<p>depth of analysis or sample sizeⁱ</p>		<p>information was consistent.</p>	<p>intravenous bisphosphonates</p>	
<p>Affective attitudes: The emotions elicited by bisphosphonates were closely related to intervention coherence. Bisphosphonates were associated predominantly with negative emotions of fear (of side effects) and annoyance (with special instructions); however positive emotions of reassurance and hope were noted in two studies, linked to the anticipated protection that bisphosphonates could incur. [16,23,27,29–32,42]</p>	<p><i>Minor</i> 2/8 papers rated moderate value due to depth of analysis or lack of reflexivityⁱ</p>	<p><i>None or very minor</i> The finding reflects the data, supported by details in the underlying studies</p>	<p><i>Moderate</i> Reports of affective attitude were mostly descriptive with little depth</p>	<p><i>Moderate</i> Uncertainties remain about affective attitudes to injectable bisphosphonates received in hospital</p>	<p>MODERATE</p>
<p>Burden: The burden or effort of oral bisphosphonates was described mostly relating to the special instructions to take oral bisphosphonates or experienced side effects, although costs incurred were also a potential source of burden. [16,23,45,27–31,40,41,44]</p>	<p><i>Minor</i> 4/11 papers rated moderate value due to sample size, depth of analysisⁱ</p>	<p><i>None or very minor</i> The finding reflects the data, and these aspects of burden are supported by details in the underlying studies</p>	<p><i>Moderate</i> Reports mostly descriptive with little depth and a possible focus on presence of burden (side effects) rather than absence</p>	<p><i>Moderate</i> Uncertainties remain about burden of indirect costs (travel, dental checks) & burden due to intravenous bisphosphonates</p>	<p>MODERATE</p>
<p>Opportunity costs Circumstances where competing priorities challenged adherence or initiation of bisphosphonates were described relating to co-morbid conditions. The presence of comorbid conditions were described as resulting in less time to support discussion about bisphosphonates in consultations and, result in recommendation of, and adherence to, bisphosphonates being given relative low priority. [16,25,46,28,30,31,33,36,39,40,45]</p>	<p><i>None or very minor</i> 4/11 papers rated moderate value, but this was mostly (n=3) due to limited relevant content rather than methodological concerns.</p>	<p><i>Moderate</i> No discussion of the alternative explanation that having co-morbid conditions may facilitate bisphosphonate acceptability</p>	<p><i>Moderate</i> Reports were limited/lacked depth 3 papers contained little content relevant to the research question</p>	<p><i>Moderate</i> No information about values, benefits that have to be given up to partake in intravenous bisphosphonates, which are likely to be different & likely limited sampling of patients with complex health needs</p>	<p>LOW</p>

ⁱ Concerns considered minor because of the methodological strength of the other papers in this domain, & low likelihood that reflexivity would affect finding

Intervention Coherence (high confidence)

Both before starting, and during treatment, patients considered the perceived need or *necessity* for bisphosphonates based on their views of osteoporosis, including its seriousness and controllability, symptoms and their *perception of their own health*. Perceived need was weighed up against *concerns* about medication, including suspicion of drugs in general and specific concerns about bisphosphonate safety, by both patients and HCPs. HCPs sometimes used principles of *ethicality* to support perceptions of low necessity and their reluctance to prescribe. The *decision process* of balancing necessity against concerns, was influenced by the doctor-patient relationship and wider societal influences including friends, family and the general media. This process influenced whether HCPs reported recommending bisphosphonates. For patients, the decision process could be explicit or tacit, was revisited over time and influenced both whether they initiated treatment and subsequently adhered.

Perceived Effectiveness (high confidence)

Both patients and HCPs expressed doubt or uncertainty about the *mechanism of effectiveness* of bisphosphonates and expressed a range of treatment expectations including strengthening bone - improving bone density, preventing worsening of osteoporosis - maintaining bone density and/or total fracture prevention. Patients wanted proof or evidence of effectiveness through more structured *monitoring and follow-up*, and were disincentivised to continue treatment in the absence of evidence of perceived effectiveness.

Self-efficacy (high confidence)

Measures to help patients integrate medication taking into daily routines (*supporting routinisation*), and the provision of information and support, enhanced their feeling of having control over their health and confidence to adhere to bisphosphonates. Clinician reported barriers to supporting adherence related to perceptions of their *knowledge and attitudes*, with several knowledge gaps and uncertainties reported, and the perception that osteoporosis was not a priority. Finally, *service level barriers* which impaired clinicians' self-efficacy in recommending and managing patients on

1
2
3 bisphosphonates, included uncertainty about professional roles and responsibilities,
4 capacity, access to intravenous drugs and communication and IT systems.
5
6
7
8

9
10 **Affective attitudes** (moderate confidence)

11
12 The *emotions* elicited by bisphosphonates were closely related to intervention
13 coherence. Bisphosphonates were associated predominantly with negative emotions
14 of fear (of side effects) and annoyance (with special instructions); however positive
15 emotions of reassurance and hope were noted in two studies, linked to the
16 anticipated protection that bisphosphonates could incur.
17
18
19
20
21
22

23
24 **Burden** (moderate confidence)

25
26 The burden or effort of oral bisphosphonates was described mostly relating to the
27 *special instructions* to take oral bisphosphonates or experienced *side effects*,
28 although *costs* incurred were also a potential source of burden. Only one study
29 included the experience of a patient on an intravenous bisphosphonate, this patient
30 described low treatment burden as she only had to go once a year, and felt no side
31 effects.[31]
32
33
34
35
36
37
38

39
40 **Opportunity costs** (low confidence)

41
42 There were few descriptions of 'benefits, profits, or values' being given up to take
43 bisphosphonates. However, circumstances where competing priorities challenged
44 adherence or initiation of bisphosphonates were described relating to *co-morbid*
45 *conditions*. The presence of comorbid conditions was described as resulting in less
46 time to support discussion about bisphosphonates in consultations and, result in
47 recommendation of, and adherence to, bisphosphonates being given relative low
48 priority.
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

This systematic review has used the lens of acceptability to understand perceptions of bisphosphonates and the problem of poor adherence. We have identified, with high confidence, how patients and HCPs make sense (coherence) of bisphosphonates by balancing perceptions of need against concerns, how uncertainty prevails about perceived effectiveness of bisphosphonates and how a number of individual and service factors have potential to increase self-efficacy in recommending and adhering to bisphosphonates. We identified with moderate confidence, that bisphosphonate taking induces fear, but has the potential to engender reassurance, and that both the side effects and special instructions for taking oral bisphosphonates can be a source of treatment burden. Finally, we identified with low confidence that multi-morbidity plays a role in people's perception of bisphosphonate acceptability.

To our knowledge, this is the first use of the Theoretical Framework for Acceptability, originally developed to evaluate acceptability of complex interventions, to evaluate the acceptability of medication. We explored the utility of the TFA from two perspectives, as an explanatory model for both patient and clinician acceptability and engagement. The TFA was useful for understanding and combining patient and clinician viewpoints; however, there was considerable overlap between domains; perceived efficacy, affective attitudes and self-efficacy beliefs are all likely to impinge on sense-making, or intervention coherence. The TFA alone does not provide a comprehensive framework for understanding patient acceptability or engagement with medicines, and of course it was not intended to do so. The sense-making aspect of the framework appeared pivotal, and the explanatory value of the framework was enhanced by the incorporation of the NCF to operationalise key engagement related beliefs. In the context of bisphosphonates, concern and associated fears predominate among patients, and perceived need may be underestimated if the consequences of osteoporosis and fragility fractures are not explained. In our findings, sense making was dynamic. Patients re-evaluated perceptions of bisphosphonates over time, expressing uncertainty relating to what represents successful treatment and citing perceived lack of effectiveness being cited as reason to discontinue. This is likely to be a particular problem for bisphosphonates, as opposed to other drugs commonly taken for prevention such as

1
2
3 statins and anti-hypertensive, where measures of feedback and effectiveness are
4 more readily available.
5
6

7 The NICE guidelines for medicines adherence emphasises the need to take into
8 account perceptions (e.g. necessity beliefs and concerns) and practicalities (e.g.
9 capability and resources) that will affect individuals' motivation and ability to start and
10 continue with treatment.[47] However, interventions designed to improve
11 bisphosphonate adherence are often designed to 'educate' or persuade the patient
12 of importance and are often not targeted to eliciting or addressing health beliefs, or
13 informed by underpinning mechanisms of change.[3] There is therefore a need to
14 ensure that any further design of interventions - to promote bisphosphonate
15 adherence - draws on more comprehensive theoretical models of patient
16 engagement with health conditions and medicines such as the Extended Common
17 Sense Model.[48] Specifically, our findings suggest a need for clinicians to support
18 patients to understand the need for treatment, to allay concerns where possible and
19 to define what constitutes successful bisphosphonate treatment. Furthermore,
20 clinicians need to support patients evaluate the advantages and disadvantages over
21 time, given the dynamic nature of these decision processes.[48]
22
23

24 It is clear from our findings that clinicians also have necessity-concern dilemmas
25 relating to bisphosphonates. A number of studies reported clinicians themselves
26 perceiving low patient need, high concerns and perceptions treatment was not
27 practical. This is perhaps in contrast with a previous quantitative study in asthma
28 which demonstrated that clinicians held stronger positive beliefs about medicines
29 than patients.[49] It is unclear to what extent the perceptions in our findings were
30 generalisations or applied in specific circumstances, or to what extent these views
31 were negotiated on an individual basis in discussion with patients. Problems may
32 arise in the consultation if clinicians assume patients share their views and then may
33 be less likely to explore patient perceptions of need or concerns. Furthermore, the
34 limitations of interviewing HCPs are well documented; the accounts presented in an
35 interview may not represent clinician underlying beliefs or behaviours meaning that
36 observational methods may be more appropriate to fully understand clinical
37 decisional making.[50] Given the clinician has a pivotal role in sense making,
38 interventions are also likely needed to address clinician knowledge, attitudes and
39 beliefs. By including the views of clinicians and managers we have also identified a
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 range of service level barriers to promoting bisphosphonate adherence relating to
4 lack of clarity about professional roles, both across primary and secondary care, and
5 within primary care, use of IT systems and access to intravenous treatments.
6
7

8
9 A strength of this review is the comprehensive search, use of underpinning
10 theoretical framework, the inclusion of clinician views in addition to patients, and the
11 use of the GRADE-CERQual to give confidence in our findings which has facilitated
12 a clear identification of where further research is needed. Areas where we have
13 identified moderate or low confidence are in need of further research and specifically
14 relate to the influence of multi-morbidity on sense making, burden and self-efficacy in
15 bisphosphonate users, the extent to which intravenous bisphosphonates may
16 overcome issues related to treatment burden and self-efficacy, and the impact of
17 bisphosphonates on affective attitudes and emotions. Furthermore, we have
18 identified gaps in our understanding of how clinicians make decisions in practice,
19 and how views of bisphosphonates may be influenced by gender. Given that many
20 osteoporosis drugs have a different evidence base and licensing arrangements in
21 men this is an area in need of further study.
22
23
24
25
26
27
28
29
30
31

32 The main limitation of this study relates to the lack of clarity in many of the included
33 studies in the results sections about which osteoporosis treatments or
34 bisphosphonates were being referred to, meaning that in some cases we may have
35 over-interpreted findings relating to bisphosphonates that were about other
36 osteoporosis drugs. However, all of our review findings were identified from
37 comparison of data from several studies, and as bisphosphonates represent the
38 mainstay of osteoporosis treatment, we consider that over-interpretation is unlikely.
39 As there was frequently little detail about medication participants were taking or
40 referring to, it is also possible that we have missed relevant studies. Only two studies
41 reported the views of managers but unfortunately neither of these studies
42 distinguished professional roles in the presentation of results, so a further need
43 exists to explore perceptions of this group, and perceptions of payors and
44 academics.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

CONCLUSIONS

In summary, using the lens of acceptability, we have identified the factors that influence how patients and clinicians make sense of bisphosphonates, described the experience of bisphosphonate taking in terms of burden and factors that both facilitate and hinder confidence in taking, and prescribing and monitoring bisphosphonates. Our findings demonstrate the need for a theoretically informed, whole-system approach' to enable clinicians and patients to get the best from bisphosphonate treatment. Patients need comprehensive support that takes account of the perceptions (e.g. treatment necessity beliefs and concerns) and practicalities (e.g. capability and resources) that influence their motivation and ability to start and continue with treatment. Clinicians need to moderate patient expectations and clarify what constitutes bisphosphonate treatment success. Finally, further research is needed to explore perspectives of managers, patients receiving intravenous bisphosphonates, men receiving bisphosphonates and the use of bisphosphonates in the context of multi-morbidity.

ACKNOWLEDGEMENTS/FUNDING

This study is funded by the National Institute for Health Research (NIHR), [HTA NIHR127550]. ZP is funded by the NIHR, Clinician Scientist Award (CS-2018-18-ST2-010)/NIHR Academy. CJ is part funded by the NIHR Applied Research Collaboration West Midlands. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health & Social Care.

CONFLICTS OF INTEREST

None declared

REFERENCES

- 1 Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: A world-wide projection. *Osteoporos Int* 1992;2:285-9. doi:10.1007/BF01623184
- 2 National Osteoporosis Society. NHS RightCare scenario: The variation between sub-optimal and optimal pathways. *Rep* 2017:1–16.
- 3 Hiligsmann, M., Cornelissen, D., Vrijens, B. et al. Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF). *Osteoporos Int* 2019;30:2155–65. <https://doi.org/10.1007/s00198-019-05104-5>
- 4 Khosla S, Shane E. A Crisis in the Treatment of Osteoporosis. *J Bone Miner Res* 2016;31:1485-7. doi:10.1002/jbmr.2888
- 5 May CR, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ* 2009;339:2830. doi:10.1136/bmj.b2803
- 6 National Institute for Health Care Excellence. Bisphosphonates for treating osteoporosis, Technology appraisal guidance (TA46) *NICE Guidance* 2017
- 7 Jha S, Wang Z, Laucis N, et al. Trends in Media Reports, Oral Bisphosphonate Prescriptions, and Hip Fractures 1996-2012: An Ecological Analysis. *J Bone Miner Res* 2015;30:2179-87 doi:10.1002/jbmr.2565
- 8 Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: A Randomized Open-Label Trial. *Obstet Gynecol* 2013;121:1291-9. doi:10.1097/AOG.0b013e318291718c
- 9 Akarirmak Ü, Koçyiğit H, Eskiuyurt N, et al. Influence of patient training on persistence, compliance, and tolerability of different dosing frequency regimens of bisphosphonate therapy: An observational study in Turkish patients with postmenopausal osteoporosis. *Acta Orthop Traumatol Turc* 2016;50:415-23. doi:10.1590/S0080-623420160000500008

- 1
2
3 10 Kishimoto H, Maehara M. Compliance and persistence with daily, weekly, and
4 monthly bisphosphonates for osteoporosis in Japan: analysis of data from the
5 CISA. *Arch Osteoporos* 2015;10:27. doi:10.1007/s11657-015-0231-6
6
7
8
9 11 Durden E, Pinto L, Lopez-Gonzalez L, et al. Two-year persistence and
10 compliance with osteoporosis therapies among postmenopausal women in a
11 commercially insured population in the United States. *Arch Osteoporos*
12 2017;12:22. doi:10.1007/s11657-017-0316-5
13
14
15
16 12 Saini SD, Schoenfeld P, Kaulback K, et al. Effect of medication dosing
17 frequency on adherence in chronic diseases. *Am J Manag Care* 2009;15:22-
18 33.
19
20
21
22 13 Hiligsmann M, Bours SPG, Boonen A. A Review of Patient Preferences for
23 Osteoporosis Drug Treatment. *Curr Rheumatol Rep* 2015;17:61.
24 doi:10.1007/s11926-015-0533-0
25
26
27
28 14 de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, et al. Patients' preferences
29 for osteoporosis drug treatment: A discrete choice experiment. *Osteoporos Int*
30 2008;19:1029-37. doi:10.1007/s00198-007-0535-5
31
32
33
34 15 Alten R, Krüger K, Rellecke J, et al. Examining patient preferences in the
35 treatment of rheumatoid arthritis using a discrete-choice approach. *Patient*
36 *Prefer Adherence* 2016;10:2217. doi:10.2147/PPA.S117774
37
38
39
40 16 Feldstein AC, Schneider J, Smith DH, et al. Harnessing stakeholder
41 perspectives to improve the care of osteoporosis after a fracture. *Osteoporos*
42 *Int* 2008;19:1527-40. doi:10.1007/s00198-008-0605-3
43
44
45
46 17 Bliuc D, Eisman JA, Center JR. A randomized study of two different
47 information-based interventions on the management of osteoporosis in
48 minimal and moderate trauma fractures. *Osteoporos Int* 2006;19:1309-17.
49 doi:10.1007/s00198-006-0078-1
50
51
52
53 18 Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions:
54 An overview of reviews and development of a theoretical framework. *BMC*
55 *Health Serv Res* 2017;17:88. doi:10.1186/s12913-017-2031-8
56
57
58
59 19 Dejean D, Giacomini M, Simeonov D, et al. Finding Qualitative Research
60

