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REVIEW

Systematic review on interventions to improve osteoporosis investigation and treatment in fragility fracture patients

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Abstract This study aims to determine osteoporosis (OP) investigation and treatment within post-fracture initiatives conducted in fracture clinics and other orthopedic environments. A systematic review was conducted. Eligibility criteria were: hip fracture patients plus all other fracture patients presenting with a fragility fracture, orthopedic setting where orthopedic physicians/staff were involved, intervention to improve OP management, primary data on ≥20 patients from randomized controlled trials (RCTs) and other study designs. We calculated outcome data within 6 months of screening from an intention-to-treat principle to derive an equated proportion (EP) across interventions. Outcomes were: (1) proportion of patients investigated with bone densitometry, (2) proportion of patients initiating OP medication, and (3) proportion of patients taking OP medication. We identified 2,259 citations, of which 57 articles that included 64 intervention groups were eligible. The median EP for patients investigated was 43% and the 75th percentile was 71%. The median EP for medication initiation was 22% and the 75th percentile was 34%. The median EP for medication taking was 27.5% and the 75th percentile was 43%. The EPs for all outcomes were higher for interventions with dedicated personnel to implement the intervention and those within which bone mineral density testing and/or treatment were included. In studies with an EP, up to 71% of patients were investigated for OP, but <35% initiated medication, and <45% were taking medication within 6 months of screening. Calculating an EP allowed us to compare outcomes across the studies, therefore capturing both RCTs and other study designs typical of real-world settings.

Keywords Fragility fracture · Investigation · Osteoporosis · Systematic review · Treatment

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Introduction

In the past 10 years, numerous initiatives to improve osteoporosis (OP) investigation and treatment in fragility fracture patients in an orthopedic environment have been established and reported on worldwide. These interventions generally intervene at the level of the patient [1, 2], the healthcare provider [3, 4], or the healthcare system [5, 6]. In some initiatives, patients and/or their general practitioners are educated [7–9], while in others, dedicated personnel may arrange bone mineral density (BMD) testing and/or treatment with medication [10, 11].

The purpose of this systematic review was to identify and describe post-fracture initiatives and to determine the outcomes of these initiatives regarding OP investigation and treatment with medication. Our outcomes were the: (1) proportion of patients investigated by bone densitometry,

(2) proportion of patients *initiating* OP medication, and (3) proportion of patients *taking* OP medication.

Methods

Search strategy

A literature search was conducted in Medline, EMBASE, and CINAHL to identify relevant publications up to and including September 2009. These databases were searched for all articles addressing OP protocols following a fragility fracture. The population was defined broadly with the medical subject heading "bone fractures", "hip fracture", and "fractures, spontaneous". These were combined with the medical subject heading "osteoporosis". The population was combined with as many protocols and screening procedures as possible including, but not limited to, the medical subject headings "diagnostic tests", "bone density", "program development", and "program evaluation". The search was limited to English language articles.

Identification and screening

Two independent reviewers read through all identified abstracts and flagged articles that addressed OP and involved any type of intervention ranging from the administration of OP-related questionnaires to coordinator-based interventions that included BMD testing. We excluded studies comparing surgical techniques. If a consensus could not be reached for articles, the article was moved forward to the next stage of the review (full article review). A third reviewer (JS) subsequently screened out letters, commentaries, editorials, one-page articles, and literature reviews before finalizing the articles for full article review.

Selection

The articles selected for full-article review were evenly divided among four reviewers (two reviewers randomly assigned to each article) who scored each article based on whether they met all of the following eligibility criteria:

Population

Any hip fracture plus all other fracture patients presenting with a fragility fracture. Fragility fracture was defined as "atraumatic", "low trauma" (or stated as "not high trauma"), "osteoporotic", "fragility", "non-traumatic", "low energy", "compression", "low velocity", "vertebral deformities", "osteoporotic vertebral collapse", "spinal", and "vertebral crush". The study was eligible even if only a subset of patients were eligible with fragility fractures (this subset had to be separated from the rest of the sample in the analyses). We excluded studies conducted on cadavers, transplant or renal patients, or patients with pathological or malignant fractures.

Setting

Any orthopedic environment (fracture clinic, emergency department, orthopedic office, in-patient orthopedic ward, hospital ward for low trauma fracture or hip fracture) or environment where orthopedic physicians and/or staff were involved. We focused this review on interventions in an orthopedic environment because this is the optimal setting to identify fragility fracture patients soon after the fracture and the role of orthopedic surgeons is becoming increasingly important in post-fracture osteoporosis care [12]

Intervention

Any type of intervention aimed at improving OP management (e.g., screening, identification, BMD testing, education, treatment rates, and prescribing medication). We excluded articles that reported only factors associated with being on care at baseline, documented post-fracture care without describing an intervention, or included only a surgical intervention or blood tests as an intervention. Etiological studies (examining the cause of fracture) and validation studies for diagnostic tests (e.g., validating BMDs with some other marker of bone health) were also excluded. Drug or supplement studies where the drug, or drug dosing, was the intervention was excluded because the purpose of this systematic review was not to determine efficacy or effectiveness of OP medication.

Methods

Any study that included primary patient data and enrolled ≥20 patients [13]. Because initiatives to improve OP management in fragility fracture patients include many "real world" setting studies, we were less restrictive about methods and included randomized controlled trials (RCTs) as well as other study designs (e.g., controlled clinical trials, cohort studies, cross-sectional studies, and retrospective chart reviews).

Outcomes

Studies that met the above eligibility were included regardless of whether they contained outcome data.

Data abstraction

Data abstraction was conducted independently by two reviewers (JS, JP) on all articles that met the eligibility criteria. If discussions between the two reviewers did not yield consensus on data abstraction, a third party (DB) was

involved in resolving differences through independent review and discussion.

