Title: Interventions to Improve Osteoporosis Medication Adherence and Persistence: A Systematic Review and Literature Appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group

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Mini-abstract

This review suggests that several interventions, including simplification of dosing regimens, patient decision aids, electronic prescription, and patient education may improve medication adherence and persistence in patients with osteoporosis. We recommend that promising interventions are subjected to further rigorous evaluation to demonstrate that improved adherence translate to greater benefits.

Abstract

PURPOSE: This study aims to systematically review, critically appraise and identify from the published literature, the most effective interventions to improve medication adherence in osteoporosis.

METHODS: A literature search using Medline, EMBASE, Cochrane library and CINAHL was undertaken to identify prospective studies published between January 1, 1999 and June 30, 2012. We included studies on adult users of osteoporosis medications that tested a patient adherence intervention (e.g. patient education, intensified patient care, different dosing regimens) and reported quantitative results of adherence. The Delphi list was modified to assess the quality of studies.

RESULTS: Of 113 articles identified, 20 studies fulfilled the inclusion criteria. The most frequent intervention was education (n=11) followed by monitoring/supervision (n=4), drug regimens (n=2), drug regimens and patient support (n=1), pharmacist intervention (n=1) and electronic prescription (n=1). Although patient education improved medication adherence in four studies, two large-scale randomized studies reported no benefits. Simplification of dosing regimens (with and without patient support program) was found to have a significant clinical impact on medication adherence and persistence. Monitoring/supervision showed no impact

on medication persistence while electronic prescription and pharmacist intervention increased medication adherence or persistence.

CONCLUSIONS: This review found that simplification of dosing regimens, decision aids, electronic prescription or patient education may help to improve adherence or persistence to osteoporosis medications. We identified wide variation of quality of studies in the osteoporosis area. The efficacy of patient education was variable across studies, while monitoring/supervision does not seem an effective way to enhance medication adherence or persistence.

Introduction

Sub-optimal adherence and persistence with appropriately prescribed medication are prevalent in osteoporosis. Several studies have demonstrated that between 50-75% of patients who were prescribed anti-osteoporotic medications have discontinued their medications within one year [1-5]. Low medication adherence leads to lower gains in bone mineral density and higher fracture rates [6], resulting in substantial clinical and economic burden [7, 8]. Approximately 50% of the potential clinical benefits of osteoporosis medications may be lost due to poor adherence, [7, 9] and the cost-effectiveness of osteoporosis management is significantly affected by reduced medication adherence [10, 11].

There are many strategies aimed at improving adherence and persistence with medications. However, evidence across multiple treatments for a diverse range of diseases, suggests that the effectiveness of current methods is both variable and modest [12, 13]. With specific reference to osteoporosis, there have been several interventions and programs developed in recent years, probably in response to the increasing use of bisphosphonates, first introduced

around 1990 [14]. This study aims to critically appraise the published literature on interventions to improve patient adherence and persistence with medications to treat osteoporosis and to determine the most effective interventions. A previous review [15] noted a lack of effective intervention in a small sample of eight studies. Since then, more interventions have been tested and published, and this review provides further examination of interventions to improve adherence and persistence in osteoporosis.

Methods

Search strategy

A literature search undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (<http://www.prisma-statement.org/>) was carried out in Medline, EMBASE, Cochrane library and Cumulative Index to Nursing and Allied Health Literature (CINAHL) and using the following key words separated by Boolean operators: [osteoporosis, low bone density, bone fragility, fractures bone, bone demineralization, pathologic osteopenia, low bone mineral density, low bone mass, low bone turnover, low bone mass density OR bisphosphonates, diphosphonates, etidronic acid, clodronic acid, pamidronate, risedronate acid, ibandronic acid, alendronate, calcium, colecalciferol, estrogens, hormone replacement therapy (HRT), raloxifene, vitamin D] AND [medication adherence, patient compliance, persistence, non-compliance, non-persistence, concordance, non-concordance], AND [interventions, clinical trial, experiment, RCT]. The search period was from January 1, 1999 to June 30, 2012. We restricted our search to the last decade because as no adherence intervention for use in osteoporosis was identified before that period [15]. References of selected articles and of a prior review [15] were also searched.