- 1
2
3 Evidence for Health Technology Assessment. *Qual Health Res* 2016;26:1307-
4 17. doi:10.1177/1049732316644429
5
6
7
8 20 Carroll C, Booth A, Cooper K. A worked example of 'best fit' framework
9 synthesis: A systematic review of views concerning the taking of some
10 potential chemopreventive agents. *BMC Med Res Methodol* 2011;11:29.
11 doi:10.1186/1471-2288-11-29
12
13
14
15 21 Horne R, Chapman SCE, Parham R, et al. Understanding patients' adherence-
16 related Beliefs about Medicines prescribed for long-term conditions: A meta-
17 analytic review of the Necessity-Concerns Framework. *PLoS One*
18 2013;8:e80633. doi:10.1371/journal.pone.0080633
19
20
21
22 22 Lewin S, Booth A, Glenton C, et al. Applying GRADE-CERQual to qualitative
23 evidence synthesis findings: Introduction to the series. *Implement Sci* 2018;2.
24 doi:10.1186/s13012-017-0688-3
25
26
27
28 23 Besser SJ, Anderson JE, Weinman J. How do osteoporosis patients perceive
29 their illness and treatment? Implications for clinical practice. *Arch Osteoporos*
30 2012;7:115-24 doi:10.1007/s11657-012-0089-9
31
32
33
34 24 Sale JEM, Hawker G, Cameron C, et al. Perceived messages about bone
35 health after a fracture are not consistent across healthcare providers.
36 *Rheumatol Int* 2015;35:91-130. doi:10.1007/s00296-014-3079-y
37
38
39
40 25 Sturrock A, Preshaw P, Hayes C, et al. Attitudes and perceptions of GPs and
41 community pharmacists towards their role in the prevention of bisphosphonate-
42 related osteonecrosis of the jaw: A qualitative study in the North East of
43 England. *BMJ Open* 2017;7:e016047. doi:10.1136/bmjopen-2017-016047
44
45
46
47 26 Sale JEM, Beaton D, Sujic R, et al. 'If it was osteoporosis, i would have really
48 hurt myself.' Ambiguity about osteoporosis and osteoporosis care despite a
49 screening programme to educate fragility fracture patients. *J Eval Clin Pract*
50 2010;16:590-6. doi:10.1111/j.1365-2753.2009.01176.x
51
52
53
54
55 27 Weston JM, Norris E V., Clark EM. The invisible disease: Making sense of an
56 osteoporosis diagnosis in older age. *Qual Health Res* 2011;21:192-704.
57 doi:10.1177/1049732311416825
58
59
60

- 1
2
3 28 Merle B, Haesebaert J, Bedouet A, et al. Osteoporosis prevention: Where are
4 the barriers to improvement in French general practitioners? A qualitative
5 study. *PLoS One* 2019;14:e0219681.
6
7
8
9 29 Lau E, Papaioannou A, Dolovich L, et al. Patients' adherence to osteoporosis
10 therapy: Exploring the perceptions of postmenopausal women. *Can Fam*
11 *Physician* 2008;54:394-402.
12
13
14 30 Salter C, McDaid L, Bhattacharya D, et al. Abandoned Acid? Understanding
15 adherence to bisphosphonate medications for the prevention of osteoporosis
16 among older women: A qualitative longitudinal study. *PLoS One* 2014;9.
17 doi:10.1371/journal.pone.0083552
18
19
20
21
22 31 Hansen CA, Abrahamsen B, Konradsen H, et al. Women's lived experiences
23 of learning to live with osteoporosis: A longitudinal qualitative study. *BMC*
24 *Womens Health* 2017;17:17. doi:10.1186/s12905-017-0377-z
25
26
27
28 32 Mazor KM, Velten S, Andrade SE, et al. Older womens views about
29 prescription osteoporosis medication: A cross-sectional, qualitative study.
30 *Drugs and Aging* 2010;27:999-1008. doi:10.2165/11584790-000000000-00000
31
32
33 33 Wozniak LA, Johnson JA, McAlister FA, et al. Understanding fragility fracture
34 patients' decision-making process regarding bisphosphonate treatment.
35 *Osteoporos Int* 2017;28:219-29. doi:10.1007/s00198-016-3693-5
36
37
38
39 34 Sippli K, Rieger MA, Huettig F. GPs' and dentists' experiences and
40 expectations of interprofessional collaboration: Findings from a qualitative
41 study in Germany. *BMC Health Serv Res* 2017;17:179. doi:10.1186/s12913-
42 017-2116-4
43
44
45
46
47 35 Ailabouni NJ, Nishtala PS, Mangin D, et al. General practitioners' insight into
48 deprescribing for the multimorbid older individual: A qualitative study. *Int J Clin*
49 *Pract* 2016;70:261-76. doi:10.1111/ijcp.12780
50
51
52
53 36 Merle B, Dupraz C, Haesebaert J, et al. Osteoporosis prevention: where are
54 the barriers to improvement in a French general population? A qualitative
55 study. *Osteoporos Int* 2019;30:177-85. doi:10.1007/s00198-018-4720-5
56
57
58
59 37 Drew S, Judge A, Cooper C, et al. Secondary prevention of fractures after hip
60

- 1
2
3 fracture: a qualitative study of effective service delivery. *Osteoporos Int*
4 2016;27:1719-27. doi:10.1007/s00198-015-3452-z
5
6
7 38 Otmar R, Reventlow SD, Nicholson GC, et al. General medical practitioners'
8 knowledge and beliefs about osteoporosis and its investigation and
9 management. *Arch Osteoporos* 2012;7:104-14. doi:10.1007/s11657-012-0088-
10 x
11
12
13
14 39 Jaglal SB, Carroll J, Hawker G, et al. How are family physicians managing
15 osteoporosis?: Qualitative study of their experiences and educational needs.
16 *Can Fam Physician* 2003;49:462-8.
17
18
19 40 Swart KMA, Van Vilsteren M, Van Hout W, et al. Factors related to intentional
20 non-initiation of bisphosphonate treatment in patients with a high fracture risk
21 in primary care: A qualitative study. *BMC Fam Pract* 2018;19:141.
22 doi:10.1186/s12875-018-0828-0
23
24
25 41 Scoville EA, de Leon Lovaton PP, Shah ND, et al. Why do women reject
26 bisphosphonates for osteoporosis? a videographic study. *PLoS One* 2011;6.
27 doi:10.1371/journal.pone.0018468
28
29
30 42 Alami S, Hervouet L, Poiraudou S, et al. Barriers to effective postmenopausal
31 osteoporosis treatment: A qualitative study of patients' and practitioners' views.
32 *PLoS One* 2016;11. doi:10.1371/journal.pone.0158365
33
34
35 43 Guzman-Clark JRS, Fang MA, Sehl ME, et al. Barriers in the management of
36 glucocorticoid-induced osteoporosis. *Arthritis Care Res* 2007;140-6.
37 doi:10.1002/art.22462
38
39
40 44 Iversen MD, Vora RR, Servi A, et al. Factors affecting adherence to
41 osteoporosis medications: A focus group approach examining viewpoints of
42 patients and providers. *J. Geriatr. Phys. Ther* 2011;34:72.
43 doi:10.1097/JPT.0b013e3181ff03b4
44
45
46 45 Sturrock A, Preshaw PM, Hayes C, et al. Perceptions and attitudes of patients
47 towards medication-related osteonecrosis of the jaw (MRONJ): A qualitative
48 study in England. *BMJ Open* 2019;9:e024376. doi:10.1136/bmjopen-2018-
49 024376
50
51
52
53
54
55
56
57
58
59
60

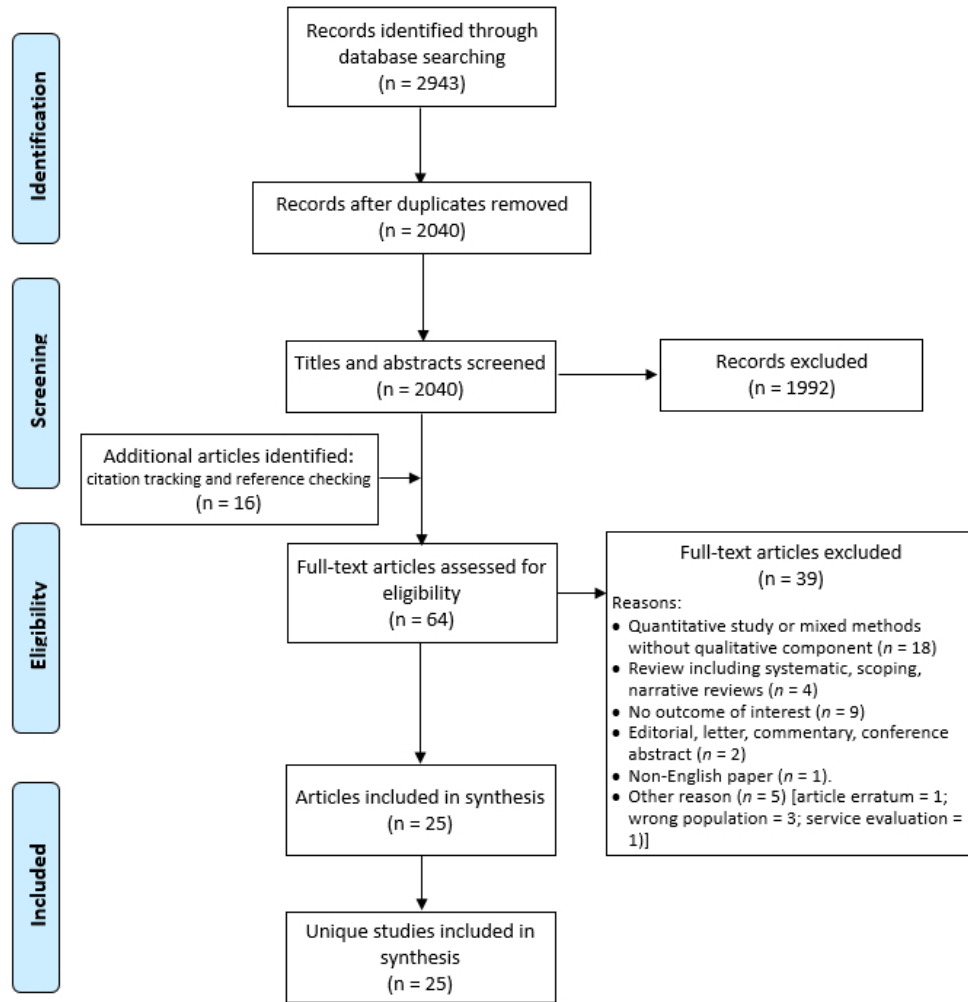
- 1
2
3 46 Sale JEM, Gignac MA, Hawker G, et al. Decision to take osteoporosis
4 medication in patients who have had a fracture and are 'high' risk for future
5 fracture: A qualitative study. *BMC Musculoskelet Disord* 2011;12:92.
6 doi:10.1186/1471-2474-12-92
7
8
9
10
11 47 Nunes V, Neilson J, O'flynn N, et al. Medicines adherence: involving patients in
12 decisions about prescribed medicines and supporting adherence (CG76).
13 *NICE Guidance* 2009.
14
15
16 48 Horne R, Cooper V, Wileman V, et al. Supporting Adherence to Medicines for
17 Long-Term Conditions. *Eur Psychol* 2019. doi: 10.1027/1016-9040/a000353
18
19
20
21 49 Driesenaar JA, De Smet PA, van Hulten R, et al. Beliefs about inhaled
22 corticosteroids: comparison of community pharmacists, pharmacy technicians
23 and patients with asthma. *J. Asthma* 2016;53:1051-8.
24
25
26 50 Checkland K, Harrison S, Marshall M. Is the metaphor of 'barriers to change'
27 useful in understanding implementation? Evidence from general medical
28 practice. *J Heal Serv Res Policy* 2007;12:95-00.
29 doi:10.1258/135581907780279657.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure legends

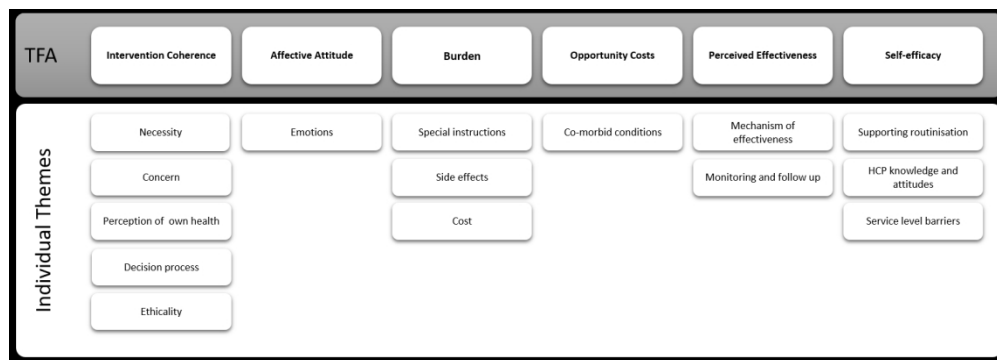
Figure 1. Prisma Diagram

Figure 2. Identified themes and subthemes mapped to the Theoretical Framework of Acceptability (TFA)

For peer review only



Prisma Diagram



Identified themes and subthemes mapped to the Theoretical Framework of Acceptability (TFA)

Supplementary Material

Table 1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done including measures of consistency (e.g., I^2) for each meta-analysis.	7-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-17
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

For peer review only

Supplementary material 2. OVID MEDLINE Search strategy

For Ovid: The following table is an explanation of the symbols used in the search strategy below.

/	indicates an index term (MeSH/EMTREE heading).
exp	before an index term indicates that all subheadings were selected.
af.	Indicates a search for a term in all fields.
.ti,ab,kf.	indicates a search for a term in title/abstract/word(s) in keyword [MEDLINE].
mp.	indicates a search for a term in 'multi-purpose' fields, including the title, abstract, floating sub-heading word, keyword heading word, subject heading word.
tw.	Indicates a search for a term in title and abstract.
\$	at the end of a term indicates that this term has been truncated.
?	optional wild card character replaces zero or one character within a word or at the end of a word
adj	indicates a search for two terms where they appear adjacent to each another
adjn	indicates a search for two terms where they appear within <i>n</i> words of each another

Searches

1	diphosphonates/ or alendronate/ or ibandronic acid/ or risedronic acid/ or zoledronic acid/ or etidronic acid/ or pamidronate/
2	diphosphon\$.ti,ab,kf.
3	bisphosphon\$.ti,ab,kf.
4	alendron\$.ti,ab,kf.
5	fosamax.ti,ab,kf.
6	risedron\$.ti,ab,kf.
7	actonel.ti,ab,kf.
8	zoledron\$.ti,ab,kf.
9	aclasta.ti,ab,kf.
10	ibandron\$.ti,ab,kf.
11	etidron\$.ti,ab,kf.
12	pamidron\$.ti,ab,kf.
13	or/1-12
14	attitude/
15	attitude of health personnel/
16	exp attitude to health/ [includes patient satisfaction and patient preference]
17	choice behavior/
18	decision making/
19	attitud\$.ti,ab,kf.
20	percept\$.ti,ab,kf.
21	expectation\$.ti,ab,kf.