Participants

We documented the total number of participants enrolled after excluding all ineligible and refusals and unable to participate, e.g., sick, cognitive impairment. The number enrolled was not necessarily the same as the number of patients who completed the study. If individuals dropped out, died, or were lost to follow-up after being enrolled in the study, we considered them as enrolled as this was the only number that could serve to equate denominators across all studies reviewed (see description below).

Intervention

We documented the sample size for each intervention group and all features of the intervention as reported. If the nature of the intervention evolved over time, we classified the changes as different interventions, e.g., intervention #1, intervention #2. In this review, control, comparison, or usual care groups were not considered.

Study design

The study design was documented as (1) cohort study (sometimes referred to as follow-up studies, longitudinal studies, or prospective studies); (2) cross-sectional study; (3) retrospective chart review; (4) administrative database; (5) non-randomized controlled trial; (6) RCT; (7) case control; or (8) other. In cases where more than one design was utilized in the study (e.g., recruitment occurred using an administrative database and then the participants were randomly assigned to an intervention), both designs were documented.

Outcomes

Outcome data were reported using an intention-to-treat principle, which means that all patients were included in the analysis for the intervention in which they were enrolled, regardless of whether they completed the study [14]. Using an "intention-to-treat" principle allowed us to calculate an equated proportion (EP) in order to compare outcome data across all interventions regardless of study design. Using this approach, we assumed that all missing persons were not investigated or treated [15]. Therefore, the denominator for each outcome was always the number of patients enrolled in, or randomized to, an intervention. Data from comparison or control groups were not included in the denominator. This allowed us to calculate a rate for comparison across studies that would have otherwise been impossible due to these studies reporting different denominators in their papers. For example, some authors reported treatment initiation relative to patients who had been investigated, whereas others reported it relative to the entire sample enrolled. As a result, the EP should be considered an *indicator* of outcome, rather than a precise rate. Some of those who were lost to follow-up may have received investigation and treatment. The EP in these cases would underestimate the true outcome.

Outcomes were considered if they occurred within 6 months of screening [16]. Percentages were rounded to the nearest whole number. Investigation and treatment proportions were only documented if there was evidence that the investigation and treatment had occurred as it has been shown that individuals who are *recommended* a BMD test may not undergo the test [17, 18] and that individuals who are *prescribed* medication may not actually take that medication [19, 20]. The range, median, and 75th percentile were calculated for the EP of all outcomes across the interventions.

Proportion of patients investigated We calculated the proportion of patients who were investigated by bone densitometry (heel ultrasound was excluded). The number of patients referred, or recommended, for investigation was noted in the comments section if it was reported.

Proportion of patients initiating medication We calculated the proportion of patients initiating OP medication. OP "medication" referred to bisphosphonates, anti-resorptives, bone sparing agents, anabolics, estrogen replacement, or HRT specifically for OP. This included calcitonin (Calcimar®), teriperatide (Forteo®), and raloxifene (Evista®). Medication could be administered orally, by i.v., or through nasal spray. Credible evidence of a prescription being filled, billed, or initiated by the patient was required. Self-report data was acceptable as long as it provided confirmation for a prescription being initiated. Patients already taking OP medication were subtracted from the denominator of the total number enrolled in, or randomized to, the intervention group(s). If we could not discriminate between those initiating during the study and those who were previously on medication, this outcome could not be calculated and was instead captured only as the proportion of patients *taking* medication (see below). If only the number of patients advised, or prescribed, to take medications was available, the EP was not calculated. We did not consider it initiation if one OP medication was exchanged for another during the study.

Proportion of patients taking medication We calculated the proportion of patients taking medication which included patients on medication at the start of the study in addition to those initiating medication during the study. Both medication initiation and medication taking were calculated at the same time within the 6 months following screening so they do not reflect adherence over time. If patients enrolled were

not on medication at baseline (e.g., they had been excluded), both initiation and taking were the same value. For example, if 25% of patients were on medication at baseline and 35% initiated medication during the study, medication taking would be 60% (25% plus 35%). As with medication initiation, a written or recommended prescription had to be filled or billed, or have other credible evidence that the patient was actually taking the medication (e.g., self-report).

Risk of bias

A risk of bias assessment was conducted independently by two reviewers (JS, JP) on all articles that were eligible for this review. For randomized controlled trials, risk of bias was assessed using the Cochrane Risk of Bias Tool [21]; for all other studies, risk of bias was using Hayden et al. [22] criteria for prognostic studies. The last two items of Hayden's criteria were not applicable to this review and were therefore not scored (personal communication with Jill Hayden, April 16, 2009). A score of "low" risk was assigned to an article if both reviewers considered all items on the respective scale to be low risk.

Comparison of outcomes based on key characteristics of the interventions

We examined the outcomes (investigation, medication initiation, and medication taking) relative to methodological and key characteristics of the interventions. These key characteristics were defined by group consensus of the authors when reviewing the descriptions of the final set of studies. First, we identified the intervention as an RCT versus other study design. Second, we determined whether risk of bias was "low" as opposed to "moderate", "high", or unable to be determined. Third, we determined whether dedicated personnel were assigned to the OP program solely to implement the program. We defined dedicated personnel as any personnel (nurse, pharmacist, dedicated coordinator, etc.) integral to implementing the intervention and paid for that specific role. For example, a study coordinator who only collected data for the evaluation of a program did not qualify as dedicated personnel. A specialist to whom the patient was referred by the surgeon was not considered dedicated staff. When a personnel's role was unclear, it was verified through direct communication with the authors. Two investigators (JS, DB) scored the personnel's role as "dedicated" vs. "not dedicated" based on the article, incorporating authors' feedback where necessary. Fourth, we classified whether BMD testing and/or treatment (medication prescribing) were carried out as part of the OP program. Some programs included BMD testing as part of their activities whereas other programs wrote referrals for BMD or sent a note to the family physician recommending a BMD test. Fifth, we considered the program as "intensive" versus not. An "intensive" model was defined as one that included dedicated personnel and BMD testing or treatment with medication within the intervention (i.e., "3" and "4" above).