Selection criteria

We included interventional studies of adult users of osteoporosis medications (not limited to bisphosphonates) or calcium and vitamin D supplements that tested any intervention for an improvement in adherence or persistence and reported quantitative measures of adherence and/or persistence. Non-English studies or observational studies were excluded.

Extracted information

Each paper was reviewed independently by two investigators (MH, MS, DH, PL, EM or FGS) and disagreements were resolved by consensus. The extracted information included study design, type of intervention, other characteristics of intervention, measurement of adherence, persistence, outcomes, population, follow-up time, ethics approval, sample size, statistical analysis, results of the intervention effect, medication possession ratios or other adherence or persistence measures, adjustment for confounders and clinical outcomes. Due to the heterogeneity in the methods of adherence measurement and of study outcomes, the analysis was focused on a qualitative assessment.

Quality criteria

The Delphi list [16] was modified to assess the quality of studies. The original checklist contains 17 domains and 8 items but elements to evaluate interventional behavioral studies were not included. Therefore, we added methodological items that were considered relevant for behavioral studies, and they included study design, type of intervention, measure of adherence, outcomes, population, follow-up time, ethics approval, sample size, statistical analysis and results. We assigned a score of 1 if the study included the required item, otherwise zero. Therefore, the maximum score for an article that included all information related to study design, data collection, analysis and interpretation of results was 30 (Appendix 1). Consistency of quality scoring was achieved by having at least two reviewers

scoring each paper independently. Only few discrepancies became evident and these were resolved by consensus.

Results

There were 113 articles identified, and a total of 20 studies [17-36] fulfilled the inclusion criteria (Figure 1). Literature reviews (n=15), research that lacked a medication adherence intervention (n=45), disease management (n=11), economic studies (n=8), descriptions of protocols (n=2), and 4 other were excluded (see Appendix 2). The most frequent intervention was education (n=11) followed by monitoring/supervision (n=4), simplification of dosing regimens (n=2), drug regimen combined with patient support (n=1), electronic prescriptions (n=1) and pharmacist intervention (n=1). Interventions were led by physicians (n=5), pharmacists (n=4), nurses (n=3), multidisciplinary teams (n=3), clinical personnel (n=3), health educators (n=1) and it was unknown in one study.

The characteristics of included studies are reported in Tables 1 and 2. Eleven out of the twenty studies [21, 22, 28-36] were published since 2010. Fifteen studies were randomized controlled trials [18, 20, 21, 24-27, 29-36] and two were cross-over designs. Other studies were non-randomized uncontrolled studies [17, 19, 22, 23, 28]. Most tested an educational program, but these varied substantially between studies [17, 19, 21-24, 27, 28, 31, 35, 36] in the content and method of delivery, which included: group-based, face-to-face, telehealth program, or telephone counseling and written information (letters, leaflets, brochures). In one study [28], pharmacists led the intervention in decentralized clinical-pharmacy managed services. Patients included in the studies were mainly postmenopausal women with osteoporosis. In total, 14,662 patients were included in the studies; 9,420 in the intervention arm and 5,242 in the control arm; 64% of which were from four trials of more than 1,000

patients per trial [20, 24, 25, 35]. Most studies reported ethics review approval, and the follow-up after conduct of the intervention ranged from 4 to 48 months.

Table 2 presents primary outcomes, method of adherence measurement, statistical analysis, results, and quality score. All studies used adherence as primary outcome except one study [20] that only reported persistence and two studies where adherence was used as a secondary outcome (persistence being the primary outcome) [28, 36]. Eight studies reported both adherence and persistence data [18, 24-26, 30-32, 35]. Adherence definitions varied: where an explicit cut-off was used to define adherence (e.g. >80% of doses taken), this was applied to calculate the proportion of patients adhering to therapy at time T, proportion of patients taking their medicine correctly, medication possession ratio. In other cases, patients were labeled as adherent without an explicit cut-off. Persistence was defined as the proportion of patients continuing treatments at a given follow-up time. Adherence and persistence outcome data were collected from prescription records (n=7), electronic monitoring (n=5), self-report questionnaire (n=6) and two did not provide the information [17, 33]. None of the studies examined adherence or persistence in relation to clinical outcomes. Eight studies had adjustments for some potential confounders [20, 21, 25, 26, 30, 31, 34, 35] which may not be necessary in properly randomized trials where confounding variables would presumably be distributed evenly across the arms of the trial. Sixteen studies described the characteristics of patients lost during follow-up [7, 18-23, 25-27, 30-32, 34, 35].