- 1
2
3
4 22 experienc\$.ti,ab,kf.
5 23 preferen\$.ti,ab,kf.
6 24 choice\$.ti,ab,kf.
7
8 25 belie\$.ti,ab,kf.
9 26 opinion\$.ti,ab,kf.
10
11 27 priorit\$.ti,ab,kf.
12
13 28 benefi\$.ti,ab,kf.
14
15 29 reason\$.ti,ab,kf.
16 30 decision\$.ti,ab,kf.
17 31 motiv\$.ti,ab,kf.
18 32 justif\$.ti,ab,kf.
19 33 (concern or concerns or concerned).ti,ab,kf.
20 34 (view or views or viewed).ti,ab,kf.
21
22 35 satisf\$.ti,ab,kf.
23 36 value\$.ti,ab,kf.
24 37 or/14-36
25 38 Qualitative Research/ [After DeJean et al., 2016. Qual Health Res **26**(10): 1307-1317]
26 39 interview/
27 40 (theme\$ or thematic).mp.
28 41 qualitative.af.
29 42 nursing methodology research/
30 43 questionnaire\$.mp.
31 44 ethnological research.mp.
32 45 ethnograph\$.mp.
33 46 ethnonursing.af.
34 47 phenomenol\$.af.
35 48 (grounded adj (theor\$ or study or studies or research or analys?s)).af.
36 49 (life stor\$ or women\$ stor\$).mp.
37 50 (emic or etic or hermeneutic\$ or heuristic\$ or semiotic\$).af.
38 51 ((data adj1 saturat\$) or participant observ\$).tw.
39 52 (social construct\$ or postmodern\$ or post modern\$ or poststructural\$ or post structural\$ or
40 feminis\$ or interpret\$).mp.
41 53 (action research or cooperative inquir\$ or co operative inquir\$).mp.
42 54 (humanistic or existential or experiential or paradigm\$).mp.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 55 (field adj (study or studies or research)).tw.
4
5 56 human science.tw.
6
7 57 biographical method.tw.
8
9 58 theoretical sampl\$.af.
10
11 59 ((purpos\$ adj4 sampl\$) or (focus adj group\$)).af.
12
13 60 (account or accounts or unstructured or open ended or text\$ or narrative\$).mp.
14
15 61 (life world or conversation analys?s or personal experience\$ or theoretical saturation).mp.
16
17 62 ((lived or life) adj experience\$).mp.
18
19 63 cluster sampl\$.mp.
20
21 64 observational method\$.af.
22
23 65 content analysis.af.
24
25 66 (constant adj (comparative or comparison)).af.
26
27 67 ((discourse\$ or discours\$) adj3 analys?s).tw.
28
29 68 narrative analys?s.af.
30
31 69 heidegger\$.tw.
32
33 70 colaizzi\$.tw.
34
35 71 spiegelberg\$.tw.
36
37 72 van manen\$.tw.
38
39 73 van kaam\$.tw.
40
41 74 merleau ponty.tw.
42
43 75 husserl\$.tw.
44
45 76 foucault\$.tw.
46
47 77 (corbin\$ adj2 strauss\$).tw.
48
49 78 glaser\$.tw.
50
51 79 (mix\$ adj2 (method\$ or design\$)).af. [filter amended to identify mixed method studies]
52
53 80 or/38-79
54
55 81 13 and 37 and 80
56
57
58
59
60

Supplementary material 3. Subtheme descriptions and illustrative key findings

Main theme	Subtheme	Description	Illustrative Key findings
Intervention Coherence	Necessity	Both patient and clinician participants described osteoporosis, falling and fracturing as a normal part of ageing and this view was associated with the perception that medication or treatment was futile.[16,30] One GP described the ‘problem is not with the treatment, it’s with the diagnosis’: perceiving that the indications for treatment had broadened over recent years.[40] The absence of symptoms was reported by clinicians as a disincentive to patients accepting treatment,[36,43] however, patients questioned whether osteoporosis really was asymptomatic.[23] Patient participants who conceptualised osteoporosis as having consequences, e.g. as a cause of disability including ‘shrinking’ and ‘stooping’, were motivated to take medication.[29] Patient participants described other way of controlling their condition and preventing fracture, for example, by not falling.[42] In some patients who initiated treatment, the notion of osteoporosis as a chronic disease was noted not to make sense with the need to take bisphosphonate medication for 5 years.[23]	Patients perceived minimal susceptibility to the negative consequence of osteoporosis in the future and did not consider osteoporosis to be a serious health condition.[35] Avoiding consequences (including shrinking, stooping, fractures) of osteoporosis was a strong motivator for adherence in PMW.[29]
	Concerns	Before starting bisphosphonates, patients noted concern and fear of bisphosphonate-specific side effects. This could be informed by vicarious experience of a family member,[41] or information from the media.[29] The special instructions for use, the limited duration of treatment and the name ‘acid’ were all cited as reasons underlying the perception that bisphosphonates must be harmful. Both patients and HCP’s also cited a mistrust of pharmaceutical companies,[30,36,40] or a general aversion to drugs.[29,40,42,44]	{Women} were concerned about the long lists of drug side effects in advertisements.[16] ‘Once you’re on it, then it stays in your system and you wonder what damage have you’ve done to yourself?’[16] Some PMW did not like the idea of taking any medications because they viewed medications as artificial and thought they had unpredictable effects.[29]
	Perceptions of own health	Some patients reported a perception that they were healthy, with some disbelieving they had osteoporosis and/or high fracture risk, and therefore and would reject medication and a label of a disease.[29] Conversely, others conceptualised bisphosphonates as a	Some patients initiated bisphosphonates to stay healthy.[33] For PMW who considered themselves healthy, the idea of

		<p>mechanism to remain healthy[33] and/or autonomous.[30] In a study of French GPs, on respondent also suggested patients wanted to know how to “age well”. [36]</p>	<p>medication was disconcerting as it meant perceiving themselves as sick.[29]</p>
	<p>Decision process</p>	<p>Across studies patients and HCPs described perceptions that the benefits did not outweigh the risks.[16,33,39,42] Often in these descriptions, the value of treatment was not clearly articulated meaning this assessment meant the patient weighing up staying as they were, or experiencing new side effects.[30] However, even when the risk of fracture was acknowledged, medication could still be seen as something to avoid.[42] The opposing view that the ‘benefits were worth the costs’ was evident in circumstances where benefits were described.[29] Others studies with patients reported that the decision was ‘difficult’ with one participant describing it as like ‘Russian roulette’.[46] Balancing necessity against concerns was influenced by contingent factors such as trust in the clinician and could either be an easy or difficult and ongoing process. Patient participants talked about ‘confidence’ and ‘trust’ in their HCP, which could be associated with minimal contemplation to take treatment, or alternatively mistrust, or a failure to be ‘convinced’.[16,26,27,29,32] Some patients reported clinicians as being persistent in their recommendation to take bisphosphonates;[32] however, conversely, patients also described by dissuaded by their doctor against treatment.[28] Often, patients described seeking information from other sources to make the final decision which often resulted in a decision against treatment.[46]</p> <p>For those who initiated medication, an ongoing re-assessment of risk and benefit was noted,[23,33,46] particularly in studies that employed longitudinal methods.[30,33,33] Patients reported their decision making was influenced by experiencing a future fracture,[46] follow-up scans,[26] experienced side effects,[29,30] views of others and other experienced illnesses or life events.[31]</p>	<p>For some, the decision to take bisphosphonate involved minimal contemplation because they liked/trusted their health care provider.[46]</p> <p>Patients who found the decision difficult sought alternative sources of information (professional and non) which often resulted in decision not to take OP medication.[46]</p>
	<p>Ethicality</p>	<p>Both orthopaedic and primary care clinicians reported a ‘bias’ against treating the elderly due to a belief ‘nothing can be done for them’.[16] However, some patients also perceived that they were too old to benefit.[42] HCPs were seen to use the using ethical principle of non-maleficence to justify not recommending bisphosphonates. They questioned the negative side effects ‘for a benefit that has not really been proven’ and worried about being blamed for causing their patients ill-health.[28,40] Patients, in some circumstances, doubted the beneficence of the health care professionals e.g. perceiving</p>	<p>Clinicians {primary care and specialists} report bias against treating elderly patients because of a general tendency to believe that nothing can be done for them.[16]</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

		their physician as a ‘pill pusher’ or the motivation for prescribing medication being to receive money in return.[32]	
Affective Attitudes	Emotions	<p>Patients described wide-ranging fears including fear of common and rare side effects and fear of new side effects emerging in the future. Patients described fear of bisphosphonates staying in their system,[16] with one patient participant describing bisphosphonates as akin to chemicals used to clean machines.[23] Patients also worried information was being withheld, or were fearful of the sheer amount of information to take in.[29] Both clinicians and patients described media reports as the source of fear, with patients also citing experiences of friends and family.[29] Fear of addiction was mentioned by patients in one study.[23] Patients and HCPs also expressed annoyance with the special instructions associated with oral bisphosphonate use, and annoyance with experienced oesophageal side effects.[32]</p> <p>In two studies, patient participants reported that they experienced feelings of safety and reassurance when taking bisphosphonates,[27] linked to the anticipated benefits.[29]</p>	<p>“..when I read the side effects it was like a <i>horror film</i> really”.[30]</p> <p>medication provided a feeling of safety and reassurance.[27]</p>
Burden	Special instructions	<p>The method of administration of oral bisphosphonates caused concern to patients both prior to initiating treatment,[40] and whilst on the treatment,[28] causing disruption to daily life. The need to remain upright after taking the medication and only being allowed to drink water was burdensome, and led to some disregarding the administration requirements.[29] Specific activities that needed to be actioned first thing in the morning also competed with taking oral bisphosphonates, with patients citing examples such as the need to have a coffee or run a family errand early every morning.[46] Primary care physicians reported that taking bisphosphonates was a ‘hassle’ for patients.[16] The frequency of the oral bisphosphonates, once a week, led to a number of reports of patients forgetting to take their medication.[16,23,29,30,44] Varying reports were identified about whether daily or weekly regimes were more or less burdensome.[16,29] Four studies reported patients’ perceptions that the special instructions were not disruptive or burdensome.[27,29,31,44]</p>	<p>Some patients were able to rearrange their daily routines to accommodate {bisphosphonate} requirements, but others would intentionally disregard the administration requirements or forget to take the medication if it did not fit into their schedules.[29]</p>
	Side effects	<p>Experienced side effects were discussed in three of the studies interviewing clinicians,[34,38,39] eight with patients[23,25,27,29-31,33,46] and five with mixed participants.[16,40-42,44] Experienced side effects were reported as a common reason for lack of adherence, with gastrointestinal disturbances being described as “horrendous</p>	<p>Gastrointestinal disturbances from taking bisphosphonates were most notable and were described as</p>

		<p>diarrhoea” and “wrecking my stomach.[29,44] Patients reported stopping medications after experiencing side effects, did not always disclose side effects to HCPs and noted that the treatment ‘was almost more disabling than the disease’.[28,31,45]</p>	<p>“horrendous diarrhoea” and “wrecking my stomach.[29]</p>
	<p>Costs</p>	<p>Financial costs were discussed in five studies, four of which were conducted in North America and one in Australia.[16,29,38,41,45] Patients did not report cost as a barrier to bisphosphonates specifically, however, medical insurance was perceived by clinicians as a barrier due to its complexity.[38,41,44] Indirect costs relating to travel and the need for increased dental checks were mentioned briefly but not described as a problem.[15,45]</p>	<p>Cost was not a limiting factor to adherence if patients had insurance coverage for medications. Even patients without insurance expressed a willingness to make sacrifices to pay for the medications because they thought the benefits were worth the cost.[29] Providers {secondary care} stated that due to cost not being covered by insurance companies, patients stop taking or alter dose/frequency.[44]</p>
<p>Opportunity costs</p>	<p>Co-morbid conditions</p>	<p>Physicians perceived bisphosphonate treatment was less important to patients who might have other more pressing health conditions [25,39] particularly in the absence of symptoms.[31,36] Patients also reported that other health conditions took priority over their prescribed bisphosphate leading them not to start or discontinue medication.[28] Within the time-limited consultation, multiple competing priorities relating to other health conditions was reported by HCPs, resulting in a ‘pecking order’, and less time to discuss bisphosphonates.[25,42]</p>	<p>(Bisphosphonates) are lower down in the pecking order of things that we look at when we are supervising polypharmacy, when we are looking at chronic disease management”.[25]</p>
<p>Perceived effectiveness</p>	<p>Mechanism of effectiveness</p>	<p><i>Mechanism of effectiveness:</i> Patients expressed confusion about how bisphosphonates work and uncertainty about whether they strengthen, prevent worsening or slow the decline in bone density.[26,27,44] Patients talked about bone density scans as providing ‘proof’ of whether their medication was effective, however, there were differing reports of whether stabilisation in density was considered as treatment success.[32,42] The lack of systematic reduction in fracture or improvement in bone density was noted to result in ambivalence about efficacy and importance.[42] Patients described wanting more explanation about, and evidence of effectiveness (including quantified benefit).[16,23,29,30,32] Prior to initiating treatment, the perceived effectiveness of bisphosphonates was influenced in patients primarily by vicarious experience of friends</p>	<p>Taking anti-osteoporosis drugs was noted to not always seem to lead to improvement in their bone density and did not systematically prevent fracture.[42]</p>

bmjopen-2020-040614 on 3 November 2021. Downloaded from <http://bmjopen.bmj.com/> April 17, 2024 by guest. Protected by copyright.

		<p>or relatives.[32,40,41] Examples of relatives who had fractured on treatment or had hip or knee joint replacements were given as examples of lack of efficacy.[40]</p> <p>Patients cited clinicians not meeting their informational needs about effectiveness, which may have been due to their own reported doubts.[39,40] Other clinicians expressed continued doubts about effectiveness in specific populations (e.g. the elderly) or in relation to fracture risk at specific sites.[42] Patients in one study reported being told by health care professionals bisphosphonates are not effective for everyone[24] and in one study, clinicians questioned predictors of response.[39]</p>	
	Monitoring and follow-up	<p>Follow-up and monitoring were reported by clinicians[37] and patients[30] to support adherence to oral treatment, but generally felt to be lacking in primary care, in part due to uncertainties about who, when and what to monitor.[37] Patients reported not feeling supported with continued persistence with treatment[30] and reported the need for more reviews, feedback and help with 'ways to keep going' with medications.[16,33,30]</p>	<p>Women anticipated the next DXA scan as being the "proof" of whether the treatment was effective.[31]</p> <p>Reviewing patients' BMD results with them helped them evaluate the status of their osteoporosis, which motivated them to either start or continue taking their medicine.[29]</p>
Self-efficacy	Supporting routinisation	<p><i>Supporting routinisation</i> Being able to successfully follow the special instructions for taking oral bisphosphonates, and incorporate the regime into daily routines appeared to be important to acceptability.[44] Other reported strategies to support self-efficacy were using pill compartments and calendar systems/reminders.[16] Patients reported that HCPs should supplement their oral instructions about BP administration with written ones.[44] Information, support and encouragement was needed throughout treatment but felt to be lacking by patients[16,30,46]. Patients and HCPs reported insufficient time in consultations to cover all the information about bisphosphonate medication.[42,44]</p>	<p>Patients noted that tips for routinizing medication use, such as using triggers (e.g., meals, calendars, placement of medications) to remember when to take medications, facilitated long-term adherence.[16]</p>
	HCP knowledge and attitudes	<p>Primary care providers did not feel confident in their own knowledge about bisphosphonates; they described guidelines as confusing and too detailed, expressing a number of uncertainties relating to who to start medication in, how long to continue medication for, the relationship between bisphosphonates and co-dependency for calcium/vitamin D, safety, when treatment should be changed including dose.[16,26,39,42] Some primary care clinicians indirectly suggested perceptions that osteoporosis was not a priority. Secondary care providers suggested osteoporosis champions in primary care would help educate primary care clinicians who were less interested in the condition.[25,44] It was also reported that non-medical clinicians</p>	<p>Physicians reported need for training in treating and help with therapeutic decision making.[42]</p>

		(pharmacists or nurses) may be more knowledgeable or have more time to discuss bisphosphonates.[25,44]	
	Service level barriers	In terms of professional roles, clinicians in two studies described uncertainty about whose role it was to start and monitor treatment.[16,37] This was compounded by perceived poor communication between primary and secondary care, including update of the patients prescriptions on the electronic medical record.[44] Further reported barriers to treatment included lack of incentivisation[37] difficulty ordering, accessing or interpreting investigations to monitor treatment,[16,39] external restrictions on prescribing and access to intravenous bisphosphonates[37] and lack of time in primary care consultations.[16]	Provider barriers to treatment include lack of knowledge, other priorities, limited access and limited time.[43] GPs regretted the absence of consensus about the professional in charge of osteoporosis.[28] A number of participants {HCPs/managers} thought that intravenous zoledronic acid should be more widely available to improve adherence.[37]

bmjopen-2020-041664 on 3 November 2024. Downloaded from <http://bmjopen.bmj.com/> on April 17, 2024 by guest. Protected by copyright.

peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

BMJ Open

Acceptability of bisphosphonates among patients, clinicians and managers: a systematic review and framework synthesis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040634.R1
Article Type:	Original research
Date Submitted by the Author:	01-Sep-2020
Complete List of Authors:	Paskins, Zoe; Keele University, School of Primary Community and Social Care; Haywood Hospital, Academic Rheumatology Centre Crawford-Manning, Fay; Keele University, School of Primary Community and Social Care; Haywood Hospital, Academic Rheumatology Centre Cottrell, Elizabeth ; Keele University, School of Primary, Community and Social Care Corp, Nadia; Keele University, School of Primary, Community and Social Care Wright, Jenny; Keele University, School of Primary Community and Social Care Jinks, Clare; Keele University, School of Primary, Community and Social Care Bishop, Simon; University of Nottingham, Centre for Health Innovation, Leadership and Learning Doyle, Alison; Royal Osteoporosis Society Ong, Terence; University of Malaya, Faculty of Medicine GITTOES, NEIL; University of Birmingham, Centre for Endocrinology Diabetes and Metabolism Leonardi-Bee, Jo; University of Nottingham, Faculty of Medicine & Health Sciences Langley, Tessa; University of Nottingham, Division of Epidemiology and Public Health Horne, Robert; University College London, School of Pharmacy Sahota, Opinder; Nottingham University Hospitals NHS Trust, Department of Geriatric Medicine
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Health services research, Patient-centred medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Title: Acceptability of bisphosphonates among patients, clinicians and managers: a**
6 **systematic review and framework synthesis.**
7
8
9

10
11 Corresponding Author: Dr. Zoe Paskins, School of Primary Community and Social Care, Keele
12 University, David Weatherall Building, Newcastle-under-Lyme, UK, ST5 5BG and Haywood
13 Academic Rheumatology Centre, Haywood Hospital, High Lane, Burslem, Stoke-on-Trent ST6
14
15
16 7AG.