The above characteristics of studies were found in different combinations, or not at all, across the 64 interventions. We sorted the studies into sub-groups according to their key characteristics and assigned each of the 64 interventions into descriptive categories. For example, one category captured a program where a dedicated coordinator screened and educated patients. Another category captured education to the general practitioner via the patient. The 12 categories in this system were reported elsewhere (presentation by DB to the International Osteoporosis Foundation White Paper Working Group, London, England June 26, 2009).

Results

We identified 2,259 articles whose abstracts were read by two independent reviewers; 422 addressed OP and described an intervention, of which 57 articles [1–11, 17–20, 23–65] reporting on 54 studies from 11 countries were eligible for data abstraction (see Fig. 1). For example, at full article review, 169 articles were ineligible because of the study setting. Table 1 describes the included studies by year of

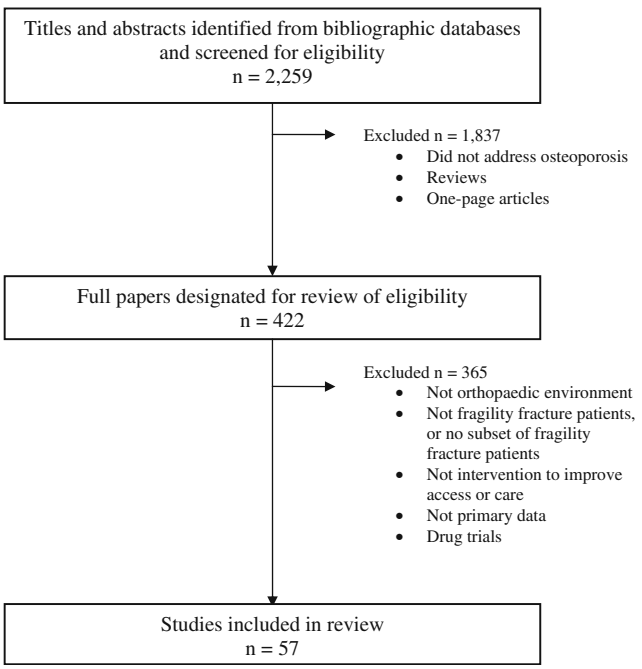

Fig. 1 Results of literature search to identify studies of interventions in orthopedic environments that address osteoporosis in fragility fracture patients

Table 1 Description of included articles (n=57)

Author, year	Study design/type of cohort	N	Country of recruitment	Setting	Fracture location(s)[a]
Gardner et al., 2002 [6]	RCT/Retrospective cohort	300	USA	Multiple sites	Femoral neck
Chevalley et al., 2002 [19]	Cohort	385	Switzerland	Inpatients/outpatients	3 or more
Liel et al., 2003 [5]	Admin/pre-post	424	Israel	Emergency department or inpatients of orthopedic surgery or rehabilitation	3 or more
McLellan et al., 2003 [43]	Cohort	4671	UK	Multiple sites	3 or more
Jachna et al., 2003 [45]	Retrospective	29	USA	Hospital inpatients	Hip
Hawker et al., 2003 [2]	Pre-post	139	Canada	Community hospital fracture clinics	3 or more
Mulherin et al., 2003 [34]	Cohort	148	UK	Accident and emergency department	Distal forearm
Schmid et al., 2004 [57]	Cohort	299	Switzerland	Urban fracture clinic	3 or more
Majumdar et al., 2004 [41]	Non-randomized controlled clinical trial	55	Canada	Emergency departments	Wrist
Skedros, 2004 [42]	Cohort	69	USA	Orthopedic trauma of community hospitals	3 or more
Ashe et al., 2004 [44]	Non-randomized controlled clinical trial	12	Canada	Fracture clinic	Wrist
Cuddihy et al., 2004 [52]	Cohort/admin database	59	USA	Cast room	Forearm
Fraser and McLellan, 2004 [18]	Cohort	2587	UK	Trauma inpatients, racture clinic outputs	3 or more
Sidwell et al., 2004 [55]	Cohort	193	New Zealand	Orthogeriatric rehab ward	3 or more
Hegeman et al., 2004 [33]	Cohort	94	The Netherlands	Departments of surgery and traumatology	Distal radius
Malochet-Guinamand et al., 2005 [3]	Cohort	78	France	Emergency department	3 or more
Gallacher, 2005 [38]	Cohort	5897	UK	Multiple sites	3 or more
Edwards et al., 2005 [39]	Cohort	221	USA	Tertiary care center	3 or more
Murray et al., 2005 [50]	Cohort/retrospective/ admin database	370	UK	Orthopedic centers	Proximal humerus or hip
Gardner et al., 2005 [51]	RCT	40	USA	Orthopedics hospital	Intertrochanteric hip or femoral neck
Harrington et al., 2005 [40]	Cohort	348	USA	Inpatients and outpatient fracture points	Cycle 1: hip, cycle 2 and 3: 3 or more
Hegeman et al., 2005 [58]	Cohort	116	The Netherlands	Fracture and osteoporosis clinic	3 or more
Prasad et al., 2006 [56]	Retrospective/ pre-post	37	UK	Departments of trauma and orthopedics	Hip
Bliuc et al., 2006 [9]	Cohort/RCT	159	Australia	Outpatient fracture clinic	3 or more
Ho et al., 2006 [8]	Cohort	23	Canada	Kingston General Hospital	3 or more
Che et al., 2006 [35]	Cohort/admin database	213	USA	Multiple sites of HMO	3 or more
Astrand et al., 2006 [36]	Cohort	256	Sweden	Orthopedics department	3 or more
Bogoch et al., 2006 [37]	Cohort	349	Canada	Fracture clinic and orthopedic ward	3 or more