Among studies including a control group (n=16), twelve reported data on adherence [18, 19, 21, 24-28, 30-32, 35]. In studies where adherence was defined as percentage of patients adherent [18, 21, 24-28, 30, 31, 35], the adherence ranged from 46% to 92% with the intervention while in the control group it varied from 28% to 87%. Nine studies showed a statistically significant ($p=0.05$) improvement in medication adherence by the intervention compared to the control group [18, 19, 21, 25, 26, 28, 30-32]. Clowes et al. [18] showed that

patients receiving feedback information in response to therapy based on bone turnover marker measurements experienced an improved adherence. Monitoring increased cumulative adherence in this study by 57% compared with no monitoring ($P=0.004$). Patient education and information were found to have a significant impact on medication adherence in two small studies [19, 21], but this result was not confirmed by two large-scale randomized studies [24, 35]. The use of a decision aid had a significant impact on the number of adherent patients (23 patients vs. 14 patients, $p = 0.009$) [32], and pharmaceutical care was shown to improve adherence in two studies [28, 31] although, in one of these, a significant improvement was only found using self-report questionnaire and not using pill count [31]. The simplification of dosing regimens was shown to significantly influence medication adherence. Cooper et al. showed that once-monthly ibandronate treatment plus a patient support program significantly increased medication adherence compared to once-weekly alendronate [25], while a subcutaneous injection of denosumab every 6 months was shown to significantly improve adherence compared with weekly oral alendronate [26, 30].

Among the thirteen studies assessing the impact of intervention on persistence [18, 20, 24-26, 29-36], only five showed a positive impact of the intervention [25, 26, 29, 30, 36]. Simplification of dosing regimens was found to have a significant impact on medication persistence [25, 26, 30]. Patients were most persistent with those having the least frequent dosing regimens. Electronic prescription also increased persistence with calcium (57% vs. 22%, study vs. control groups, $p = 0.001$) [29] and education by pharmacists increased calcium intake at 4 months (30% vs. 19%, study vs. control groups, $p = 0.011$). None of the four studies assessing monitoring/supervision intervention showed an impact on persistence [18, 20, 33, 34] and most education programs had no significant impact on persistence [24, 31, 35], including the patient support program [32].

The quality of the studies was variable with an average quality score of 74% (range from 50% to 93%). Improved quality scores were obtained in more recent studies with an average quality score increasing from 66% to 80% for studies published before and after 2010, respectively.

Discussion

We reviewed studies that assessed interventions designed to enhance patient adherence and persistence to osteoporosis medications. This study considered new interventions to previous reviews [15]. Some of these provided further evidence on the impact of patient education and monitoring/supervision on medication adherence while others tested new interventions or programs. From our update, it emerged that the efficacy of patient education is still uncertain. Nielsen et al. [21] reported an improvement in adherence but a large-scale randomized trial found no statistically significant improvement in adherence of a telephonic motivational interviewing intervention [35]. A large well conducted RCT is definitive within the study context, but perhaps not generalizable to all forms of education. Other studies [33, 34] confirmed that monitoring and providing feedback to patients on bone marker results is not an effective way to enhance persistence and adherence. New interventions being tested suggested that less frequent dosing regimens [26, 30], electronic prescription [29] and patient decision aids to facilitate decision-making by describing the available options [32] could be effective patient-focused intervention to improve adherence and persistence.