17
18
19 z.paskins@keele.ac.uk, 01782 733975
20

21 Author List:
22

23
24 Dr. Zoe Paskins, School of Primary, Community and Social Care, Keele University & Haywood
25 Academic Rheumatology Centre, Stoke-on-Trent, UK
26

27
28 Dr. Fay Crawford-Manning, School of Primary, Community and Social Care, Keele University
29 & Haywood Academic Rheumatology Centre, Stoke-on-Trent, UK
30

31
32 Dr. Elizabeth Cottrell, School of Primary, Community and Social Care, Keele University,
33 Newcastle-under-Lyme, UK
34

35
36 Dr. Nadia Corp, School of Primary, Community and Social Care, Keele University, Newcastle-
37 under-Lyme, UK
38

39
40 Dr. Jenny Wright, School of Primary, Community and Social Care, Keele University,
41 Newcastle-under-Lyme, UK
42

43
44 Prof. Clare Jinks, School of Primary, Community and Social Care, Keele University,
45 Newcastle-under-Lyme, UK
46

47
48 Dr. Simon Bishop, Centre for Health Innovation, Leadership and Learning, University of
49 Nottingham, Nottingham, UK
50

51
52 Alison Doyle, Royal Osteoporosis Society, Bath, UK
53

54
55 Dr. Terence Ong, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala
56 Lumpar, Malaysia
57
58
59
60

1
2
3 Prof. Neil Gittoes, Centre for Endocrinology Diabetes and Metabolism, University of
4 Birmingham, Birmingham, UK
5

6
7 Prof. Jo Leonardi-Bee, Faculty of Medicine & Health Sciences, University of Nottingham,
8 Nottingham, UK
9

10
11 Associate Prof. Tessa Langley, Division of Epidemiology and Public Health, University of
12 Nottingham, Nottingham, UK
13

14
15 Prof. Robert Horne, School of Pharmacy, University College London, London, UK
16

17
18 Prof. Opinder Sahota, Department of Geriatric Medicine, Nottingham University Hospitals
19 NHS Trust, Nottingham, UK
20
21

22
23
24
25 Key Words:

26
27 Acceptability; Theoretical Framework of Acceptability, Bisphosphonates;
28 Osteoporosis
29

30
31 **Current word count: 4097**
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Abstract** (299/300 words):
4

5 *OBJECTIVE:* To explore the acceptability of different bisphosphonate regimens for
6 the treatment of osteoporosis among patients, clinicians and managers, payers and
7 academics.
8

9
10 *DESIGN:* A systematic review of primary qualitative studies. Seven databases were
11 searched from inception to July 2019. Screening, data extraction and quality
12 assessment of full-articles selected for inclusion were performed independently by
13 two authors. A framework synthesis was applied to extracted data based on the
14 Theoretical Framework of Acceptability (TFA). The TFA includes seven domains
15 relating to sense-making, emotions, opportunity costs, burden, perceived
16 effectiveness, ethicality and self-efficacy. Confidence in synthesis findings was
17 assessed.
18
19

20
21 *SETTING:* Any developed country healthcare setting
22

23
24 *PARTICIPANTS:* Patients, healthcare professionals, managers, payers and
25 academics
26

27
28 *INTERVENTION:* Experiences and views of oral and intravenous bisphosphonates.
29

30
31 *RESULTS:* Twenty-five studies were included, mostly describing perceptions of oral
32 bisphosphonates. We identified, with high confidence, how patients and HCPs make
33 sense (coherence) of bisphosphonates by balancing perceptions of need against
34 concerns, how uncertainty prevails about bisphosphonate perceived effectiveness
35 and a number of individual and service factors that have potential to increase self-
36 efficacy in recommending and adhering to bisphosphonates. We identified, with
37 moderate confidence, that bisphosphonate taking induces concern, but has the
38 potential to engender reassurance, and that both side effects and special
39 instructions for taking oral bisphosphonates can result in treatment burden. Finally,
40 we identified with low confidence that multi-morbidity plays a role in people's
41 perception of bisphosphonate acceptability.
42

43
44 *CONCLUSION:* By using the lens of acceptability, our findings demonstrate with
45 high confidence that a theoretically informed, whole-system approach is necessary
46 to both understand and improve adherence. Clinicians and patients need supporting
47 to understand the need for bisphosphonates, and clinicians need to clarify to
48 patients what constitutes bisphosphonate treatment success. Further research is
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 needed to explore perspectives of male patients and those with multi-morbidity
4 receiving bisphosphonates, and patients receiving intravenous treatment.
5
6
7

8 9 **Strengths and Limitations**

- 10 • Comprehensive search strategy
- 11 • Robust framework synthesis underpinned by theory
- 12 • Inclusion of clinician and manager views in addition to patient perspectives.
- 13 • Use of GRADE-CERQual to give confidence in findings
- 14 • Qualitative studies reviewed for inclusion were frequently not specific about
15 the anti-osteoporosis drugs participants were taking, meaning we may have
16 missed papers or over-interpreted findings
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION/BACKGROUND

Osteoporosis is a disease that is characterised by skeletal fragility and changes in bone microarchitecture resulting in increased risk of fractures with no or low trauma.[1] The management and care of people with low trauma or fragility fractures results in considerable societal economic burden, annual cost in the UK alone is £4.4 billion.[2] Furthermore, the personal impact of fragility fractures is considerable, with potential deleterious effects on physical and psychological health, ability to live independently and increased risk of death. Many of these fractures are potentially preventable with appropriate cost- and clinically-effective drug treatments such as bisphosphonates, the mainstay of osteoporosis treatment. However, the success of treatment depends on patients initiating (starting), executing (or implementing - taking correctly) and persisting (continuing) medication; collectively these processes are described as adherence. Adherence with osteoporosis medications is notoriously poor and reported to be poorer than other disease areas. Oral bisphosphonate persistence rates at 1 year are commonly estimated between 16 and 60%. [3] Worldwide, many people who would benefit from osteoporosis drugs are not receiving them, and this treatment gap has been described as an 'osteoporosis crisis'. [4] The treatment gap is compounded by poor adherence which results in potentially preventable fragility fractures with their associated burden for patients and their carers, difficulties in professional-patient relationships, and wasted healthcare resources. [5]

There are a number of different bisphosphonates, some are administered orally others intravenously. A variety of regimes in terms of dose frequency also exists. Alendronic acid, an oral once-weekly bisphosphonate, is considered first-line and most commonly used. [6] Bisphosphonates work to reduce fracture risk. A recent network meta-analysis demonstrated that bisphosphonate treatment reduces the risk of fragility fracture (depending on site) by 33-54%. [7] Oesophageal or gastrointestinal related side effects are the most common adverse effects of oral bisphosphonate use. To counter these, patients taking oral bisphosphonates are required to remain upright and fast for half an hour after ingestion. Rare side effects of bisphosphonates include osteonecrosis of the jaw and atypical femur fractures, both of which have received significant media attention. Such media reports are temporally related to declining bisphosphonate use. [7] Due to the gastrointestinal

1
2
3 side effects and special instructions for taking oral treatment, it has been suggested
4 that alternative bisphosphonate regimens, for example annual intravenous
5 zoledronic acid, may promote long-term adherence.[8-11] Studies to date which
6
7 have examined patient preferences for osteoporosis treatment, suggest that patients
8
9 prefer injections given less frequently;[12-14] however, research in other chronic
10
11 diseases shows that although adherence is improved with less frequent medications
12
13 and that patients prefer oral to injection treatment.[15] In osteoporosis, the majority
14
15 of studies that explore patient preferences employ quantitative methods, for
16
17 example, discrete choice experiments where patients are asked to choose between
18
19 hypothetical treatments in regards to various attributes (e.g. efficacy, side effects,
20
21 route and frequency of administration).[13] Such studies cannot provide
22
23 comprehensive insight into patient views, experiences or the explanations for these
24
25 preferences.

26
27 In order to fully understand the osteoporosis treatment gap, and ultimately improve
28
29 adherence, it is important to understand perspectives of all relevant stakeholders:
30
31 patients, healthcare professionals (HCPs), managers, payors and academics.[16,17]
32
33 This can be achieved using the lens of 'acceptability', defined as "a multi-faceted
34
35 construct that reflects the extent to which people delivering, or, receiving a
36
37 healthcare intervention consider it to be appropriate, based on anticipated or
38
39 experienced cognitive and emotional responses to the intervention".[18,19] In the
40
41 context of a research program designed to determine the research agenda for
42
43 optimising bisphosphonate treatment, the primary aim of this systematic review is to
44
45 explore the acceptability of different bisphosphonates regimens among patients, and
46
47 clinicians and managers.

48 **METHODS**

49
50 We conducted a systematic review and framework synthesis of qualitative studies
51
52 exploring patient and clinician views and experiences of bisphosphonates. The
53
54 conduct and reporting of this review followed the Preferred Reporting Items for
55
56 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see supplementary
57
58 file 1 for PRISMA checklist). The protocol of the systematic review is registered in
59
60 PROSPERO [CRD42019143526].

Eligibility

To be eligible for inclusion, studies needed to report on patients', clinicians', academics', and/or manager/payers' experiences and preferences regarding bisphosphonate regimes for adults (≥ 18 years) with osteoporosis. Bisphosphonates needed to be mentioned by name, or there needed to be sufficient information that was specific to bisphosphonate (e.g. reference to the special instructions for use of oral bisphosphonates), to deduce that study findings related to bisphosphonates, as agreed by two clinically experienced authors independently. Papers describing experiences of osteoporosis more generally were included if there were findings relating to bisphosphonate treatment in the study abstract. Studies were only included if they were qualitative in design, or mixed methods with a qualitative component, relevant to a developed country setting and written in English language. Studies were excluded that involved paediatric patients; patients and clinicians receiving/recommending other treatments for osteoporosis; and studies in which bisphosphonates were being used for other indications (e.g. malignancy or Paget's disease).

Search Methods

Systematic searches were conducted in 7 bibliographic databases (MEDLINE, EMBASE, AMED, CINAHLPlus, PsycINFO, ASSIA, and Web of Science [Social Science Citation Index (SSCI) and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)] from inception to 15th July 2019. The search strategy utilised database subject headings and text word searching in title, abstract or keywords, combining terms for: 1) bisphosphonates; 2) experiences and preferences; and 3) qualitative research, based on DeJean et al.'s search filter (see supplementary file 2 for full MEDLINE search strategy).[19] Search terms were adapted as appropriate for each database platform.

In addition, grey literature was searched (DART Europe, Open Grey, and NDLTD (National Digital Library of Theses and Dissertations)); the reference lists of all included studies and relevant systematic reviews identified were checked and key studies were citation tracked.

Study Selection

1
2
3 Two-stage screening of articles against eligibility criteria was undertaken. Firstly,
4 titles and abstracts were screened, then full texts. At both stages screening was
5 conducted by sets of two reviewers independently (NC, EC, ZP) and articles were
6 excluded by agreement. Disagreements were resolved through discussion or by third
7 reviewer adjudication.
8
9

10 11 12 **Data extraction**

13
14 For each paper data extraction was completed independently by two researchers
15 (ZP and JW or EC and FM). Key findings from the results sections of papers relating
16 to bisphosphonates were extracted; a 'key finding' was defined as any sentence or
17 statement relating to views or experiences of bisphosphonates from the results
18 section of the paper or abstract. Wherever possible, the key finding was extracted as
19 written by the author, with minimal edits only for clarification, description of context or
20 for consistency across papers. For each paper, two authors extracted key findings
21 independently, and subsequently agreed a final list of key findings for each paper.
22 Data were also extracted on participant numbers and demographics, data collection
23 technique, setting and country. Additionally, if available for patients, information was
24 extracted on their bisphosphonate use including type of drug and current status
25 (adherent, non-adherent, decliner).
26
27
28
29
30
31
32
33
34
35

36 **Quality appraisal**

37
38 The quality of each study was assessed using the CASP qualitative tool. This tool
39 consists of 10 items split into 3 sections (qualitative suitability, data analysis and
40 overall quality) (Supplementary File 2). The first two sections consist of items related
41 to qualitative suitability and data analysis, which were evaluated as "yes", "no",
42 "unclear" or "partial". The final question was an assessment based on the overall
43 quality of the paper; this was informed by response to the previous items (indicating
44 methodological quality) and by the relevance of the study to the review objectives
45 and was rated as "high", "moderate" or "low". All papers were quality appraised by
46 two researchers independently (FM, SB, JW). Disagreements were resolved through
47 discussion with a fourth reviewer (ZP).
48
49
50
51
52
53
54

55 **Synthesis**

56
57 We used a framework synthesis approach informed by the 'Best Fit' model described
58 by Carroll et al.[20] The "best fit" method offered a means to test, reinforce and build
59
60

1
2
3 on an existing published model, conceived for a different but relevant purpose. This
4 approach was chosen as a published theory was identified from the literature that
5 conceptualised acceptability - the Theoretical Framework of Acceptability (TFA).[18]
6 The TFA is a relatively new framework which was developed to inform the
7 understanding of acceptability of complex interventions, and consists of seven
8 constructs: affective attitudes - the emotions elicited by an intervention; intervention
9 coherence - the extent to which an intervention makes sense; perceived
10 effectiveness - the perceived extent to which intervention will achieve purpose;
11 burden – the amount of effort required to participate in an intervention; self-efficacy –
12 individual’s confidence that they can perform the behaviour(s) required to participate
13 in the intervention; opportunity-costs - the extent to which benefits, profits, or values
14 must be given up to engage in an intervention; and ethicality – the extent to which an
15 intervention has a good fit with an individual’s values. The framework also
16 incorporates temporal perspectives on *anticipated* and *experienced* acceptability at
17 three time points before (prospective), during (experienced) and after (retrospective)
18 experience of an intervention.
19
20
21
22
23
24
25
26
27
28
29
30

31 The TFA has not previously been used to evaluate drug acceptability. We anticipated
32 the seven constructs of the TFA would be relevant to engagement with drug
33 treatment; for example, burden could relate to treatment burden associated with
34 administering the drug or side effects. However, one aspect which did not appear to
35 be explicitly conceptualised within the framework was patient beliefs about
36 medicines. Studies across a range of long term conditions, healthcare systems and
37 cultures have consistently shown that engagement with treatment is influenced by
38 patients’ personal evaluation of the medicine in question.[21] Particularly important is
39 how they judge their personal need for treatment relative to their concerns about it.
40 For this reason, we therefore included the Necessity Concerns Framework (NCF)
41 [21], to further explore the TFA domain relating to intervention coherence.
42
43
44
45
46
47
48
49
50

51 The first author initially conducted inductive open coding on the data extracted,
52 before mapping the codes to a draft framework derived from a priori themes (the
53 domains of the TFA). Authors then met to first discuss the themes and compare
54 findings for each study and the ‘fit’ to the draft framework. A preliminary synthesis
55 was achieved using tabulation of studies, organising the studies into groups relating
56
57
58
59
60

1
2
3 to temporal perspectives and research question, and exploring relationships between
4 studies and between groups.
5

6
7 A final coding framework was agreed at a second meeting of authors. A second
8 author (FM) recoded the original key findings, where necessary, to the new
9 framework to ensure all findings were represented. Finally, relationships between
10 themes and TFA and NCF domains were explored by further group discussion. We
11 used the Grades of Recommendation, Assessment, Development, and Evaluation
12 Confidence in the Evidence from Qualitative Reviews (GRADE-CERQual) approach
13 to determine confidence in our synthesised findings.[22]
14
15
16
17
18

19 20 **Patient and Public Involvement**

21
22 Members of the Nottingham National, Royal Osteoporosis Society Support Group
23 were involved in a series of meetings to discuss the design of the overarching
24 research programme in which this study sits, and confirmed that understanding
25 acceptability of bisphosphonates from a range of perspectives was important. Patient
26 were not directly involved in the conduct of this study.
27
28
29
30

31 32 **RESULTS**

33
34 The literature search identified 2040 unique articles, of which 25 met eligibility criteria
35 (Figure 1), a summary of the studies is shown in Table 1.
36

37
38 The included studies were categorised into three groups: perceptions of
39 osteoporosis generally; [23-29] healthcare service delivery issues unrelated to
40 osteoporosis (de-prescribing) [30] and inter-professional communication in primary
41 care[31]) and studies specific to osteoporosis treatments. The latter group was
42 further subdivided into: those examining treatment barriers;[16,32-36]
43 adherence;[37-39] decision-making;[40-44] or bisphosphonate-related side
44 effects.[45,46] Only one study examining adherence and one examining decision
45 making had research questions which specifically related to bisphosphonates.[38,43]
46
47
48
49
50

51
52 The majority (23) of studies were conducted in North America or Europe. Eighteen
53 studies explored patient views,[16,23-27,33,35,37-46] of which eight included males,
54 and one study recruited patients taking anti-osteoporosis drugs for glucocorticoid-
55 induced osteoporosis [36]. Twelve studies explored HCPs' views,[16, 28-32,34-
56 36,39,42,43,] and two studies interviewed managers.[16,34] No studies included
57
58
59
60