Table 1 (continued)

Author, year	Study design/type of cohort	*N*	Country of recruitment	Setting	Fracture location(s)[a]
Becker et al., 2006 [54]	Retrospective	185	USA	Orthopedic or rehab services	3 or more
Feldstein et al., 2006 [49]	RCT	211	USA	Non-Profit HMO	3 or more
Streeten et al., 2006 [20]	Cohort/retrospective/ admin database	53	USA	Orthopedic inpatients and outpatients	3 or more
Levasseur et al., 2007 [17]	Cohort	313	France	Orthopedics department	3 or more
van Helden et al., 2007 [27]	Cohort	33	The Netherlands	Emergency departments	3 or more
Harrington et al., 2007 [47]	Cohort	232	USA	Inpatients and outpatients	3 or more
Davis et al., 2007 [28]	RCT	28	Canada	Orthopedic trauma ward	Hip
Langridge et al., 2007 [29]	Cohort	2489	UK	Multiple sites	3 or more
Ward et al., 2007 [30]	Retrospective	83	Canada	Fracture clinic and orthopedics unit	Wrist, hip
Majumdar et al., 2007a [48]	RCT	110	Canada	Multiple sites	Hip
Vaile et al., 2007 [23]	Cohort/retrospective	812	Australia	Fracture clinics	Not specified
Blonk et al., 2007 [31]	Cohort	1,058	The Netherlands	Emergency departments	3 or more
Quintos-Macasa et al., 2007 [32]	Cohort/retrospective	78	USA	Rheumatology and internal medicine departments	Femur or intertrochanteric hip
Laslett et al., 2007 [11]	Non-randomized controlled clinical trial/pre-post	93	Australia	Dept of orthopedics and trauma	3 or more
Kuo et al., 2007 [24]	Cohort	155	Australia	Outpatient fracture clinics	3 or more
Majumdar et al., 2007b [53]	Non-randomized controlled clinical trial	55	Canada	Emergency departments	Wrist
Tosi et al., 2008 [26]	Cohort/retrospective/ pre-post	359	USA	Orthopedic departments (multiple)	3 or more
van Helden et al., 2008 [25]	Cohort, cross-sectional and "Other"	455	The Netherlands	Emergency department and inpatients	3 or more
Cranney et al., 2008 [60]	Cluster randomized trial (rcT)	125	Canada	Emergency department and fracture clinics	Wrist
Miki et al., 2008 [62]	RCT	31	USA	Orthopedic osteoporosis clinic	Hip
Nadrash et al., 2008 [10]	Cohort	137	USA	Outpatient medical offices	3 or more
Bessette et al., 2008 [1]	RCT	–[b]	Canada	Multiple sites	3 or more
Rozental et al., 2008 [65]	Retrospective/RCT	50	USA	Orthopedic outpatients clinic	Distal Radius
Majumdar et al., 2008 [7]	RCT	137	Canada	Emergency deparments and fracture clinics	Distal forearm
Yoon et al., 2008 [63]	Cohort	139	USA	Inpatients at academic medical center	3 or more
Al-Dabagh et al., 2009 [4]	Cohort	32	USA	Emergency department	3 or more
Carpintero et al., 2009 [59]	Cohort/Retrospective	6826	Spain	Multiple sites	3 or more
Morrish et al., 2009 [61]	RCT	110	Canada	Multiple sites	Hip

Table 1 (continued)

Author, year	Study design/type of cohort	*N*	Country of recruitment	Setting	Fracture location(s)[a]
Majumdar et al., 2009 [64]	RCT	110	Canada	Multiple sites	Hip

N total number of patients in all intervention groups

[a] "3 or more" refers to 3 or more fracture locations

[b] Unable to determine

publication. No studies pre-dating 2002 were identified despite searching before this time. Six articles required a third reviewer to confirm our calculated EP; in these cases, consensus was reached with the third reviewer. The total number of patients per intervention group ranged from 12 to 6,826. There were 64 intervention groups: eight studies each described two intervention groups, and one study described three intervention groups; the remaining studies each described one intervention group. Of the 64 intervention groups, 15 were part of an RCT, four were scored as "low" for risk of bias, 36 had dedicated personnel to implement the intervention, 33 reported BMD testing and/or treatment within, and 25 were categorized as "intensive" (see Table 2).

Table 3 shows the EPs for investigation, medication initiation, and medication taking of the 64 interventions. In general, the studies reported higher rates than the EP because they used more specific denominators such as the number of patients who returned for a follow-up appointment. We calculated an EP for investigation in 45 interventions (70% of the interventions). In seven interventions, we were unable to calculate the proportion investigated, and 12 interventions reported no data on investigation. The EP of patients investigated ranged from 3% to 100%; the median was 43% and the 75th percentile was 71%. Four of the 45 interventions had an EP of 100% and an additional six studies had an EP ≥80%.

We calculated an EP for medication *initiation* in 33 interventions (52% of the interventions). In 22 interventions, we were unable to calculate initiation, and nine interventions reported no data on OP medication. The EP of patients initiating medication ranged from 0% to 65%; the median was 22% and the 75% percentile was 34%. Four of the 33 interventions had an EP between 51-54% and one