The existing literature on interventions to improve patient adherence and persistence has several limitations. First, studies were of limited quality - only 15 studies were randomized trials and only one of the studies was a double-blinded trial. While an improvement in the quality of studies was observed over time, well-designed randomized controlled trials are needed to assess the efficacy of enhancing adherence to osteoporosis medications. We

acknowledge, however, that conducting a doubled-blind trial for testing an intervention for improving adherence and persistence may be difficult and sometimes impossible (e.g. blinding participants to an educational intervention). However, the use of cluster randomized controlled trials could be one way to mitigate specific methodological constraints. Second, the definitions and measurement of medication adherence and persistence were inconsistent, precluding any quantitative synthesis of the evidence. The International Society for Pharmacoeconomics & Outcomes Research (ISPOR) has previously provided guidance on how to conduct research on medication adherence using both retrospective and prospective designs [37, 38]. A new taxonomy for describing and defining adherence to medications was also recently published by the ABC project team [39], which may facilitate standardization of future research. Adherence to medication is defined as “the process by which patients take their medication as prescribed” and persistence to medication as “the time from initiation until discontinuation” [39]. Third, information reported by authors of each article was limited. Where mean adherence scores were provided for RCTs, no information was available on the standard deviations, making it difficult to calculate a standardized effect size, which could be used as a comparative measure across studies. There was limited information reported on specific relevant points including the extent of patient co-payments, and setting of care (i.e. at research centers or within the community). Fourth, no studies examined the impact of the interventions on clinical outcomes. Although testing for efficacy using proxy outcomes (e.g. adherence) is informative, it would also be appropriate for future studies to assess clinical outcomes (e.g. fractures) alongside persistence and adherence. Finally, the durability of intervention effect, and appropriate period of follow-up are important considerations which are largely overlooked. Osteoporosis is a chronic disease requiring long-term treatment. A single intervention is unlikely to yield anything more than transient improvements in adherence. Increased treatment effectiveness is most probable with repeated administration of

interventions, and can only be demonstrated with long-term follow-up of patients, greater than 1 year.

Problems with internal and external validity of the presented data, and potential biases, could also limit the usefulness of some studies. Non-randomized uncontrolled trials [17, 19, 22, 23, 28] are prone to non-equivalent patient characteristics at the beginning of the study and differential rates of patient drop-out during follow-up. This reduces internal validity, as does the confounding effect of time in studies that adopt a pre-post group research design. External validity could also be uncertain since samples may not be wholly representative of populations with osteoporosis [17]. Measurement bias may also have occurred in those studies that used only measures of self-report to determine adherence [21, 22, 27]. It could also occur in those studies where there was lack of blinding between the data analysts and treatment groups involved. Lack of appropriate training of staff in the use of tools could lead to an undermining of the interventions' fidelity.

There were potential issues in relation to the methodology and execution of the review. While only one person conducted the literature search, it was undertaken as comprehensively as possible using multiple search terms, increasing confidence that all relevant studies were identified. The quality score was used to ensure consistency in the way we evaluated papers, with only a few discrepancies observed between reviewers which were only a matter of interpretation. Since the interventions varied across studies, we presented the information by study, and by broad intervention category. So, if an intervention was focused on educating patients using different tools, we did not focus on the tools, we grouped them as "educational intervention". Adherence is a multifactorial problem, and therefore, there is no single intervention that works across different individuals' needs. We proposed to compare different intervention types and try to identify if there were clear differences among them. We would

expect to update our review when new relevant interventions become available, especially with advances in telehealth technology and social media.

In summary, this review indicates that several interventions (simplification of dosing regimens, electronic prescription, patient decision aids or patient education) may improve adherence and persistence to medicines for osteoporosis, although, there were variations in the quality of studies. Of the largest and least biased studies, patient education showed however only marginal improvement in medication adherence and persistence, while monitoring/supervision seems ineffective in enhancing medication adherence. To demonstrate the societal benefits of adherence improvement, we recommend that the most promising interventions are subjected to rigorous evaluation of clinical effectiveness in pragmatically-designed, randomized, controlled trials. It may be necessary to target interventions to specific causes of non-adherence, in an approach consistent with personalized medicine, in acknowledgment that the average effect from trials masks some patients who are very responsive to interventions.