1
2
3 academic or payor participants. Of the 18 studies that included patients, 10 studies
4 described how many of the patients were on anti-osteoporotic medication, however,
5 only two reported the specific type of medication. Only one study reporting patient
6 experience of receiving intravenous bisphosphonate.[27]
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1: Summary of included studies

Studies in Group 1: Views of Osteoporosis							
First author and year	Participantsⁱ	Participant No. (male:female)	Bisphosphonate use and adherenceⁱⁱ	Data collection methods	Qualitative approach or analysis methodⁱⁱⁱ	Recruitment setting	Country
Besser 2012[23]	Pts	14 (0:14)	AOD unspecified	Interview	Framework analysis	One hospital	UK
Jaglal 2003[29]	HCPs Family Physicians	32 (12:20)	N/A	Focus group	Constant Comparison	Primary Care	Canada
Otmar 2012[328]	HCPs GP (n = 14), Practice nurse (n = 2)	16 (11:5)	N/A	Focus group	Analytic comparison Constant comparison	Primary care	Australia
Sale 2015[24]	Pts	28 (2:26)	19/28 pts on AOD adherent (n=19) declined (n= 4)	Interview	Phenomenological study	National osteoporosis patient group	Canada
Sale 2010[25]	Pts	24 (6:18)	9/24 pts on AOD, risedronate (n=8), etidronate (n=1)	Focus group	Descriptive qualitative study	Fracture Clinic	Canada
Weston 2011[26]	Pts	10 (0:10)	AOD unspecified	Interview	Interpretative phenomenological analysis	Primary Care	UK
Hansen 2017[27]	Pts	15 (0:15)	AOD unspecified adherent (n=12) declined/stopped AOD (n=3)	Interview	Phenomenological hermeneutic approach	Women attending DXA at 2 hospitals	Denmark
Studies in Group 2: Views of Osteoporosis Treatment (treatment barriers)							
Alami 2016[35]	Mixed	Pts: 37 (0:37) HCPs: 18 (8:10)	23/47 pts on AOD, adherent (n=19) declined/stopped AOD (n=18)	Focus group	Grounded theory	Hospital/community over 5 regions	France
Drew 2016[34]	HCPs Nurse (n = 14), GP (n= 2), Specialists (n =17), Orthopaedic Surgeon (n = 4) Managers (n = 5), DXA technician (n=1)	43 (not given)	N/A	Interview	Thematic approach	11 hospitals in one region	UK
Feldstein 2008[16]	Mixed	Pts: 10 (0:10) HCPs: 57 (not given)	AOD unspecified	Interview and focus group	Content analysis	Primary and secondary care	USA
Guzman-Clarke 2007[36]	HCPs	23(13:10)	24/100 pts on AOD	Focus group	Thematic content analysis	Urban academic Medical Centre	USA
Merle 2019(a)[32]	HCPs (GP)	16 (11:5)	N/A	Interview	Descriptive thematic analysis	Primary Care	France
Merle 2019(b)[33]	Pts	98 (53:45)	AOD Unspecified	Focus group	Inductive thematic analysis	Recruited from 2 existing research studies and community (medical insurance company)	France
Studies in Group 2: Views of Osteoporosis Treatment (adherence)							

1	Iversen 2011[39]	Mixed	Pts: 32 (2:30) HCPs: 12 (5:7)	AOD unspecified	Focus group	Open coding (thematic analysis)	Secondary care	USA	
2	Lau 2008[37]	Pts	37 (0:37)	33/37 pts on AOD, alendronate (n=9), etidronate (n=5), risedronate (n=19)	Focus group	Mixed phenomenological design	Primary care, secondary care and community pharmacies	Canada	
3									
4									
5									
6	Salter 2014[38]	Pts	30 (0:30)	20/30 pts on AOD adherent (n=19) declined (n=1) stopped AOD (n=10)	Interview	Framework analysis	Primary Care	UK	
7									
8									
9									
10		Studies in Group 2: Views of Osteoporosis Treatment (Decision Making)							
11	Mazor 2016[40]	Pts	36 (0:36)	15/36 pts on AOD adherent (n=15) declined (n=10) stopped (n=11)	Telephone Interview	(thematic analysis)	Primary Care	USA	
12									
13									
14	Sale 2011[44]	Pts	24 (6:15)	14/21 pts on AOD	Telephone Interview	Phenomenological study	Hospital based fracture screening programme	Canada	
15									
16	Swart 2018[42]	Mixed	Pts: 26 (4:22) HCPs: 13 (not given)	10/26 pts on AOD adherent (n=10) declined (n=16)	Interview	Thematic analysis with elements of grounded theory	Recruited from a fracture prevention study	Netherlands	
17									
18									
19	Scoville 2011[43]	Mixed	Pt: 18 (0:18) HCP: 19 (12:7)	N/A	Videographic	(deductive checklist and descriptive)	Primary care (osteoporosis choice trial)	USA	
20									
21	Wozniak 2017[41]	Pts	12 (3:9)	7/12 pts on AOD, adherent (n=7) stopped (n=5)	Interview	Grounded theory	Recruited from a fracture prevention trial nested in secondary care	Canada	
22									
23									
24		Studies in Group 2: Views of Osteoporosis Treatment (Bisphosphonate side effects)							
25	Sturrock 2019[46]	Pts	23 (4:19)	13/23 pts on AOD	Interview	Grounded theory	Three regions including from secondary care	UK	
26									
27	Sturrock 2017[45]	Pts	17 (7:10)	N/A	Interview	Grounded theory	Primary Care	UK	
28									
29		Studies in Group 3: Non-Specific Osteoporosis Issues							
30	Ailabouni 2016[30]	HCPs	10 GPs	N/A	Interview	Constant comparison	Primary Care	New Zealand	
31									
32	Sippli 2017[31]	HCPs	28 (6:22)	N/A	Interview	Content analysis	Primary Care	Germany	
33									
34									
35									
36	ⁱ Pts – patients; HCPs – healthcare professionals								
37	ⁱⁱ Where specified. AOD – anti-osteoporosis drug. N/A not applicable								
38	ⁱⁱⁱ Text in parentheses – qualitative approach not explicitly stated								
39									
40									
41									
42									
43									
44									
45									
46									

1
2
3 The findings related to quality appraisal are summarised in Table 2. The most
4 common limitations of the included studies were lack of description of author
5 reflexivity, lack of depth of analysis, use of normative statements and relatively small
6 samples or studies conducted in a single site which may limit transferability of the
7 findings. Furthermore, although the characteristics of the sample were generally
8 reasonably described, in order to address our research question, we required
9 information about medication use of participants which was frequently not described.
10
11

12
13 Using the CASP tool, 12 (48%) studies were scored as high value and the remaining
14 13 (52%) studies as moderate value. For 5/13 (38%) studies scored as moderate in
15 value, this was due to methodological issues, and, for 8/13 (62%) studies this was
16 because the focus of the paper was less relevant to our research question.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 2. Quality Appraisal

First author and year	CASP tool Question										Comments ⁱ
	1	2	3	4	5	6	7	8	9	10	
Group 1: Views of Osteoporosis											
Besser 2012[23]	✓	✓	✓	p	✓		✓	p	✓	Moderate	Small sample, no mention of data saturation, limited to 'psychological' factors affecting adherence (discounting other factors by omission) and some use of normative statements
Jaglal 2003[29]	✓	✓	✓	✓	✓	u	✓	✓	✓	Moderate	Few findings relevant to our research question
Otmar 2012[28]	✓	✓	✓	✓	✓		✓	✓	✓	Moderate	Well conducted study, but limited findings relating to bisphosphonates
Sale 2015[24]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
Sale 2010[25]	✓	✓	✓	p	✓	u	✓	p	✓	Moderate	Small single site study, although data saturation reached. Language does not always appear to match approach (e.g. reporting patient 'inability' to link fractures to osteoporosis suggests prior normative assumptions)
Weston 2011[26]	✓	✓	✓	✓	✓	✓	✓	✓	✓	High	
Group 2: Views of Osteoporosis Treatment											
Alami 2016[35]	✓	✓	✓	✓	✓		✓	✓	✓	High	
Drew 2016[34]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
Feldstein 2008[16]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
Guzman-Clarke 2007[36]	✓	✓	✓	✓	✓	u	✓	u	✓	Moderate	Only partially relevant for our review given the focus on a specific population (Glucocorticoid-Induced Osteoporosis)
Merle 2019[32]	✓	✓	✓	p	✓	u	✓	u	✓	Moderate	Small sample (although data saturation reached) without attempt to structure to population and analysis lacks depth to answer our objective relating to bisphosphonate acceptability
Merle 2019[33]	✓	✓	✓	✓	✓	u	✓	✓	✓	Moderate	Limited information relevant to our research question in view of general focus on osteoporosis
Iversen 2011[39]	✓	✓	✓	p	✓		✓	p	✓	Moderate	Single centre study, although data saturation reached, limited information on coding/analysis and no discussion of findings with relevance to wider literature
Lau 2008[37]	✓	✓	✓	✓	✓		✓	✓	✓	High	
Salter 2014[38]	✓	✓	✓	✓	✓		✓	✓	✓	High	

1	Hansen 2017[27]	✓	✓	✓	✓	✓	✓	✓	✓	✓	High	
2												
3	Mazor 2016[40]	✓	✓	✓	✓	✓	u	✓	u	✓	Moderate	Good relevance, single site. Descriptive approach without critical reflexivity or discussion of prior assumptions
4												
5	Sale 2011[4446]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
6												
7	Swart 2018[42]	✓	✓	✓	✓	✓	✓	✓	✓	✓	High	
8												
9	Scoville 2011[43]	✓	✓	✓	✓	✓	u	✓	✓	✓	Moderate	Well conducted videographic study, but data coded against deductive categories of reasons to reject treatment, so limited potential to inform our objective about acceptability
10												
11	Wozniak 2017[41]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
12												
13	Sturrock 2019[46]	✓	✓	✓	✓	✓	u	✓	✓	✓	High	
14												
15	Sturrock 2017[45]	✓	✓	✓	✓	✓		✓	✓	✓	Moderate	Aim only partially relevant to study question
16												
17												
18												
19												
20	Group 3: Non-specific Osteoporosis Issues											
21	Ailabouni 2016[30]	✓	✓	✓	p	✓	✓	✓	✓	✓	Moderate	Relatively small (10 respondents) study, although data saturation reached. Only partial relevant for current review with brief coverage of GPs views on discontinuing bisphosphonates in light of multimorbidities
22												
23	Sippli 2017[31]	✓	✓	✓	✓	✓		✓	✓	✓	Moderate	Limited findings related to our research question
24												
25												
26												
27												
28												
29	i CASP Quality assessment questions; 1, Was there a clear statement of the aims of the research? 2, Is a qualitative methodology appropriate? 3, Was the research design appropriate to address the aims of the research? 4, Was the recruitment strategy appropriate to the aims of the research? 5, Was the data collected in a way that addressed the research issue? 6, Has the relationship between researcher and participants been adequately considered? 7, Have ethical issues been taken into consideration? 8, Was the data analysis sufficiently rigorous? 9, Is there a clear statement of findings? 10, Value of study and relevance to review objectives. ✓ = Yes, u = Unsure, p = partial, blank = No.											
30												
31												
32												
33												
34	ii Comments only made for those ranked Moderate or Low.											
35												
36												
37												
38												
39												
40												
41												
42												
43												
44												
45												
46												

1
2
3 Fifteen individual sub-themes were identified which mapped to the seven domains of
4 the TFA. Key findings relating to ethicality related to conflict between
5 bisphosphonates and participants' values and were usually discussed as part of
6 sense making. For this reason, issues relating to 'ethicality' were considered as part
7 of 'intervention coherence', leaving six main themes, as shown schematically in
8 Figure 2. Although it was possible to distinguish between two temporal perspectives,
9 related to anticipated and experienced acceptability within most domains (with the
10 exception of self-efficacy) the majority of anticipated acceptability findings related to
11 intervention coherence.
12
13
14
15
16
17
18

19 The findings of the review are discussed below with GRADE-CERQual ratings of
20 confidence in Table 3 and illustrative key findings for each theme/subtheme shown in
21 Supplementary file 2. Subthemes are identified in the text in italics.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 3: GRADE-CERQual Summary of qualitative findings table

Review Finding [and contributing studies]	Methodological limitations	Coherence	Adequacy	Relevance	CERQual Confidence assessment
	Concerns				
<p>Intervention coherence: Both before starting, and during treatment, patients considered the perceived need or necessity for bisphosphonates based on their views of osteoporosis, including its seriousness and controllability, symptoms and their perception of their own health. Perceived need was weighed up against concerns about medication, including suspicion of drugs in general and specific concerns about bisphosphonate safety by both patients and HCPs. HCPs sometimes used principles of ethicality to support perceptions of low necessity and their reluctance to prescribe. The decision process of balancing necessity against concerns, was influenced by the doctor-patient relationship and wider societal influences including friends, family and the general media. This process influenced whether HCPs reported recommending bisphosphonates. For patients, the decision process could be explicit or tacit, was revisited over time and influenced both whether they initiated treatment and subsequently adhered. [16,23,25-30,32,33,35-44,46]</p>	<p><i>Minor</i> 12/22 papers rated moderate value due to sample size, depth of analysis or lack of reflexivityⁱ</p>	<p><i>None or very minor</i> The finding reflects the complexity and variation of the data, and these influences on sense making are well supported by details in the underlying studies</p>	<p><i>None or very minor</i> 22 papers contributed to this finding, and although some gave little detail, in-depth insights were reported in 10 papers and information was consistent across studies</p>	<p><i>Minor</i> Spread of studies from primary and secondary care and range of countries. Uncertainties remain about sense making related patients taking intravenous bisphosphonates and influence of gender</p>	<p>HIGH</p>
<p>Perceived effectiveness Both patients and HCPs expressed doubt or uncertainty about the mechanism of effectiveness of bisphosphonates and expressed a range of treatment expectations including strengthening bone - improving bone density, preventing worsening of osteoporosis - maintaining bone density and/or total fracture prevention. Patients wanted proof or evidence of effectiveness through more structured monitoring and follow-up, and were disincentivised to continue treatment in the absence of evidence of perceived effectiveness. [16,23,24,29,34,35,38-40,42,43]</p>	<p><i>Minor</i> 7/15 papers rated moderate value, mostly (4/7) due to limited relevant content. Methodological concerns relate to depth of analysis or lack of reflexivityⁱ</p>	<p><i>None or very minor</i> The finding reflects the complexity and variation of the data, and these issues are supported by details in the underlying studies</p>	<p><i>None or very minor</i> 15 papers contributed to this finding. Some gave little detail, but in-depth insights were reported in 6 papers and information was consistent</p>	<p><i>Minor</i> Spread of studies from primary and secondary care and range of countries. Uncertainties remain about perceived effectiveness of intravenous bisphosphonates</p>	<p>HIGH</p>
<p>Self-efficacy Measures to help patients integrate medication taking into daily routines (supporting routinisation), and the provision of information and support, enhanced their feeling of having control over their health and confidence to adhere to bisphosphonates. Clinician reported barriers to supporting adherence related to perceptions of their knowledge and attitudes, with several knowledge gaps and uncertainties reported, and the perception that osteoporosis was not a priority. Finally, service level barriers which impaired clinicians' self-efficacy in recommending and managing patients on bisphosphonates, included uncertainty</p>	<p><i>Minor</i> 7/15 papers rated moderate value, mostly (4/7) due to limited relevant content. Methodological concerns relate to</p>	<p><i>None or very minor</i> The finding reflects the complexity and variation of the data, and these issues are supported by details in the underlying studies</p>	<p><i>None or very minor</i> 17 papers contributed to this finding. Some gave little detail, but in-depth insights were reported in 5 papers and</p>	<p><i>Minor</i> Spread of studies from primary and secondary care and range of countries. Uncertainties remain about self-efficacy relating to</p>	<p>HIGH</p>