Table 2 Key characteristics of 64 interventions

Author, year	Intervention #	RCT	Low risk of bias	Dedicated personnel	BMD or treatment within	"Intensive" model
Gardner et al., 2002 [6]						
Chevalley et al., 2002 [19]				Yes	Yes	Yes
Liel et al., 2003 [5]						
McLellan et al., 2003 [43]				Yes	Yes	Yes
Jachna et al., 2003 [45]						
Hawker et al., 2003 [2]						
Mulherin et al., 2003 [34]				Yes		
Schmid et al., 2004 [57]						
Majumdar et al., 2004 and 2007b [41, 53]				Yes		
Skedros, 2004 [42]				Yes		
Ashe et al., 2004 [44]						
Cuddihy et al., 2004 [52]				Yes	Yes	Yes
Fraser and McLellan, 2004 [18]				Yes	Yes	Yes
Sidwell et al., 2004 [55]						
Hegeman et al., 2004 [33]					Yes	
Malochet-Guinamand et al., 2005 [3]						
Gallacher, 2005 [38]				Yes	Yes	Yes
Edwards et al., 2005 [39]	1			Yes		
	2			Yes	Yes	Yes

Table 2 (continued)

Author, year	Intervention #	RCT	Low risk of bias	Dedicated personnel	BMD or treatment within	"Intensive" model
Murray et al., 2005 [50]				Yes	Yes	Yes
Gardner et al., 2005 [51]		Yes		Yes		
Harrington et al., 2005 [40]	1			Yes		
	2			Yes	Yes	Yes
	3			Yes	Yes	Yes
Hegeman et al., 2005 [58]				Yes	Yes	Yes
Prasad et al., 2006 [56]			Yes			
Bliuc et al., 2006 [9]	1	Yes				
	2	Yes			Yes	
Ho et al., 2006 [8]				Yes		
Che et al., 2006 [35]				Yes	Yes	Yes
Astrand et al., 2006 [36]				Yes	Yes	Yes
Bogoch et al., 2006 [37]				Yes	Yes	Yes
Becker et al., 2006 [54]			Yes		Yes	
Feldstein et al., 2006 [49]	1	Yes				
	2	Yes				
Streeten et al., 2006 [20]					Yes	
Levasseur et al., 2007 [17]					Yes	
van Helden et al., 2007 [27]				Yes	Yes	Yes
Harrington et al., 2007 [47]				Yes	Yes	Yes
Davis et al., 2007 [28]		Yes				
Langridge et al., 2007 [29]				Yes	Yes	Yes
Ward et al., 2007 [30]				Yes		
Majumdar et al., 2007a and 2009 [48, 64]; Morrish et al., 2009 [61]	1	Yes		Yes	Yes	Yes
	2	Yes		Yes	Yes	Yes
Vaile et al., 2007 [23]	1					
	2			Yes	Yes	Yes
Blonk et al., 2007 [31]				Yes	Yes	Yes
Quintos-Macasa et al., 2007 [32]					Yes	
Laslett et al., 2007 [11]	1			Yes	Yes	Yes
	2			Yes	Yes	Yes
Kuo et al., 2007 [24]				Yes	Yes	Yes
Tosi et al., 2008 [26]				Yes		
van Helden et al., 2008 [25]				Yes	Yes	Yes
Cranney et al., 2008 [60]		Yes	Yes			
Miki et al., 2008 [62]		Yes			Yes	
Nadrash et al., 2008 [10]				Yes	Yes	Yes
Bessette et al. 2008 [1]	1	Yes				
	2	Yes				
Rozental et al., 2008 [65]	1	Yes			Yes	
	2	Yes				
Majumdar et al., 2008 [7]		Yes	Yes	Yes		
Yoon et al., 2008 [63]				Yes		
Al-Dabagh et al., 2009 [4]						
Carpintero et al., 2009 [59]						

Table 3 Equated proportions for investigation and treatment of the 64 interventions

Author, year	Intervention #	Investigated (%)	Initiated medication (%)	Taking medication (%)
Gardner et al., 2002 [6]		N	U	6
Chevalley et al., 2002 [19]		63	8	8
Liel et al., 2003 [5]		N	7	12
McLellan et al., 2003 [43]		44	U	23
Jachna et al., 2003 [45]		7	7	U
Hawker et al., 2003 [2]		35	U	U
Mulherin et al., 2003 [34]		61	N	N
Schmid et al., 2004 [57]		10	U	11
Majumdar et al., 2004 and 2007 [41, 53]		62	40	40
Skedros, 2004 [42]		35	36	36
Ashe et al., 2004 [44]		U	U	U
Cuddihy et al., 2004 [52]		71	26	51
Fraser et al., 2004 [18]		U	U	25
Sidwell et al., 2004 [55]		7	21	21
Hegeman et al., 2004 [33]		100	U	51
Malochet-Guinamand et al., 2005 [3]		N	0	0
Gallacher, 2005 [38]		U	U	27
Edwards et al., 2005 [39]	1	N	N	N
	2	U	U	45
Murray et al., 2005 [50]		43	U	35
Gardner et al., 2005 [51]		30	25	25
Harrington et al., 2005 [40]	1	20	U	U
	2	100	U	83
	3	35	U	U
Hegeman et al., 2005 [58]		86	N	N
Prasad et al., 2006 [56]		N	0	11
Bliuc et al., 2006 [9]	1	6	6	6
	2	38	5	5
Ho et al., 2006 [8]		30	21	52
Che et al., 2006 [35]		79	22	22
Astrand et al., 2006 [36]		93	U	U
Bogoch et al., 2006 [37]		U	U	U
Becker et al., 2006 [54]		33	35	43
Feldstein et al., 2006 [49]	1	40	28	28
	2	33	20	20
Streeten et al., 2006 [20]		51	53	53
Levasseur et al., 2007 [17]		10	10	10
van Helden et al., 2007 [27]		30	N	N
Harrington et al., 2007 [47]		68	U	U
Davis et al., 2007 [28]		29	54	54
Langridge et al., 2007 [29]		U	U	U
Ward et al., 2007 [30]		N	N	N
Majumdar et al., 2007 and 2009 [48, 64]; Morrish et al., 2009 [61]	1	80	51	51
	2	55	21	38
Vaile et al., 2007 [23]	1	N	11	U
	2	100	51	U
Blonk et al., 2007 [31]		96	27	U
Quintos-Macasa et al., 2007 [32]		N	U	U