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Table 1. Characteristics of studies identified which tested a patient adherence and/or persistence intervention

References	Design	Interventions / Description / Lead by	Population (inclusion criteria) / drug(s) being assessed	N intervention / control	Planned follow-up
Blalock et al. (2002) [17]	Non randomized non-controlled trial	Patient education / 1 st intervention: tailored educational intervention delivered to individuals (written materials and telephone counseling session). 2 nd intervention included the Osteoporosis resource center, workshop and free bone density screening / Not stated	Women / Calcium	714 / 0	1 year
Clowes et al. (2004) [18]	Randomized controlled trial	Monitoring / Arm A: Patients with nurse at 12, 24 and 36 weeks. Arm B: Idem + information on response to therapy based on BTM measurements / Nurses	Subjects with osteopenia at either the spine or hip / Raloxifene	24 and 25 (Arm A and B) / 24	1 year
Cook et al. (2007) [19]	Non randomized non-controlled trial	Patient education / Telehealth program using motivational interviewing and cognitive–behavioral techniques / Nurses	Patients who received a prescription for risedronate	402 / 0	6 months
Cooper et al. (2006) [25]	Randomized controlled trial	Drug regimens and patient support / Monthly ibandronate tablet and patient support (information on osteoporosis, newsletter at 3 months) / Physicians	Postmenopausal women diagnosed with osteoporosis / Weekly alendronate or monthly ibandronate tablet	529 / 547	6 months
Delmas et al. (2007) [20]	Randomized controlled trial	Monitoring / At week 13 and 25, all patients received information about the need to continue treatment. Intervention group received feedback on their response to therapy based on BTM measurements / Physicians	Postmenopausal women diagnosed with osteoporosis / Risedronate	2302 / 1113	1 year
Freemantle et al. (2012) [26]	Randomized (crossover) controlled trial	Drug regimens / Subcutaneous denosumab, 60 mg every 6 month versus oral alendronate, 70 mg once weekly / Clinic	Postmenopausal women diagnosed with osteoporosis / Denosumab or alendronate	106 (denosumab) / 115	24 months

Guilera et al. (2006) [27]	Randomized controlled trial	personnel Patient education / Educational leaflet with general information about osteoporosis, and attending physician spent 15 min reviewing the contents of the leaflet with each participant / Physicians	Postmenopausal women diagnosed with osteoporosis / Raloxifene	(alendronate)* 366 / 379	12 months
Heilmann et al. (2012) [28]	Non-randomized controlled trial	Pharmacist-directed intervention / Decentralized clinical-pharmacy-based osteoporosis management service / Pharmacists	Women with a diagnosis code for a fracture / Osteoporosis medications	291 / 71	12 months
Hill et al. (2010) [29]	Randomized controlled trial	Electronic prescription / Electronic prescription for the calcium carbonate product with the Electronic medical record system / Physicians	Women between 19 and 50 years old, who attended a general obstetrics and gynecology practice / Calcium	123 / 122	6 months
Kendler et al. (2011) [30]	Randomized (crossover) controlled trial	Drug regimens / Subcutaneous denosumab, 60 mg every 6 month versus oral alendronate, 70 mg once weekly / Clinic personal	Postmenopausal women diagnosed with osteoporosis / Denosumab or alendronate	126 (denosumab) / 124 (alendronate)*	12 months
Lai et al. (2011) [31]	Randomized controlled trial	Patient education and counseling / Participants received counseling on osteoporosis, risk factors, lifestyle modifications, goals of therapy, side effects and the importance of adherence / Pharmacists	Postmenopausal women diagnosed with osteoporosis / Weekly alendronate or risedronate	100 / 98	12 months
Montori et al. (2011) [32]	Randomized controlled trial	Patient education and shared-decision making / Patients received the osteoporosis choice decision aid / Physicians	Postmenopausal women with osteoporosis or osteopenia / Bisphosphonates	52 / 48	6 months
Nielsen et al. (2010) [21]	Randomized controlled trial	Patient education and information / Group-based education program, i.e. “school” group (12 hour) / Multidisciplinary team	Patients diagnosed with osteoporosis / Osteoporosis medications	300 / 150	2 years