<p>about professional roles and responsibilities, capacity, access to intravenous drugs and communication and IT systems. [16,24,26,27,30-32,37,38,45]</p>	<p>depth of analysis or sample sizeⁱ</p>		<p>information was consistent.</p>	<p>intravenous bisphosphonates</p>	
<p>Affective attitudes: The emotions elicited by bisphosphonates were closely related to intervention coherence. Bisphosphonates were associated predominantly with negative emotions of fear (of side effects) and annoyance (with special instructions); however positive emotions of reassurance and hope were noted in two studies, linked to the anticipated protection that bisphosphonates could incur. [16,23,26,27,35,37,38,40]</p>	<p><i>Minor</i> 2/8 papers rated moderate value due to depth of analysis or lack of reflexivityⁱ</p>	<p><i>None or very minor</i> The finding reflects the data, supported by details in the underlying studies</p>	<p><i>Moderate</i> Reports of affective attitude were mostly descriptive with little depth</p>	<p><i>Moderate</i> Uncertainties remain about affective attitudes to injectable bisphosphonates received in hospital</p>	<p>MODERATE</p>
<p>Burden: The burden or effort of oral bisphosphonates was described mostly relating to the special instructions to take oral bisphosphonates or experienced side effects, although costs incurred were also a potential source of burden. [16,23,26,27,32,37-39,42,43,46]</p>	<p><i>Minor</i> 4/11 papers rated moderate value due to sample size, depth of analysisⁱ</p>	<p><i>None or very minor</i> The finding reflects the data, and these aspects of burden are supported by details in the underlying studies</p>	<p><i>Moderate</i> Reports mostly descriptive with little depth and a possible focus on presence of burden (side effects) rather than absence</p>	<p><i>Moderate</i> Uncertainties remain about burden of indirect costs (travel, dental checks) & burden due to intravenous bisphosphonates</p>	<p>MODERATE</p>
<p>Opportunity costs Circumstances where competing priorities challenged adherence or initiation of bisphosphonates were described relating to co-morbid conditions. The presence of comorbid conditions were described as resulting in less time to support discussion about bisphosphonates in consultations and, result in recommendation of, and adherence to, bisphosphonates being given relative low priority. [16, 27,29,32,33,38, 41,42,44-46]</p>	<p><i>None or very minor</i> 4/11 papers rated moderate value, but this was mostly (n=3) due to limited relevant content rather than methodological concerns.</p>	<p><i>Moderate</i> No discussion of the alternative explanation that having co-morbid conditions may facilitate bisphosphonate acceptability</p>	<p><i>Moderate</i> Reports were limited/lacked depth 3 papers contained little content relevant to the research question</p>	<p><i>Moderate</i> No information about values, benefits that have to be given up to partake in intravenous bisphosphonates, which are likely to be different & likely limited sampling of patients with complex health needs</p>	<p>LOW</p>

ⁱ Concerns considered minor because of the methodological strength of the other papers in this domain, & low likelihood that reflexivity would affect finding

Intervention Coherence (high confidence)

Both before starting, and during treatment, patients considered the perceived need or *necessity* for bisphosphonates based on their views of osteoporosis, including its seriousness and controllability, symptoms and their *perception of their own health*. Perceived need was weighed up against *concerns* about medication, including suspicion of drugs in general and specific concerns about bisphosphonate safety, by both patients and HCPs. HCPs sometimes used principles of *ethicality* to support perceptions of low necessity and their reluctance to prescribe. The *decision process* of balancing necessity against concerns, was influenced by the doctor-patient relationship and wider societal influences including friends, family and the general media. This process influenced whether HCPs reported recommending bisphosphonates. For patients, the decision process could be explicit or tacit, was revisited over time and influenced both whether they initiated treatment and subsequently adhered.

Perceived Effectiveness (high confidence)

Both patients and HCPs expressed doubt or uncertainty about the *mechanism of effectiveness* of bisphosphonates and expressed a range of treatment expectations including strengthening bone - improving bone density, preventing worsening of osteoporosis - maintaining bone density and/or total fracture prevention. Patients wanted proof or evidence of effectiveness through more structured *monitoring and follow-up*, and were disincentivised to continue treatment in the absence of evidence of perceived effectiveness.

Self-efficacy (high confidence)

Measures to help patients integrate medication taking into daily routines (*supporting routinisation*), and the provision of information and support, enhanced their feeling of having control over their health and confidence to adhere to bisphosphonates. Clinician reported barriers to supporting adherence related to perceptions of their *knowledge and attitudes*, with several knowledge gaps and uncertainties reported, and the perception that osteoporosis was not a priority. Finally, *service level barriers* which impaired clinicians' self-efficacy in recommending and managing patients on

1
2
3 bisphosphonates, included uncertainty about professional roles and responsibilities,
4 capacity, access to intravenous drugs and communication and IT systems.
5
6
7
8

9
10 **Affective attitudes** (moderate confidence)

11
12 The *emotions* elicited by bisphosphonates were closely related to intervention
13 coherence. Bisphosphonates were associated predominantly with negative emotions
14 of fear (of side effects) and annoyance (with special instructions); however positive
15 emotions of reassurance and hope were noted in two studies, linked to the
16 anticipated protection that bisphosphonates could incur.
17
18
19
20
21
22

23
24 **Burden** (moderate confidence)

25
26 The burden or effort of oral bisphosphonates was described mostly relating to the
27 *special instructions* to take oral bisphosphonates or experienced *side effects*,
28 although *costs* incurred were also a potential source of burden. Only one study
29 included the experience of a patient on an intravenous bisphosphonate, this patient
30 described low treatment burden as she only had to go once a year, and felt no side
31 effects.[31]
32
33
34
35
36
37
38

39
40 **Opportunity costs** (low confidence)

41
42 There were few descriptions of 'benefits, profits, or values' being given up to take
43 bisphosphonates. However, circumstances where competing priorities challenged
44 adherence or initiation of bisphosphonates were described relating to *co-morbid*
45 *conditions*. The presence of comorbid conditions was described as resulting in less
46 time to support discussion about bisphosphonates in consultations and, result in
47 recommendation of, and adherence to, bisphosphonates being given relative low
48 priority.
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

This systematic review has used the lens of acceptability to understand perceptions of bisphosphonates and the problem of poor adherence. We have identified, with high confidence, how patients and HCPs make sense (coherence) of bisphosphonates by balancing perceptions of need against concerns, how uncertainty prevails about perceived effectiveness of bisphosphonates and how a number of individual and service factors have potential to increase self-efficacy in recommending and adhering to bisphosphonates. We identified with moderate confidence, that bisphosphonate taking induces fear, but has the potential to engender reassurance, and that both the side effects and special instructions for taking oral bisphosphonates can be a source of treatment burden. Finally, we identified with low confidence that multi-morbidity plays a role in people's perception of bisphosphonate acceptability.

To our knowledge, this is the first use of the Theoretical Framework for Acceptability, originally developed to evaluate acceptability of complex interventions, to evaluate the acceptability of medication. We explored the utility of the TFA from two perspectives, as an explanatory model for both patient and clinician acceptability and engagement. The TFA was useful for understanding and combining patient and clinician viewpoints; however, there was considerable overlap between domains; perceived efficacy, affective attitudes and self-efficacy beliefs are all likely to impinge on sense-making, or intervention coherence. The TFA alone does not provide a comprehensive framework for understanding patient acceptability or engagement with medicines, and of course it was not intended to do so. The sense-making aspect of the framework appeared pivotal, and the explanatory value of the framework was enhanced by the incorporation of the NCF to operationalise key engagement related beliefs. In the context of bisphosphonates, concern and associated fears predominate among patients, and perceived need may be underestimated if the consequences of osteoporosis and fragility fractures are not explained. In our findings, sense making was dynamic. Patients re-evaluated perceptions of bisphosphonates over time, expressing uncertainty relating to what represents successful treatment and citing perceived lack of effectiveness being cited as reason to discontinue. This is likely to be a particular problem for bisphosphonates, as opposed to other drugs commonly taken for prevention such as

1
2
3 statins and anti-hypertensive, where measures of feedback and effectiveness are
4 more readily available.
5

6
7 The NICE guidelines for medicines adherence emphasises the need to take into
8 account perceptions (e.g. necessity beliefs and concerns) and practicalities (e.g.
9 capability and resources) that will affect individuals' motivation and ability to start and
10 continue with treatment.[47] However, interventions designed to improve
11 bisphosphonate adherence are often designed to 'educate' or persuade the patient
12 of importance and are often not targeted to eliciting or addressing health beliefs, or
13 informed by underpinning mechanisms of change.[3] There is therefore a need to
14 ensure that any further design of interventions - to promote bisphosphonate
15 adherence - draws on more comprehensive theoretical models of patient
16 engagement with health conditions and medicines such as the Extended Common
17 Sense Model.[48] This model situates individual's perceptions about drugs, and
18 practical issues related to capability, in the context of illness and treatment
19 representations.
20
21
22
23
24
25
26
27
28
29

30 Specifically, our findings suggest a need for clinicians to support patients to
31 understand the need for treatment, to allay concerns where possible and to define
32 what constitutes successful bisphosphonate treatment. Furthermore, clinicians need
33 to support patients evaluate the advantages and disadvantages over time, given the
34 dynamic nature of these decision processes.[48]
35
36
37
38
39

40 It is clear from our findings that clinicians also have necessity-concern dilemmas
41 relating to bisphosphonates. A number of studies reported clinicians themselves
42 perceiving low patient need, high concerns and perceptions treatment was not
43 practical. This is perhaps in contrast with a previous quantitative study in asthma
44 which demonstrated that clinicians held stronger positive beliefs about medicines
45 than patients.[49] It is unclear to what extent the perceptions in our findings were
46 generalisations or applied in specific circumstances, or to what extent these views
47 were negotiated on an individual basis in discussion with patients. Problems may
48 arise in the consultation if clinicians assume patients share their views and then may
49 be less likely to explore patient perceptions of need or concerns. Furthermore, the
50 limitations of interviewing HCPs are well documented; the accounts presented in an
51 interview may not represent clinician underlying beliefs or behaviours meaning that
52
53
54
55
56
57
58
59
60

1
2
3 observational methods may be more appropriate to fully understand clinical
4 decisional making.[50] Given the clinician has a pivotal role in sense making,
5 interventions are also likely needed to address clinician knowledge, attitudes and
6 beliefs. By including the views of clinicians and managers we have also identified a
7 range of service level barriers to promoting bisphosphonate adherence relating to
8 lack of clarity about professional roles, both across primary and secondary care, and
9 within primary care, use of IT systems and access to intravenous treatments.

10
11 A strength of this review is the comprehensive search, use of underpinning
12 theoretical framework, the inclusion of clinician views in addition to patients, and the
13 use of the GRADE-CERQual to give confidence in our findings which has facilitated
14 a clear identification of where further research is needed. Areas where we have
15 identified moderate or low confidence are in need of further research and specifically
16 relate to the influence of multi-morbidity on sense making, burden and self-efficacy in
17 bisphosphonate users, the extent to which intravenous bisphosphonates may
18 overcome issues related to treatment burden and self-efficacy, and the impact of
19 bisphosphonates on affective attitudes and emotions. Furthermore, we have
20 identified gaps in our understanding of how clinicians make decisions in practice,
21 and how views of bisphosphonates may be influenced by gender. Given that many
22 osteoporosis drugs have a different evidence base and licensing arrangements in
23 men this is an area in need of further study.

24
25 The main limitation of this study relates to the lack of clarity in many of the included
26 studies in the results sections about which osteoporosis treatments or
27 bisphosphonates were being referred to, meaning that in some cases we may have
28 over-interpreted findings relating to bisphosphonates that were about other
29 osteoporosis drugs. However, all of our review findings were identified from
30 comparison of data from several studies, and as bisphosphonates represent the
31 mainstay of osteoporosis treatment, we consider that over-interpretation is unlikely.
32 As there was frequently little detail about medication participants were taking or
33 referring to, it is also possible that we have missed relevant studies. The views of
34 males were underrepresented; although 8/18 studies included men, men
35 represented less than 20% of the total patient population in the included studies. It is
36 important for future studies to include males and specific populations such as those
37 with glucocorticoid-induced osteoporosis who are likely to have different experiences
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 and needs.[51] Only two studies reported the views of managers but unfortunately
4 neither of these studies distinguished professional roles in the presentation of
5 results, so a further need exists to explore perceptions of this group, and perceptions
6 of payors and academics. Finally, although the population from which each study
7 sampled was reasonably well described, it was not always possible to appreciate if
8 the setting was primary or secondary care; the majority of studies appeared to recruit
9 from primary care which may explain the lack of findings related to intravenous
10 bisphosphonates and limit the transferability of our findings to non-primary care
11 settings.
12
13
14
15
16
17
18
19
20

21 **CONCLUSIONS**

22
23 In summary, using the lens of acceptability, we have identified the factors that
24 influence how patients and clinicians make sense of bisphosphonates, described the
25 experience of bisphosphonate taking in terms of burden and factors that both
26 facilitate and hinder confidence in taking, and prescribing and monitoring
27 bisphosphonates. Our findings demonstrate the need for a theoretically informed,
28 whole-system approach' to enable clinicians and patients to get the best from
29 bisphosphonate treatment. Patients need comprehensive support that takes account
30 of the perceptions (e.g. treatment necessity beliefs and concerns) and practicalities
31 (e.g. capability and resources) that influence their motivation and ability to start and
32 continue with treatment. Clinicians need to moderate patient expectations and clarify
33 what constitutes bisphosphonate treatment success. Finally, further research is
34 needed to explore perspectives of managers, patients receiving intravenous
35 bisphosphonates, men receiving bisphosphonates and the use of bisphosphonates
36 in the context of multi-morbidity.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

A. CONTRIBUTION STATEMENT

Conceptualisation: ZP, SB, EC, AD, TO, NG, JLB, TL, OS. Protocol: ZP, EC, NC, SB, LLB, TL, TO, OS, NG, AD. Search Implementation: ZP, EC, NC, JW, FCM. Data extraction and Quality: ZP, EC, NC, JW, FCM, SB. Synthesis: ZB, SB, EC, FCM, RH, CJ. Writing- Original draft: ZP, FCM. Writing- Review and Editing: ZP, SB, AD, TO, NG, JLB, CJ, TL, OS, FCM, JW, NC, NH, EC

B. CONFLICTS OF INTEREST

There are no competing interests for any author

C. FUNDING

This study is funded by the National Institute for Health Research (NIHR), [HTA NIHR127550]. ZP is funded by the NIHR, Clinician Scientist Award (CS-2018-18-ST2-010)/NIHR Academy. CJ is part funded by the NIHR Applied Research Collaboration West Midlands. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health & Social Care.

D. DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information

E. ACKNOWLEDGEMENTS

None to declare.

REFERENCES

- 1 Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: A world-wide projection. *Osteoporos Int* 1992;2:285-9. doi:10.1007/BF01623184
- 2 National Osteoporosis Society. NHS RightCare scenario: The variation between sub-optimal and optimal pathways. *Rep* 2017:1–16.
- 3 Hiligsmann, M., Cornelissen, D., Vrijens, B. et al. Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF). *Osteoporos Int* 2019;30:2155–65. <https://doi.org/10.1007/s00198-019-05104-5>
- 4 Khosla S, Shane E. A Crisis in the Treatment of Osteoporosis. *J Bone Miner Res* 2016;31:1485-7. doi:10.1002/jbmr.2888
- 5 May CR, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ* 2009;339:2830. doi:10.1136/bmj.b2803
- 6 National Institute for Health Care Excellence. Bisphosphonates for treating osteoporosis, Technology appraisal guidance (TA46) *NICE Guidance* 2017
- 7 Jha S, Wang Z, Laucis N, et al. Trends in Media Reports, Oral Bisphosphonate Prescriptions, and Hip Fractures 1996-2012: An Ecological Analysis. *J Bone Miner Res* 2015;30:2179-87 doi:10.1002/jbmr.2565
- 8 Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: A Randomized Open-Label Trial. *Obstet Gynecol* 2013;121:1291-9. doi:10.1097/AOG.0b013e318291718c
- 9 Akarirmak Ü, Koçyiğit H, Eskiuyurt N, et al. Influence of patient training on persistence, compliance, and tolerability of different dosing frequency regimens of bisphosphonate therapy: An observational study in Turkish patients with postmenopausal osteoporosis. *Acta Orthop Traumatol Turc* 2016;50:415-23. doi:10.1590/S0080-623420160000500008

- 1
2
3 10 Kishimoto H, Maehara M. Compliance and persistence with daily, weekly, and
4 monthly bisphosphonates for osteoporosis in Japan: analysis of data from the
5 CISA. *Arch Osteoporos* 2015;10:27. doi:10.1007/s11657-015-0231-6
6
7
8
9 11 Durden E, Pinto L, Lopez-Gonzalez L, et al. Two-year persistence and
10 compliance with osteoporosis therapies among postmenopausal women in a
11 commercially insured population in the United States. *Arch Osteoporos*
12 2017;12:22. doi:10.1007/s11657-017-0316-5
13
14
15
16 12 Saini SD, Schoenfeld P, Kaulback K, et al. Effect of medication dosing
17 frequency on adherence in chronic diseases. *Am J Manag Care* 2009;15:22-
18 33.
19
20
21
22 13 Hiligsmann M, Bours SPG, Boonen A. A Review of Patient Preferences for
23 Osteoporosis Drug Treatment. *Curr Rheumatol Rep* 2015;17:61.
24 doi:10.1007/s11926-015-0533-0
25
26
27
28 14 de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, et al. Patients' preferences
29 for osteoporosis drug treatment: A discrete choice experiment. *Osteoporos Int*
30 2008;19:1029-37. doi:10.1007/s00198-007-0535-5
31
32
33
34 15 Alten R, Krüger K, Rellecke J, et al. Examining patient preferences in the
35 treatment of rheumatoid arthritis using a discrete-choice approach. *Patient*
36 *Prefer Adherence* 2016;10:2217. doi:10.2147/PPA.S117774
37
38
39
40 16 Feldstein AC, Schneider J, Smith DH, et al. Harnessing stakeholder
41 perspectives to improve the care of osteoporosis after a fracture. *Osteoporos*
42 *Int* 2008;19:1527-40. doi:10.1007/s00198-008-0605-3
43
44
45
46 17 Bliuc D, Eisman JA, Center JR. A randomized study of two different
47 information-based interventions on the management of osteoporosis in
48 minimal and moderate trauma fractures. *Osteoporos Int* 2006;19:1309-17.
49 doi:10.1007/s00198-006-0078-1
50
51
52
53 18 Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions:
54 An overview of reviews and development of a theoretical framework. *BMC*
55 *Health Serv Res* 2017;17:88. doi:10.1186/s12913-017-2031-8
56
57
58
59 19 Dejean D, Giacomini M, Simeonov D, et al. Finding Qualitative Research
60