Table 3 (continued)

Author, year	Intervention #	Investigated (%)	Initiated medication (%)	Taking medication (%)
Laslett et al., 2007 [11]	1	21	U	U
	2	29	U	U
Kuo et al., 2007 [24]		61	28	43
Tosi et al., 2008 [26]		3	3	U
van Helden et al., 2008 [25]		100	N	N
Cranney et al., 2008 [60]		51	28	28
Miki et al., 2008 [62]		84	65	65
Nadrash et al., 2008 [10]		15	34	34
Bessette et al. 2008 [1]	1	N	N	N
	2	N	N	N
Rozental et al., 2008 [65]	1	93	30	30
	2	30	22	22
Majumdar et al., 2008 [7]		52	22	22
Yoon et al., 2008 [63]		U	U	16
Al-Dabagh et al., 2009 [4]		N	N	N
Carpintero et al., 2009 [59]		N	U	U

U unable to calculate, *N* not reported, e.g., only prescribing or referrals reported but not actual investigation or medication initiation/taking

intervention had an EP of 65%. The 28 remaining interventions had EPs ≤40%.

We calculated an EP for medication *taking* in 38 interventions (59% of the interventions). In 17 interventions, we were unable to calculate the proportion taking, and nine interventions reported no data on OP medication. The EP of patients initiating medication ranged from 0% to 83%; the median was 27.5% and the 75th percentile was 43%. Eight of the 38 interventions had an EP >50%. The majority of interventions (n=30) had an EP ≤45%.

In Tables 4 and 5, EPs of the outcomes are reported by methodological and key characteristics of the interventions. Interventions identified as part of RCTs had a lower EP (both median and 75th percentile) for investigation but a higher median for medication initiation and medication taking compared with interventions not identified as part of RCTs. Interventions scored as having "low" risk of bias had a higher median for investigation and medication initiation but a lower median for medication taking than interventions scored with a risk of bias of "moderate-to-high/unsure". However, the 75th percentiles for "low" risk of bias interventions were lower across all outcomes possibly because only four interventions were scored as "low" for risk of bias.

Interventions with dedicated personnel had higher EPs (both medians and 75th percentiles) across all outcomes than interventions without dedicated personnel. Interventions characterized as "BMD and/or treatment within" had higher EPs (both medians and 75th percentiles) across all outcomes, with a doubling of the median in the proportion of patients investigated compared with interventions that did not include BMD and/or treatment. Interventions characterized as "intensive" had higher EPs (both medians and 75th percentiles) across all outcomes with a doubling of the median in the proportion of patients investigated

Table 4 Equated proportions for investigation and treatment relative to methodological characteristics of the interventions, median (75th percentile)

Characteristic	Investigated (n=45/64 interventions)	Initiated medication (n=33/64 interventions)	Taking medication (n=38/64 interventions)
Randomized controlled trial			
Yes	40.0 (55.0), n=13/15	25.0 (30.0), n=13/15	28.0 (38.0), n=13/15
No	43.5 (73.0), n=32/49	21.5 (34.25), n=20/49	27.0 (43.0), n=25/49
Low risk of bias			
Yes	51.0 (51.5), n=3/4	25.0 (29.75), n=4/4	25.0 (31.75), n=4/4
No	41.5 (77.0), n=42/60	22.0 (34.0), n=29/60	27.5 (44.5), n=34/60

Sample sizes refer to the number of interventions with an EP/total number of interventions in the category

Table 5 Equated proportions for investigation and treatment relative to key characteristics of the interventions, median (75th percentile)

Characteristic	Investigated (n=45/64 interventions)	Initiated medication (n=33/64 interventions)	Taking medication (n=38/64 interventions)
Dedicated personnel			
Yes	58.0 (79.25), n=28/36	26.0 (35.0), n=15/36	35.0 (44.0), n=19/36
No	33.0 (51.0), n=17/28	20.5 (29.5), n=18/28	21.0 (36.5), n=19/36
BMD or treatment within			
Yes	63.0 (89.5), n=27/33	28.0 (43.0), n=15/33	36.5 (51.0), n=20/33
No	30.0 (38.75), n=18/31	21.0 (27.25), n=18/31	21.5 (28.0), n=18/31
"Intensive" model			
Yes	65.5 (87.75), n=20/25	27.0 (34.0), n=9/25	35.0 (45.0), n=13/25
No	33.0 (51.0), n=25/39	21.5 (31.25), n=24/39	22.0 (40.0), n=25/39

Sample sizes refer to the number of interventions with an EP/total number of interventions in the category

compared with interventions that were not characterized as "intensive".

When comparing the medians across the above characteristics, the highest median for investigation was demonstrated in the "intensive" model, but the highest medians for medication initiation and medication taking were demonstrated in the interventions characterized as "BMD and/or treatment within".

Table 6 shows the outcomes of the 64 interventions according to the descriptive categories defined in our previous work (presentation by DB to the International Osteoporosis Foundation White Paper Working Group, London, England June 26, 2009). Most interventions fit under categories #2, #3, and #6; the majority of these interventions had dedicated personnel to implement the intervention. Higher EPs for investigation (>65%) were

Table 6 Equated proportions for investigation and treatment by descriptive categories, median (75th percentile)