Ojeda-Bruno et al. (2010) [22]	Non randomized non-controlled trial	Patient education / 2 hour education session / Nurses and physicians	Adults older than 50 years of age with a fragility fracture / Bisphosphonates	380 / 0	4 years
Robbins et al. (2004) [23]	Non randomized non-controlled trial	Patient education / Teaching about osteoporosis, estrogen and calcium / Nurses	Some women from the on-going 3 year low-dose estrogen study	109 / 0	1 year
Roux et al. (2012) [33]	Cluster randomized controlled trial	Monitoring / Bone marker was given at week 6 visit, together with a standardized message about the change compared to baseline / Physicians	Postmenopausal women with osteoporosis / Oral ibandronate	249 / 343	12 months
Shu et al. (2009) [24]	Randomized controlled trial	Patient and physician education / Physicians learned specific teaching techniques while patients received letters and automated telephone calls / Trained pharmacists (for physicians)	Participants from the parent trial and at risk for osteoporosis / Osteoporosis medications	1867 patients and 436 GPs / 875 patients	10 months
Silverman et al. (2012) [34]	Randomized controlled trial	Monitoring and education / (A) bone marker results at baseline, 3 and 12 months; (B) educational materials every month and a membership in the National Osteoporosis Foundation; (C) bone marker and educational information / Study personnel or primary care provider	Postmenopausal women with osteoporosis / Oral bisphosphonates	60 (A) / 60 (B) / 60 (C) / 59 (control)	12 months
Solomon et al. (2012) [35]	Randomized controlled trial	Patient education and counseling / Program of telephone based counseling / Health educators	Individuals newly prescribed a medication for osteoporosis / Osteoporosis medications	1046 / 1041	12 months
Yuksel et al. (2010) [36]	Randomized controlled trial	Screening and patient education / Tailored education program on aspects of osteoporosis / Pharmacists	Patients with osteoporosis / Calcium	129 / 133	4 months

* Per protocol Analysis

Table 2. Continuation of studies identified which tested a patient adherence and/or persistence intervention

References	Measures method	Assessment method	Statistical analysis			Results	Quality score
	Outcome(s)		Statistical method	Losses of patients to follow-up taken into account	Adjustment for confounders		
Blalock et al. (2002) [17]	Adherence to calcium intake but no explicit definition	No information	Not reported	No	No	Calcium intake increased of 500 mg/d in the intervention group.	16/30
Clowes et al. (2004) [18]	Adherence was the proportion of patients adhering to therapy (>75%) at 1 year Persistence was defined as continuing to take tablets for more than 7 of any 14 days immediately before the 1 year visit	Electronic monitoring devices	Kaplan-Meier survival curves	Yes	No	Arm A: 63% (95% CI 43%, 82%) Arm B: 68% (49%, 86%) Control: 42% (22%, 62%) P = 0.15 (Arm A) and 0.05 (Arm B) Monitored group: 84% (74%, 94%) Control: 67% (54%, 87%) P = 0.06 (Arm A) and 0.26 (Arm B)	24/30
Cook et al. (2007) [19]	Adherence (percentage of patients still adherent at 6 months) but no explicit definition	Pharmacy fill records	Not reported	Yes	No	Intervention: 69% Control (unpublished national data): 41% P < .001 Effect size: 0.19	19/30
Cooper et al.	Persistence (percentage of	Prescription	Kaplan-Meier	Yes	Yes	Intervention: 56.6%	24/30

(2006) [25]	patients still persistent at 6 months) was defined using discontinuation of at least 1-month without any medication available Adherence was defined as the proportion of patients who had at least five of the six prescriptions	filling	survival curves			Control: 38.6% Hazard ratio = 0.54 (0.44-0.66) P < 0.0001	
Delmas et al. (2007) [20]	Persistence at one year	Electronic monitoring	Kaplan-Meier survival curves	Yes	Yes	Intervention: 80.2% Control: 73.3% P = 0.008	25/30
Freemantle et al. (2012) [26]	Adherence was defined as the proportion of patients who were both compliant and persistent to treatment. Persistence was defined as the proportion persisting with treatment after crossover	Medication event monitoring system	Cochran-Mantel-Haenszel test	Yes	Yes	Non-adherence with denosumab (2 nd year): 7.5% Alendronate: 36.5% Risk ratio = 0.20 P < 0.001 Denosumab: 97.2% Alendronate: 72.6% Risk ratio = 0.09 P < 0.001	28/30
Guilera et al. (2006) [27]	Adherence was assessed using the Morisky test (four questions)	Self-completed questionnaire	Student t test and Mann Whitney test	Yes	No	Intervention: 52.5% Control: 47.4% P = 0.38	21/30
Heilmann et al. (2012) [28]	Adherence was defined as the proportion of patients who had a medication possession ratio of at least 80%	Pharmacy databases	Chi-square analysis	No	No	Intervention: 46% Control: 28% P = 0.007	18/30
Hill et al. (2010) [29]	Proportion of women who reported calcium intake at 6	Telephone survey	Chi-square analysis and t tests	No	No	Intervention: 57.0% Control: 26.5%	25/30