- 1
2
3 Evidence for Health Technology Assessment. *Qual Health Res* 2016;26:1307-
4 17. doi:10.1177/1049732316644429
5
6
7
8 20 Carroll C, Booth A, Cooper K. A worked example of 'best fit' framework
9 synthesis: A systematic review of views concerning the taking of some
10 potential chemopreventive agents. *BMC Med Res Methodol* 2011;11:29.
11 doi:10.1186/1471-2288-11-29
12
13
14
15 21 Horne R, Chapman SCE, Parham R, et al. Understanding patients' adherence-
16 related Beliefs about Medicines prescribed for long-term conditions: A meta-
17 analytic review of the Necessity-Concerns Framework. *PLoS One*
18 2013;8:e80633. doi:10.1371/journal.pone.0080633
19
20
21
22 22 Lewin S, Booth A, Glenton C, et al. Applying GRADE-CERQual to qualitative
23 evidence synthesis findings: Introduction to the series. *Implement Sci* 2018;2.
24 doi:10.1186/s13012-017-0688-3
25
26
27
28 23 Besser SJ, Anderson JE, Weinman J. How do osteoporosis patients perceive
29 their illness and treatment? Implications for clinical practice. *Arch Osteoporos*
30 2012;7:115-24 doi:10.1007/s11657-012-0089-9
31
32
33
34 24 Sale JEM, Hawker G, Cameron C, et al. Perceived messages about bone
35 health after a fracture are not consistent across healthcare providers.
36 *Rheumatol Int* 2015;35:91-130. doi:10.1007/s00296-014-3079-y
37
38
39
40 25 Sale JEM, Beaton D, Sujic R, et al. 'If it was osteoporosis, i would have really
41 hurt myself.' Ambiguity about osteoporosis and osteoporosis care despite a
42 screening programme to educate fragility fracture patients. *J Eval Clin Pract*
43 2010;16:590-6. doi:10.1111/j.1365-2753.2009.01176.x
44
45
46
47 26 Weston JM, Norris E V., Clark EM. The invisible disease: Making sense of an
48 osteoporosis diagnosis in older age. *Qual Health Res* 2011;21:192-704.
49 doi:10.1177/1049732311416825
50
51
52
53 27 Hansen CA, Abrahamsen B, Konradsen H, et al. Women's lived experiences
54 of learning to live with osteoporosis: A longitudinal qualitative study. *BMC*
55 *Womens Health* 2017;17:17. doi:10.1186/s12905-017-0377-z
56
57
58
59 28 Otmar R, Reventlow SD, Nicholson GC, et al. General medical practitioners'
60

- 1
2
3 knowledge and beliefs about osteoporosis and its investigation and
4 management. *Arch Osteoporos* 2012;7:104-14. doi:10.1007/s11657-012-0088-
5
6 x
7
8
9 29 Jaglal SB, Carroll J, Hawker G, et al. How are family physicians managing
10 osteoporosis?: Qualitative study of their experiences and educational needs.
11 *Can Fam Physician* 2003;49:462-8.
12
13 30 Ailabouni NJ, Nishtala PS, Mangin D, et al. General practitioners' insight into
14 deprescribing for the multimorbid older individual: A qualitative study. *Int J Clin*
15 *Pract* 2016;70:261-76. doi:10.1111/ijcp.12780
16
17 31 Sippli K, Rieger MA, Huettig F. GPs' and dentists' experiences and
18 expectations of interprofessional collaboration: Findings from a qualitative
19 study in Germany. *BMC Health Serv Res* 2017;17:179. doi:10.1186/s12913-
20 017-2116-4
21
22 32 Merle B, Haesebaert J, Bedouet A, et al. Osteoporosis prevention: Where are
23 the barriers to improvement in French general practitioners? A qualitative
24 study. *PLoS One* 2019;14:e0219681.
25
26 33 Merle B, Dupraz C, Haesebaert J, et al. Osteoporosis prevention: where are
27 the barriers to improvement in a French general population? A qualitative
28 study. *Osteoporos Int* 2019;30:177–85. doi:10.1007/s00198-018-4720-5
29
30 34 Drew S, Judge A, Cooper C, et al. Secondary prevention of fractures after hip
31 fracture: a qualitative study of effective service delivery. *Osteoporos Int*
32 2016;27:1719-27. doi:10.1007/s00198-015-3452-z
33
34 35 Alami S, Hervouet L, Poiraudau S, et al. Barriers to effective postmenopausal
35 osteoporosis treatment: A qualitative study of patients' and practitioners' views.
36 *PLoS One* 2016;11. doi:10.1371/journal.pone.0158365
37
38 36 Guzman-Clark JRS, Fang MA, Sehl ME, et al. Barriers in the management of
39 glucocorticoid-induced osteoporosis. *Arthritis Care Res* 2007;140-6.
40 doi:10.1002/art.22462
41
42 37 Lau E, Papaioannou A, Dolovich L, et al. Patients' adherence to osteoporosis
43 therapy: Exploring the perceptions of postmenopausal women. *Can Fam*
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 *Physician* 2008;54:394-402.
4
5
6 38 Salter C, McDaid L, Bhattacharya D, et al. Abandoned Acid? Understanding
7 adherence to bisphosphonate medications for the prevention of osteoporosis
8 among older women: A qualitative longitudinal study. *PLoS One* 2014;9.
9 doi:10.1371/journal.pone.0083552
10
11
12
13 39 Iversen MD, Vora RR, Servi A, et al. Factors affecting adherence to
14 osteoporosis medications: A focus group approach examining viewpoints of
15 patients and providers. *J. Geriatr. Phys. Ther* 2011;34:72.
16 doi:10.1097/JPT.0b013e3181ff03b4
17
18
19
20 40 Mazor KM, Velten S, Andrade SE, et al. Older womens views about
21 prescription osteoporosis medication: A cross-sectional, qualitative study.
22 *Drugs and Aging* 2010;27:999-1008. doi:10.2165/11584790-000000000-00000
23
24
25
26 41 Wozniak LA, Johnson JA, McAlister FA, et al. Understanding fragility fracture
27 patients' decision-making process regarding bisphosphonate treatment.
28 *Osteoporos Int* 2017;28:219-29. doi:10.1007/s00198-016-3693-5
29
30
31
32 42 Swart KMA, Van Vilsteren M, Van Hout W, et al. Factors related to intentional
33 non-initiation of bisphosphonate treatment in patients with a high fracture risk
34 in primary care: A qualitative study. *BMC Fam Pract* 2018;19:141.
35 doi:10.1186/s12875-018-0828-0
36
37
38
39
40 43 Scoville EA, de Leon Lovaton PP, Shah ND, et al. Why do women reject
41 bisphosphonates for osteoporosis? a videographic study. *PLoS One* 2011;6.
42 doi:10.1371/journal.pone.0018468
43
44
45
46 44 Sale JEM, Gignac MA, Hawker G, et al. Decision to take osteoporosis
47 medication in patients who have had a fracture and are 'high' risk for future
48 fracture: A qualitative study. *BMC Musculoskelet Disord* 2011;12:92.
49 doi:10.1186/1471-2474-12-92
50
51
52
53 45 Sturrock A, Preshaw P, Hayes C, et al. Attitudes and perceptions of GPs and
54 community pharmacists towards their role in the prevention of bisphosphonate-
55 related osteonecrosis of the jaw: A qualitative study in the North East of
56 England. *BMJ Open* 2017;7:e016047. doi:10.1136/bmjopen-2017-016047
57
58
59
60

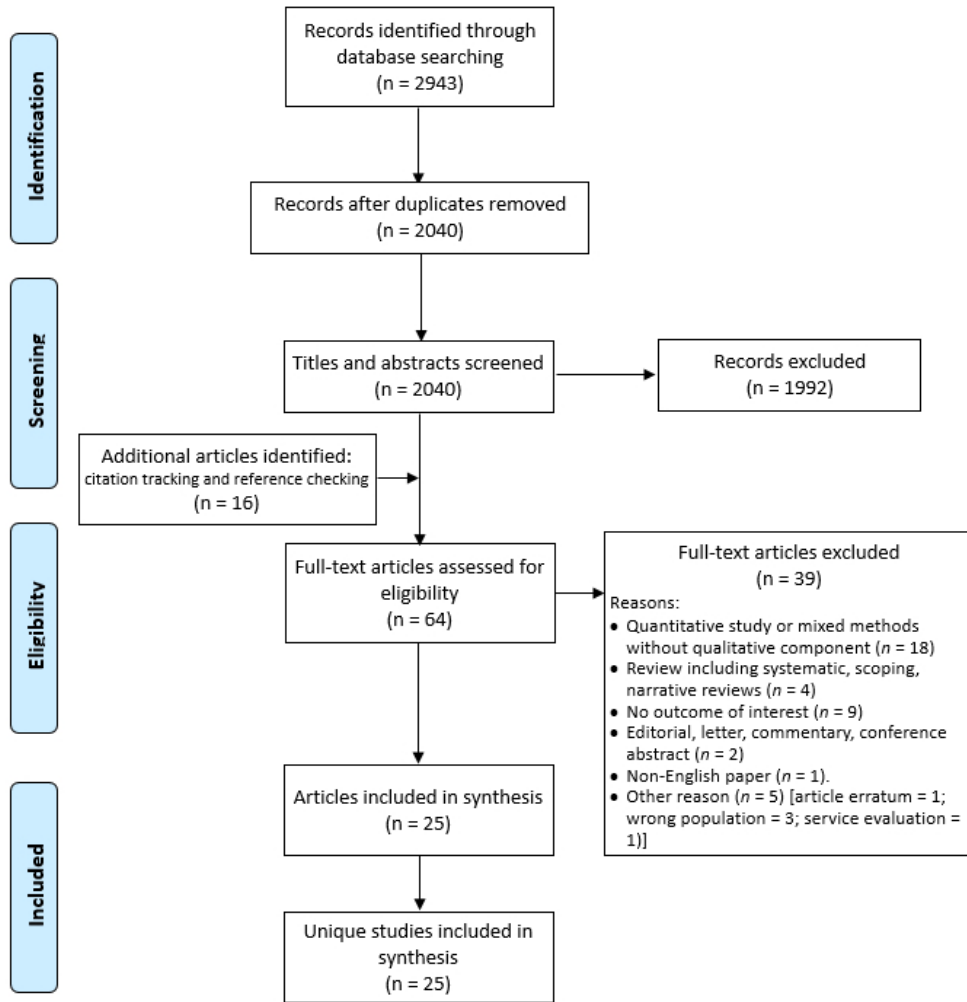
- 1
2
3 46 Sturrock A, Preshaw PM, Hayes C, et al. Perceptions and attitudes of patients
4 towards medication-related osteonecrosis of the jaw (MRONJ): A qualitative
5 study in England. *BMJ Open* 2019;9:e024376. doi:10.1136/bmjopen-2018-
6 024376
7
8
9
10
11 47 Nunes V, Neilson J, O'flynn N, et al. Medicines adherence: involving patients in
12 decisions about prescribed medicines and supporting adherence (CG76).
13 *NICE Guidance* 2009.
14
15
16 48 Horne R, Cooper V, Wileman V, et al. Supporting Adherence to Medicines for
17 Long-Term Conditions. *Eur Psychol* 2019. doi: 10.1027/1016-9040/a000353
18
19
20
21 49 Driesenaar JA, De Smet PA, van Hulten R, et al. Beliefs about inhaled
22 corticosteroids: comparison of community pharmacists, pharmacy technicians
23 and patients with asthma. *J. Asthma* 2016;53:1051-8.
24
25
26 50 Checkland K, Harrison S, Marshall M. Is the metaphor of 'barriers to change'
27 useful in understanding implementation? Evidence from general medical
28 practice. *J Heal Serv Res Policy* 2007;12:95-00.
29
30
31
32
33
34
35 51 Beauvais, C., Poivret, D., Lespessailles, E. et al. Understanding Patients'
36 Perspectives and Educational Needs by Type of Osteoporosis in Men and
37 Women and People with Glucocorticosteroid-Induced Osteoporosis: A
38 Qualitative Study to Improve Disease Management. *Calcif Tissue Int* 105,
39 589–608 (2019). <https://doi.org/10.1007/s00223-019-00607-z>
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure legends**
4

5 Figure 1. Prisma Diagram
6

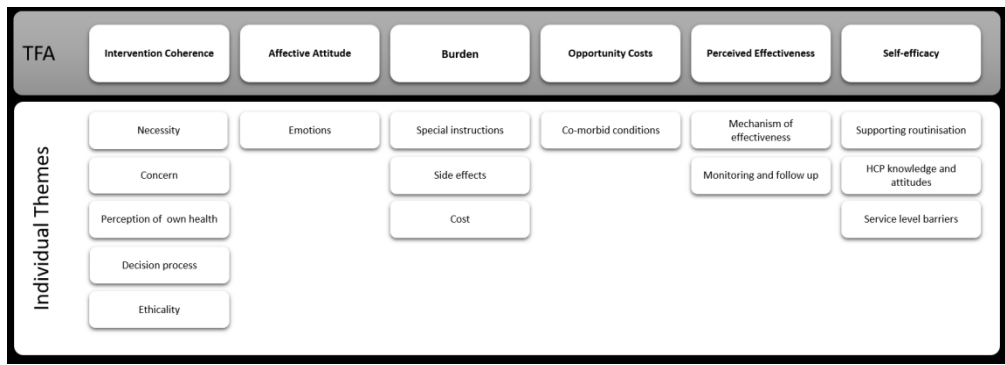
7 Figure 2. Identified themes and subthemes mapped to the Theoretical Framework of
8 Acceptability (TFA)
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



Prisma Diagram

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Identified themes and subthemes mapped to the Theoretical Framework of Acceptability (TFA)

Supplementary Table 1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done including measures of consistency (e.g., I^2) for each meta-analysis.	7-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-17
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23
---------	----	--	----

For peer review only

bmjopen-2020-041664 on 13 November 2020. Downloaded from <http://bmjopen.bmj.com/> on April 17, 2024 by guest. Protected by copyright.

Supplementary Material 1. OVID MEDLINE Search strategy

For Ovid: The following table is an explanation of the symbols used in the search strategy below.

/	indicates an index term (MeSH/EMTREE heading).
exp	before an index term indicates that all subheadings were selected.
af.	Indicates a search for a term in all fields.
.ti,ab,kf.	indicates a search for a term in title/abstract/word(s) in keyword [MEDLINE].
mp.	indicates a search for a term in 'multi-purpose' fields, including the title, abstract, floating sub-heading word, keyword heading word, subject heading word.
tw.	Indicates a search for a term in title and abstract.
\$	at the end of a term indicates that this term has been truncated.
?	optional wild card character replaces zero or one character within a word or at the end of a word
adj	indicates a search for two terms where they appear adjacent to each another
adjn	indicates a search for two terms where they appear within <i>n</i> words of each another

Searches

1	diphosphonates/ or alendronate/ or ibandronic acid/ or risedronic acid/ or zoledronic acid/ or etidronic acid/ or pamidronate/
2	diphosphon\$.ti,ab,kf.
3	bisphosphon\$.ti,ab,kf.
4	alendron\$.ti,ab,kf.
5	fosamax.ti,ab,kf.
6	risedron\$.ti,ab,kf.
7	actonel.ti,ab,kf.
8	zoledron\$.ti,ab,kf.
9	aclasta.ti,ab,kf.
10	ibandron\$.ti,ab,kf.
11	etidron\$.ti,ab,kf.
12	pamidron\$.ti,ab,kf.
13	or/1-12
14	attitude/
15	attitude of health personnel/
16	exp attitude to health/ [includes patient satisfaction and patient preference]
17	choice behavior/
18	decision making/
19	attitud\$.ti,ab,kf.
20	percept\$.ti,ab,kf.
21	expectation\$.ti,ab,kf.