Classification	Investigated (n=45/64 interventions)	Initiated medication (n=33/64 interventions)	Taking medication (n=38/64 interventions)
1. Dedicated personnel screens and educates patients (n=3)	50.5 (60.75), n=2/3	23.5 (24.75), n=2/3	51.5 (51.75), n=2/3
2. Dedicated personnel as part of intense program with treatment and sometimes BMD done within program (n=11)	33.0 (79.0), n=9/11	35.0 (51.0), n=5/11	39.0 (44.5), n=6/11
3. Dedicated personnel, BMD+within intervention; Customized education; return patient to GP for follow-up (n=13)	65.5 (91.25), n=10/13	24.0 (27.25), n=4/13	27.0 (40.5), n=7/13
4. No dedicated personnel; BMD+within intervention; no follow-up described (n=2)	69.0 (84.5), n=2/2	5.0 (5.0), n=1/2	28.0 (39.5), n=2/2
5. Dedicated personnel delivers general education to the patient; return patient to GP (n=3)	52.0 (56.5), n=3/3	23.5 (24.25), n=2/3	23.5 (24.25), n=2/3
6. Education to GP directly±dedicated personnel (n=12)	33.0 (40.0), n=9/12	25.0 (30.0), n=8/12	22.0 (28.0), n=9/12
7. Education to the GP via the patient (rather than education directly to the GP); no dedicated personnel (n=6)	29.0 (32.0), n=3/6	30.0 (42.0), n=2/6	30.0 (42.0), n=2/6
8. Education/alert from the surgeon to the specialist; no dedicated personnel (n=5)	30.5 (59.25), n=4/5	31.5 (56.0), n=4/5	53.0 (59.0), n=3/5
9. Education to the GP directly, including BMD results; ±dedicated personnel (n=3)	93.0 (96.5), n=3/3	25.5 (27.75), n=2/3	25.5 (27.75), n=2/3
10. Audits of guidelines in practice; no dedicated personnel (n=3)	n=0/3[a]	0.0 (0.0), n=1/3	8.5 (9.75), n=2/3
11. Increased drug coverage (n=1)	n=0/1[a]	7.0 (7.0), n=1/1	12.0 (12.0), n=1/1
12. Efforts to increase general awareness of need for OP management (to health care providers and/or patients); no dedicated personnel (n=2)	n=0/2[a]	11.0 (11.0), n=1/2	n=0/2[a]

GP general practitioner

Sample sizes refer to the number of interventions with an EP/total number of interventions in the category

[a] Data not reported or unable to calculate equated proportion

demonstrated in categories #3, #4, and #9 (category #9 had a median EP of 93% but this should be interpreted with caution as only three interventions were included in this category). A common element of these descriptive categories was dedicated personnel to implement the intervention and a BMD test done within the program. Because BMD testing was conducted within the program, we would expect, and observed the highest investigation EPs within these categories. The highest median EP for medication initiation was in category #2 (35%) and the highest median EP for medication taking was in category #8 (53%; these EPs should be interpreted with caution as they were based on ≤5 interventions each).

Discussion

In this systematic review, we derived an EP that represented approximately 60% of the interventions and demonstrated that up to 71% of patients were investigated, but <35% initiated medication and <45% were taking medication within 6 months of screening. Although the EP likely underestimates the true rate because it assumes that those lost to follow-up were not investigated or treated, it provides us with a greater number of studies with comparable denominators. It has been shown that having a BMD test is associated with treatment initiation [24, 65–70], however, some of those interventions with very high investigation rates, such as Rozental et al. [65] at 93% and Blonk et al. [31] at 96%, reported relatively low proportions of fracture patients initiating antiresorptive medication (30% and 27%, respectively). According to Table 4, the interventions with higher EPs for investigation and treatment were those characterized as "BMD and/or treatment within". According to Table 5, interventions with dedicated personnel and those with BMD testing within the program had the highest investigation rates. The latter appears obvious but the former points to an increasing trend supporting the need for dedicated personnel to facilitate such programs. The results for medication initiation and taking were less clear. While it may appear that there was no added benefit for combining the two key characteristics, there was considerable overlap among the studies so many studies with dedicated personnel were already performing BMD testing within. We believe that initiatives adopting a "systems approach", either with dedicated personnel, BMD testing within the program, or both, "performed better."

Calculating an EP for all outcomes allowed us to compare our rates across studies including RCTs and other study designs. We believed it was important to include both RCT and non-RCT designs to reflect what might be closer to the "real world" application of the findings; most of the interventions reviewed (n=49/64) were conducted in a non-RCT setting. We appraised the potential for bias in these two types of studies accordingly, to accommodate the differences in design. However, based on the respective criteria used to appraise the quality of the studies, RCTs did not appear to have higher quality than non-RCTs based on our risk of bias assessment; four studies (two RCT interventions and two non-RCT interventions) were assigned a score of "low" for risk of bias. One limitation of using EPs was that we were not able to calculate such a proportion for every intervention. For example, we only had data to calculate an EP for investigation, medication initiation, and medication taking in 45, 33, and 38 of the 64 interventions, respectively. In some cases, we were unable to calculate an EP with the data reported; in other cases, there were no reported data on a particular outcome. However, we would have also been limited in a comparison across the rates reported by authors in the published papers because of different numerators and denominators used.

Another limitation of using EPs across all study designs was that we assumed that all missing persons were not investigated or treated [15]. As a result, the EPs for the non-RCT interventions may have been a conservative estimate given that participants who died or were unable to complete the study were included in the denominator even though they could not be considered for investigation and treatment. Similarly, EPs for non-RCTs may also have been conservative due to stricter inclusion/exclusion criteria that led to lower attrition rates in the RCTs. For example, RCTs exclude up to 90% of patients assessed for eligibility [48]. Having said this, the EPs of patients investigated, initiating, and taking medication were not markedly different between RCTs and non-RCTs (EPs for medication taking were conservative for RCTs because many of these studies excluded patients already on OP medication at baseline).

This systematic review revealed problematic levels of heterogeneity in the reporting of simple outcomes (investigation and treatment with medication). The studies in this review were heterogeneous across several attributes. Many studies that were not RCTs used a variety of designs, for example, an administrative database to identify patients, a cohort study to carry out the intervention, and a BMD chart review to verify investigation [50]. The quality of the studies included in our review also varied considerably, and in most cases, we were unable to definitively score study quality due to incomplete reporting. As a result, with the exception of interventions scored as "low" for risk of bias, we were hesitant to score the remaining articles as "moderate" or "high" for risk of bias. Therefore, it is difficult to determine whether risk of bias had a major impact on the main data reported in this review.