	months					RR = 2.2 (1.5–3.1) P = 0.001	
Kendler et al. (2011) [30]	Adherence was defined as the proportion of patients who were both compliant and persistent to treatment at the end of treatment period. Persistence was defined as the proportion persisting with treatment at the end of treatment period	Medication event monitoring system	Cochran–Mantel–Haenszel test	Yes	Yes	Denosumab: 87.3% Alendronate: 76.6% Risk ratio = 0.58 P = 0.043	28/30
Lai et al. (2011) [31]	Adherence is defined as the average percentage of participants who were both persistent and compliant	Pill count and self-report	Mann-Whitney U test	Yes	Yes	Denosumab: 89.7% Alendronate: 79.8% Risk ratio = 0.54 P = 0.049 Self-report: higher adherence in the intervention group (98.9% vs. 96.8%; P = 0.015 at 6 months); (98.0% vs. 96.2%; P = 0.047 at 12 months) Pill count: 98.8% vs. 97.0%; P = 0.028 (6 months) and 97.7% vs. 96.5%; P=0.32 (12 months) Intervention: 89.8% Control: 87.0% P = 0.481	27/30
Montori et al. (2011) [32]	Persistence was the percentage of patients who continued bisphosphonate at 12 months Adherence was defined as the proportion of patients who had 80% or greater adherence to bisphosphonates	Prescription filling Self-report (telephone survey) and pharmacy fill records	Kaplan-Meier survival curves and log rank test Wilcoxon rank-sum tests	Yes	No	Intervention: 23 patients Control: 14 patients P = 0.009	22/30

	Persistence was measured as the number of days covered					Intervention: 170 days Control: 180 days P = 0.38	
Nielsen et al. (2010) [21]	Adherence was defined as patients taking their medicine correctly at the appropriate time. An explicit definition was not provided	Self-completed questionnaire	Kaplan-Meier survival curves	Yes	Yes	Intervention: 92% Control: 80% P = 0.006	25/30
Ojeda-Bruno et al. (2010) [22]	Adherence with treatment but no clear definition	Self-report (telephone survey)	No statistical analysis	Yes	No	Intervention: 71%	15/30
Robbins et al. (2004) [23]	Adherence but no explicit definition	Pill counts and electronic monitoring	Not reported	Yes	No	Baseline: 95% (SD 1.7) 12-months: 96% (SD 1.8)	15/30
Roux et al. (2012) [33]	Persistence was defined as the proportion patients still treated at the last visit, and having taken at least 10 out of 12 pills	Not reported	Chi-square analysis	Yes	No	Persistence at one year: Intervention: 75.1% Control: 74.8% P = 0.932	22/30
Shu et al. (2009) [24]	Adherence was expressed as medical possession ratio	Prescription filling	Poisson distribution regression analysis	NR	No	Intervention: 74% (19%, 93%) Control: 73% (0%, 93%) P = 0.18	20/30
	Persistence was expressed as median days until discontinuation, where discontinuation was defined as at least 30 days without any medication available					Interventions: 85 days (58, 174 days) Control: 79 days (31, 158 days) P = 0.16	
Silverman et	Persistence was defined as	Prescription	Survival analysis	Yes	Yes	RR group1/control:	22/30

al. (2012) [34]	patients who refilled their prescription	filling				1.09 (p>0.97. RR group 2/ control: 0.95 (p>0.91). RR group 3/control: 1.18 (p>0.23). Intervention: 49% Control: 41% P = 0.07 P = 0.34	
Solomon et al. (2012) [35]	Adherence was expressed as medication possession ratio Persistence was defined as days from initial prescription until the first period during which the patient experienced an interruption in prescription filling lasting longer than 60 days	Prescription filling	Kruskal-Wallis test Kaplan-Meier survival curves and log rank test	Yes	Yes		24/30
Yuksel et al. (2010) [36]	Calcium intake at the end of 16 weeks	During a pharmacy visit	Frequencies and chi-square analyses	Yes	No	Patients reaching total daily calcium of 1,500 mg (diet + supplement): Intervention: 30% Control: 19% RR = 1.6 (1.0–2.5). P = 0.011	24/30