- 1
2
3
4 22 experienc\$.ti,ab,kf.
5 23 preferen\$.ti,ab,kf.
6 24 choice\$.ti,ab,kf.
7
8 25 belie\$.ti,ab,kf.
9 26 opinion\$.ti,ab,kf.
10
11 27 priorit\$.ti,ab,kf.
12
13 28 benefi\$.ti,ab,kf.
14
15 29 reason\$.ti,ab,kf.
16
17 30 decision\$.ti,ab,kf.
18
19 31 motiv\$.ti,ab,kf.
20
21 32 justif\$.ti,ab,kf.
22 33 (concern or concerns or concerned).ti,ab,kf.
23
24 34 (view or views or viewed).ti,ab,kf.
25
26 35 satisf\$.ti,ab,kf.
27
28 36 value\$.ti,ab,kf.
29
30 37 or/14-36
31 38 Qualitative Research/ [After DeJean et al., 2016. Qual Health Res **26**(10): 1307-1317]
32 39 interview/
33
34 40 (theme\$ or thematic).mp.
35
36 41 qualitative.af.
37
38 42 nursing methodology research/
39
40 43 questionnaire\$.mp.
41
42 44 ethnological research.mp.
43
44 45 ethnograph\$.mp.
45
46 46 ethnonursing.af.
47
48 47 phenomenol\$.af.
49
50 48 (grounded adj (theor\$ or study or studies or research or analys?s)).af.
51
52 49 (life stor\$ or women\$ stor\$).mp.
53
54 50 (emic or etic or hermeneutic\$ or heuristic\$ or semiotic\$).af.
55
56 51 ((data adj1 saturat\$) or participant observ\$).tw.
57
58 52 (social construct\$ or postmodern\$ or post modern\$ or poststructural\$ or post structural\$ or
59
60 53 (action research or cooperative inquir\$ or co operative inquir\$).mp.
54 (humanistic or existential or experiential or paradigm\$).mp.

- 1
2
3 55 (field adj (study or studies or research)).tw.
4
5 56 human science.tw.
6
7 57 biographical method.tw.
8
9 58 theoretical sampl\$.af.
10
11 59 ((purpos\$ adj4 sampl\$) or (focus adj group\$)).af.
12
13 60 (account or accounts or unstructured or open ended or text\$ or narrative\$).mp.
14
15 61 (life world or conversation analys?s or personal experience\$ or theoretical saturation).mp.
16
17 62 ((lived or life) adj experience\$).mp.
18
19 63 cluster sampl\$.mp.
20
21 64 observational method\$.af.
22
23 65 content analysis.af.
24
25 66 (constant adj (comparative or comparison)).af.
26
27 67 ((discourse\$ or discours\$) adj3 analys?s).tw.
28
29 68 narrative analys?s.af.
30
31 69 heidegger\$.tw.
32
33 70 colaizzi\$.tw.
34
35 71 spiegelberg\$.tw.
36
37 72 van manen\$.tw.
38
39 73 van kaam\$.tw.
40
41 74 merleau ponty.tw.
42
43 75 husserl\$.tw.
44
45 76 foucault\$.tw.
46
47 77 (corbin\$ adj2 strauss\$).tw.
48
49 78 glaser\$.tw.
50
51 79 (mix\$ adj2 (method\$ or design\$)).af. [filter amended to identify mixed method studies]
52
53 80 or/38-79
54
55 81 13 and 37 and 80
56
57
58
59
60

Supplementary Material 2. CASP Quality Appraisal Checklist

All ten questions answered with one of four options: Yes, unsure, partial, or No

Section A: Are the results of the study valid?

1. Was there a clear statement of the aims of the research?
2. Is a qualitative methodology appropriate?
3. Was the research design appropriate to address the aims of the research?
4. Was the recruitment strategy appropriate to the aims of the research?
5. Was the data collected in a way that addressed the research issue?
6. Has the relationship between researcher and participants been adequately considered?

Section B: What are the results?

7. Have ethical issues been taken into consideration?
8. Was the data analysis sufficiently rigorous?
9. Is there a clear statement of findings?

Section C: Will the results help locally?

10. How valuable is the research?

Supplementary Material 3. Subtheme descriptions and illustrative key findings

Main theme	Subtheme	Description	Illustrative Key findings
Intervention Coherence	Necessity	Both patient and clinician participants described osteoporosis, falling and fracturing as a normal part of ageing and this view was associated with the perception that medication or treatment was futile.[16,38] One GP described the ‘problem is not with the treatment, it’s with the diagnosis’: perceiving that the indications for treatment had broadened over recent years.[42] The absence of symptoms was reported by clinicians as a disincentive to patients accepting treatment,[33,36] however, patients questioned whether osteoporosis really was asymptomatic.[23] Patient participants who conceptualised osteoporosis as having consequences, e.g. as a cause of disability including ‘shrinking’ and ‘stooping’, were motivated to take medication.[37] Patient participants described other way of controlling their condition and preventing fracture, for example, by not falling.[35] In some patients who initiated treatment, the notion of osteoporosis as a chronic disease was noted not to make sense with the need to take bisphosphonate medication for 5 years.[23]	Patients perceived minimal susceptibility to the negative consequence of osteoporosis in the future and did not consider osteoporosis to be a serious health condition.[30] Avoiding consequences (including shrinking, stooping, fractures) of osteoporosis was a strong motivator for adherence in PMW.[37]
	Concerns	Before starting bisphosphonates, patients noted concern and fear of bisphosphonate-specific side effects. This could be informed by vicarious experience of a family member,[43] or information from the media.[37] The special instructions for use, the limited duration of treatment and the name ‘acid’ were all cited as reasons underlying the perception that bisphosphonates must be harmful. Both patients and HCP’s also cited a mistrust of pharmaceutical companies,[33,38,42] or a general aversion to drugs.[35,37,39,42]	{Women} were concerned about the long lists of drug side effects in advertisements.[16] ‘Once you’re on it, then it stays in your system and you wonder what damage have you’ve done to yourself?’[16] Some PMW did not like the idea of taking any medications because they viewed medications as artificial and thought they had unpredictable effects.[37]
	Perceptions of own health	Some patients reported a perception that they were healthy, with some disbelieving they had osteoporosis and/or high fracture risk, and therefore and would reject medication and a label of a disease.[37] Conversely, others conceptualised bisphosphonates as a	Some patients initiated bisphosphonates to stay healthy.[41] For PMW who considered themselves healthy, the idea of

		<p>mechanism to remain healthy[41] and/or autonomous.[38] In a study of French GPs, on respondent also suggested patients wanted to know how to “age well”.[33]</p>	<p>medication was disconcerting as it meant perceiving themselves as sick.[37]</p>
	<p>Decision process</p>	<p>Across studies patients and HCPs described perceptions that the benefits did not outweigh the risks.[16,29,35,41,] Often in these descriptions, the value of treatment was not clearly articulated meaning this assessment meant the patient weighing up staying as they were, or experiencing new side effects.[38] However, even when the risk of fracture was acknowledged, medication could still be seen as something to avoid.[35] The opposing view that the ‘benefits were worth the costs’ was evident in circumstances where benefits were described.[37] Others studies with patients reported that the decision was ‘difficult’ with one participant describing it as like ‘Russian roulette’.[44] Balancing necessity against concerns was influenced by contingent factors such as trust in the clinician and could either be an easy or difficult and ongoing process. Patient participants talked about ‘confidence’ and ‘trust’ in their HCP, which could be associated with minimal contemplation to take treatment, or alternatively mistrust, or a failure to be ‘convinced’.[16,25,26,37,40] Some patients reported clinicians as being persistent in their recommendation to take bisphosphonates;[40] however, conversely, patients also described by dissuaded by their doctor against treatment.[32] Often, patients described seeking information from other sources to make the final decision which often resulted in a decision against treatment.[44]</p> <p>For those who initiated medication, an ongoing re-assessment of risk and benefit was noted,[23,41,44] particularly in studies that employed longitudinal methods.[27,38, 41] Patients reported their decision making was influenced by experiencing a future fracture,[44] follow-up scans,[25] experienced side effects,[37,38] views of others and other experienced illnesses or life events.[27]</p>	<p>For some, the decision to take bisphosphonate involved minimal contemplation because they liked/trusted their health care provider.[44]</p> <p>Patients who found the decision difficult sought alternative sources of information (professional and non) which often resulted in decision not to take OP medication.[44]</p>
	<p>Ethicality</p>	<p>Both orthopaedic and primary care clinicians reported a ‘bias’ against treating the elderly due to a belief ‘nothing can be done for them’.[16] However, some patients also perceived that they were too old to benefit.[35] HCPs were seen to use the using ethical principle of non-maleficence to justify not recommending bisphosphonates. They questioned the negative side effects ‘for a benefit that has not really been proven’ and worried about being blamed for causing their patients ill-health.[28,40] Patients, in some circumstances, doubted the beneficence of the health care professionals e.g. perceiving</p>	<p>Clinicians {primary care and specialists} report bias against treating elderly patients because of a general tendency to believe that nothing can be done for them.[16]</p>

bmjopen-2020-044694 on 3 November 2020. Downloaded from <http://bmjopen.bmj.com/> on April 17, 2024 by guest. Protected by copyright.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

		their physician as a 'pill pusher' or the motivation for prescribing medication being to receive money in return.[40]	
Affective Attitudes	Emotions	<p>Patients described wide-ranging fears including fear of common and rare side effects and fear of new side effects emerging in the future. Patients described fear of bisphosphonates staying in their system,[16] with one patient participant describing bisphosphonates as akin to chemicals used to clean machines.[23] Patients also worried information was being withheld, or were fearful of the sheer amount of information to take in.[37] Both clinicians and patients described media reports as the source of fear, with patients also citing experiences of friends and family.[37] Fear of addiction was mentioned by patients in one study.[23] Patients and HCPs also expressed annoyance with the special instructions associated with oral bisphosphonate use, and annoyance with experienced oesophageal side effects.[40]</p> <p>In two studies, patient participants reported that they experienced feelings of safety and reassurance when taking bisphosphonates,[26] linked to the anticipated benefits.[37]</p>	<p>"..when I read the side effects it was like a <i>horror film</i> really".[38]</p> <p>medication provided a feeling of safety and reassurance.[26]</p>
Burden	Special instructions	<p>The method of administration of oral bisphosphonates caused concern to patients both prior to initiating treatment,[42] and whilst on the treatment,[32] causing disruption to daily life. The need to remain upright after taking the medication and only being allowed to drink water was burdensome, and led to some disregarding the administration requirements.[37] Specific activities that needed to be actioned first thing in the morning also competed with taking oral bisphosphonates, with patients citing examples such as the need to have a coffee or run a family errand early every morning.[44] Primary care physicians reported that taking bisphosphonates was a 'hassle' for patients.[16] The frequency of the oral bisphosphonates, once a week, led to a number of reports of patients forgetting to take their medication.[16,23,37-39] Varying reports were identified about whether daily or weekly regimes were more or less burdensome.[16,37] Four studies reported patients' perceptions that the special instructions were not disruptive or burdensome.[26,27,37,39]</p>	<p>Some patients were able to rearrange their daily routines to accommodate {bisphosphonate} requirements, but others would intentionally disregard the administration requirements or forget to take the medication if it did not fit into their schedules.[37]</p>
	Side effects	<p>Experienced side effects were discussed in three of the studies interviewing clinicians,[28,29,31] eight with patients[23,26,27,37,38,41,44,45] and five with mixed participants.[16,35,39,42,43] Experienced side effects were reported as a common reason for lack of adherence, with gastrointestinal disturbances being described</p>	<p>Gastrointestinal disturbances from taking bisphosphonates were most notable and were described as</p>

		“horrendous diarrhoea” and “wrecking my stomach.[37,39] Patients reported stopping medications after experiencing side effects, did not always disclose side effects to HCPs and noted that the treatment ‘was almost more disabling than the disease’.[27,32,46]	“horrendous diarrhoea” and “wrecking my stomach.[37]
	Costs	Financial costs were discussed in five studies, four of which were conducted in North America and one in Australia.[16,28,37,43,46] Patients did not report cost as a barrier to bisphosphonates specifically, however, medical insurance was perceived by clinicians as a barrier due to its complexity.[29,39,43] Indirect costs relating to travel and the need for increased dental checks were mentioned briefly but not described as a problem.[25,46]	Cost was not a limiting factor to adherence if patients had insurance coverage for medications. Even patients without insurance expressed a willingness to make sacrifices to pay for the medications because they thought the benefits were worth the cost.[37] Providers {secondary care} stated that due to cost not being covered by insurance companies, patients stop taking or alter dose/frequency.[39]
Opportunity costs	Co-morbid conditions	Physicians perceived bisphosphonate treatment was less important to patients who might have other more pressing health conditions [29,45] particularly in the absence of symptoms.[27,33] Patients also reported that other health conditions took priority over their prescribed bisphosphate leading them not to start or discontinue medication.[32] Within the time-limited consultation, multiple competing priorities relating to other health conditions was reported by HCPs, resulting in a ‘pecking order’, and less time to discuss bisphosphonates.[35,45]	(Bisphosphonates) are lower down in the pecking order of things that we look at when we are supervising polypharmacy, when we are looking at chronic disease management”.[45]
Perceived effectiveness	Mechanism of effectiveness	<i>Mechanism of effectiveness:</i> Patients expressed confusion about how bisphosphonates work and uncertainty about whether they strengthen, prevent worsening or slow the decline in bone density.[25,26,39] Patients talked about bone density scans as providing ‘proof’ of whether their medication was effective, however, there were differing reports of whether stabilisation in density was considered as treatment success.[35,40] The lack of systematic reduction in fracture or improvement in bone density was noted to result in ambivalence about efficacy and importance.[35] Patients described wanting more explanation about, and evidence of effectiveness (including quantified benefit).[16,23,37,38,40] Prior to initiating treatment, the perceived effectiveness of bisphosphonates was influenced in patients primarily by vicarious experience of friends	Taking anti-osteoporosis drugs was noted to not always seem to lead to improvement in their bone density and did not systematically prevent fracture.[35]

bmjopen-2020-040664
 Downloaded from <http://bmjopen.bmj.com/> on November 29, 2024 by guest. Protected by copyright.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

		or relatives.[40,42,43] Examples of relatives who had fractured on treatment or had hip or knee joint replacements were given as examples of lack of efficacy.[42] Patients cited clinicians not meeting their informational needs about effectiveness, which may have been due to their own reported doubts.[29,42] Other clinicians expressed continued doubts about effectiveness in specific populations (e.g. the elderly) or in relation to fracture risk at specific sites.[35] Patients in one study reported being told by health care professionals bisphosphonates are not effective for everyone[24] and in one study, clinicians questioned predictors of response.[29]	
	Monitoring and follow-up	Follow-up and monitoring were reported by clinicians[34] and patients[38] to support adherence to oral treatment, but generally felt to be lacking in primary care, in part due to uncertainties about who, when and what to monitor.[34] Patients reported not feeling supported with continued persistence with treatment[38] and reported the need for more reviews, feedback and help with 'ways to keep going' with medications.[16,33,38]	Women anticipated the next DXA scan as being the "proof" of whether the treatment was effective.[27,31] Reviewing patients' BMD results with them helped them evaluate the status of their osteoporosis, which motivated them to either start or continue taking their medicine.[37]
Self-efficacy	Supporting routinisation	<i>Supporting routinisation</i> Being able to successfully follow the special instructions for taking oral bisphosphonates, and incorporate the regime into daily routines appeared to be important to acceptability.[39] Other reported strategies to support self-efficacy were using pill compartments and calendar systems/reminders.[16] Patients reported that HCPs should supplement their oral instructions about BP administration with written ones.[39] Information, support and encouragement was needed throughout treatment but felt to be lacking by patients[16,38,44]. Patients and HCPs reported insufficient time in consultations to cover all the information about bisphosphonate medication.[35,39]	Patients noted that tips for routinizing medication use, such as using triggers (e.g., meals, calendars, placement of medications) to remember when to take medications, facilitated long-term adherence.[16]
	HCP knowledge and attitudes	Primary care providers did not feel confident in their own knowledge about bisphosphonates; they described guidelines as confusing and too detailed, expressing a number of uncertainties relating to who to start medication in, how long to continue medication for, the relationship between bisphosphonates and co-dependency for calcium/vitamin D, safety, when treatment should be changed including dose.[16,25,29,35] Some primary care clinicians indirectly suggested perceptions that osteoporosis was not a priority. Secondary care providers suggested osteoporosis champions in primary care would help educate primary care clinicians who were less interested in the condition.[39,45] It was also reported that non-medical clinician	Physicians reported need for training in treating and help with therapeutic decision making.[35]

		(pharmacists or nurses) may be more knowledgeable or have more time to discuss bisphosphonates.[39,45]	
	Service level barriers	In terms of professional roles, clinicians in two studies described uncertainty about whose role it was to start and monitor treatment.[16,34] This was compounded by perceived poor communication between primary and secondary care, including update of the patients prescriptions on the electronic medical record.[39] Further reported barriers to treatment included lack of incentivisation[34] difficulty ordering, accessing or interpreting investigations to monitor treatment,[16,29] external restrictions on prescribing and access to intravenous bisphosphonates[34] and lack of time in primary care consultations.[16]	Provider barriers to treatment include lack of knowledge, other priorities, limited access and limited time.[36] GPs regretted the absence of consensus about the professional in charge of osteoporosis.[32] A number of participants {HCPs/managers} thought that intravenous zoledronic acid should be more widely available to improve adherence.[34]

peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46