There was heterogeneity in the interventions themselves. For example, eligibility for investigation and treatment varied between studies. Despite including similar fracture populations, Langridge et al. [29] offered BMD testing to patients only if it was thought the results would influence the patient's use of OP medication; Blonk et al. [31] only advised drug therapy for those patients with OP on BMD; and Streeten et al. [20] recommended a bisphosphonate to all patients unless contraindicated. In part, this heterogeneity was probably due to differences in guidelines across the 11 countries represented in this review regarding BMD T-scores and treatment. For example, the 2002 Canadian OP guidelines used at the time the studies in this review were conducted [71], (now revised [72]), state that patients 40+years with a fragility fracture and a T-score below −1.5 should be considered for OP therapy. The Australian 2002 OP guidelines strongly recommend treatment in post-menopausal women with OP (T-score<−2.5) and in patients with osteoporotic fractures [73]. The 2008 National Osteoporosis Foundation guidelines consider treatment for postmenopausal women and men age 50+years with: a hip or vertebral fracture; a T-score≤−2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes; or low bone mass and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20% [74]. Also, most clinical decisions in the various programs were made at a time when a T-score of –2.5 was the principal threshold for medication prescription, whereas 10-year fracture risk assessment models (e.g., FRAX [75, 76]) are currently widely utilized.

There was also heterogeneity regarding outcome reporting. Our purpose was to report on the effect of post-fracture interventions on various aspects of OP management within 6 months of the intervention. However, not all studies captured data within the 6-month window. For example, Harrington [47] reported that 56% of patients were taking medication at 1–2 years post-fracture. The relationship between investigation and initiating or taking medication was sometimes unexplained. In some studies, the proportion investigated was *lower* than the proportion initiating/taking medication and this was not explained. For example, in the intervention group of Davis et al. [28], 29% of patients were investigated but 54% initiated medication. Finally, BMD testing could not always be distinguished from other investigation. For example, Ashe et al. [44] combined reporting of bone densitometry with blood tests and diagnostic ultrasound.

There are several limitations to our systematic review. First, we required some indication that patients had actually undergone investigation. Referrals or recommendations for bone densitometry (e.g., Ward et al. [30]) were not sufficient. We believe the distinction between recommendations and actual BMD testing to be an important one. For example, in one study (LeVasseur et al. [17]), it appeared that 140 patients <80 years old were recommended for BMD during their hospital stay but only 32 attended for BMD. In another study [18], 55% of all patients were given appointments for a BMD but it was unclear how many actually had the test; the authors of this study acknowledged that 19% of all cases failed to attend for the test or declined to be assessed. Similarly, McLellan et al. [43] reported that 31% of those "considered" for BMD declined the assessment or did not appear for the test. We also required evidence of initiation/taking of OP medication. While some studies only reported recommendations or prescriptions for medication (e.g., Ward et al. [30]), others reported both recommendations and evidence of initiating/taking OP medication. For example, Streeten et al. [20] reported that recommendations for medication were given to 41 patients but only 28 patients initiated medication. Chevalley et al. [19] reported that recommendations for medication were given to 72 patients but only 45 patients were prescribed medication by their family physicians and only 30 patients were still on medication after 6 months of the recommendation by the physician of the screening program.

A second limitation is that we relied solely on prescription medication use and did not capture the use of supplements such as calcium and vitamin D. There were some abstraction difficulties concerning the distinction between medication and supplements. For example, in Hawker et al. [2] and Laslett et al. [11], combinations of OP medications and supplements were reported such that we could not discriminate between medication and supplements. Similarly, Quintos-Macasa [32] reported "treatment" as calcium, vitamin D, or OP medication and Gardner et al. [6] reported "treatment" as including calcium and OP medication together.

A third limitation is that not all studies reported current OP medication use by patients, and therefore we were unable to calculate medication *initiation* in all cases. In order to abstract treatment data from as many studies as possible, we also included medication *taking* as an outcome. As a result, we were able to capture medication taking data on 38 (versus 33) interventions. Similarly, not all studies reported patients switching from one OP medication to another, and therefore we cannot comment on whether this had an effect on the EPs of patients initiating and/or taking OP medication.

Despite these limitations, this systematic review is timely in cataloging the considerable volume of studies focused on improving osteoporosis care after fractures, and comparing those in detail that met the inclusion criteria. Developing the EP as an approach to comparing various studies and interventions is an important innovation. The EP for intervention, medication initiation, and medication taking can also be used within programs for continuous

performance measurement, improvement, and sustained performance. Comparing various types of interventions, and demonstrating the superiority of system level coordination of care is a key finding of this review. The low performance of educational, general awareness, and medication coverage programs underscores the ineffectiveness of these commonly mentioned, less disruptive interventions in achieving high performance. The fact that controlled trials and continuous improvement projects performed comparably is also important for care systems considering these alternative approaches to improvement.

In conclusion, this systematic review identified and described 57 articles that included 64 interventions to improve OP management post-fracture. While the EP does not necessarily reflect accurate rates or targeted goals for care, and we could not calculate an EP in all interventions, calculating this proportion allowed us to compare studies across the review and to include both RCTs and non-RCTs in this review. According to our EPs, the majority of interventions resulted in up to 71% of fracture patients investigated but <35% initiating medication, and <45% taking medication within 6 months of screening. Based on the various ways to categorize the interventions, we demonstrated that the highest EPs of patients investigated and treated with OP medication were in interventions within which BMD and/or treatment were conducted and in interventions that included dedicated personnel to implement the intervention.

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