NR Not reported, RR relative risk

Figure 1. Flow diagram of studies

Appendix 1. Modified version of the Delphi list

Domains	Original Delphi List	Modified List
1. Study question		Was the research question/objective/hypothesis or aim clearly described Yes (1)/ No (0)
2. Population	Were the eligibility criteria specified? Yes/No/Don't know	Were inclusion criteria clearly described? Yes (1)/No (0) Were exclusion criteria clearly described? Yes (1)/No (0)
3. Sample size and power Calculations a priori		Was sample size and power calculated a priori? Yes (1)/ No (0) Were the total number of individuals, the total number of participants in the study group and total number of patients in the controlled group clearly specified? Yes (3, one per each)/ No (0)
4. Treatment allocation	a) Was a method of randomization performed? Yes/No/Don't know b) Was the treatment allocation concealed? Yes/No/Don't know	Was randomization used in the study Yes (1)/ No (0)
5. Confounders		Were potential confounders clearly described? Yes (1)/No (0)

6. Ethics	<p>Was the protocol approved by the Ethics Committee and/or patients signed informed consent?</p> <p>Yes (1)/No (0)</p>
7. Intervention	<p>Was intervention clearly defined?</p> <p>Yes (1)/No (0)</p> <p>Was the intervention clearly described (who did what, to whom, where and how often)?</p> <p>Yes (1)/No (0)</p>
Comparator	<p>Was a comparator included in the study?</p> <p>Yes (1)/No (0)</p> <p>Was comparator clearly described?</p> <p>Yes (1)/No (0)</p>
8. Outcome measures	<p>Was (were) measure (s) of adherence defined?</p> <p>Yes (1)/No (0)</p> <p>Was (were) measure (s) of adherence clearly described in the study?</p> <p>Yes (1)/No (0)</p> <p>Were clinical outcomes included in the study?</p> <p>Yes (1)/No (0)</p>
9. Follow-up/withdrawals	<p>Was followed-up time specified in the study?</p> <p>Yes (1)/No (0)</p>

10. Blinding	<p>Was the outcome assessor blinded? Yes/No/Don't know</p> <p>Was the care provider blinded? Yes/No/Don't know</p> <p>Was the patient blinded? Yes/No/Don't know</p>	<p>Was the study:</p> <p>a. Double blind Yes (2)/No (0)</p> <p>b. Single blind Yes (1)/No (0)</p>
15. Analysis	<p>Were the groups similar at baseline regarding the most important prognostic indicators? Yes/No/Don't know</p> <p>Were point estimates and measures of variability presented for the primary outcome measures? Yes/No/Don't know</p> <p>Did the analysis include an intention-to treat analysis? Yes/No/Don't know</p>	<p>Was the statistical method appropriate? Yes (1)/No (0)</p> <p>Was the analysis adjusted by confounders? Yes (1)/No (0)</p> <p>Were losses of patients to follow-up taken into account? Yes (1)/No (0)</p> <p>Were characteristics of patients lost to follow-up clearly described? Yes (1)/No (0)</p>
Results		<p>Were adherence results clearly presented (e.g. baseline, interim, and at the end of the study)? Yes (3)/No (0)</p> <p>Were clinical results clearly presented (e.g. baseline, interim, and at the end of the study)? Yes (1)/No (0)</p> <p>Were results adjusted by</p>

	confounders?
	Yes (1)/No (0)
16. External Validity	Was the included population representative of study population?
	Yes (1)/No (0)
Total	30 (100% Quality Score)

Appendix 2. List of excluded studies

Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y, Russo PA, Kreusch T. "Bis-phossy jaws" - high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg.* 2008 Mar;36(2):95-103.

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