ADVERSE EFFECTS AND PERSISTENCE WITH THERAPY IN PATIENTS TAKING ORAL ALENDRONATE, ETIDRONATE OR RISEDRONATE: SYSTEMATIC REVIEWS

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EXECUTIVE SUMMARY

Systematic review: adverse events associated with oral alendronate, etidronate or risedronate therapy

Background

Whilst a number of adverse effects have been associated with oral bisphosphonates, the most common relate to the gastrointestinal tract. Of these, the most clinically important are oesophagitis and oesophageal ulceration.

Adverse events: number of studies, and direction of evidence

34 relevant studies were identified. Although short randomised studies of tolerability found no increased incidence of adverse events in patients randomised to alendronate, UK prescription event monitoring studies suggest that therapy with daily alendronate or risedronate is associated with a high level of reporting of a number of conditions in the first month of therapy, particularly those affecting the upper gastrointestinal tract: there were around 30 reports of dyspepsia, the most commonly reported condition, per 1000 patient-months of exposure. This incidence is approximately five times that seen in comparable patients in other PEM studies receiving other prescriptions, and is consistent with the finding that new bisphosphonate users are three times as likely as controls to require prescribed acid suppression agents. Other cohort studies suggest that over 30% of patients starting alendronate therapy may report gastrointestinal adverse effects.

In randomised trials of effectiveness, the incidence of gastrointestinal adverse events is similar in the bisphosphonate and placebo arms. Although for alendronate this may be attributed, at least in part, to the exclusion from those trials of patients with a history of upper gastrointestinal disease, this is not true of the risedronate trials. It is plausible that the high level of reporting of gastrointestinal adverse events both in patients taking oral bisphosphonates in real life and in the placebo arms of the clinical trials may be partly due to a heightened awareness of the potential for gastrointestinal adverse events with such medication.

Systematic review: persistence with oral alendronate, etidronate or risedronate therapy

Background

Persistence refers to the length of time for which a patient continues to take a prescribed medication. It is generally measured indirectly, using methods such as patient self-reporting, pill counts, or review of prescription records and

claims. Prescription monitoring cannot take into account patients who, for whatever reason, continue to refill the prescription even though they do not intend to take the medication.

For a number of reasons, persistence is likely to be substantially better in clinical trials than in community settings.

Persistence: number of studies, and direction of evidence

Seventeen relevant studies were identified. The UK PEM studies, whose findings are likely to be representative of normal clinical practice, found that persistence with daily risedronate was 70% at six months and with daily alendronate was 75% at one year. These figures only relate to patients for whom the prescribed bisphosphonates were actually dispensed; an unknown proportion will presumably have failed to accept their physician's recommendation of bisphosphonate therapy. While there is no UK evidence, and very little evidence worldwide, for longer-term persistence with oral bisphosphonate therapy, short-term studies suggest that many patients who discontinue therapy do so within the first month or two, and the risk of discontinuation may therefore be substantially reduced in patients who complete six months of therapy.

Persistence may be improved by weekly rather than daily dosing regimens.

ADVERSE EFFECTS ASSOCIATED WITH ORAL ALENDRONATE, ETIDRONATE OR RISEDRONATE THERAPY

INTRODUCTION

Systematic reviews of hierarchies of evidence

The traditional hierarchy of clinical evidence used in the evaluation of clinical efficacy is not the most appropriate hierarchy of evidence to apply to the study of adverse effects.[1] Randomised controlled trials whose main focus is the efficacy of the study intervention are considered to provide the highest level of evidence for assessing the therapeutic efficacy of drugs. However, such RCTs have limited ability to assess drug toxicity: they are generally not powered to reliably detect rare adverse drug reactions, nor is their follow-up period long enough to permit the detection either of adverse drug reactions widely separated in time from the original use of the drug or of delayed consequences associated with long-term therapy.[2] Their populations are often not wholly typical of the target population: they tend to exclude older patients and those with comorbidities who may be at risk of unique adverse drug reactions or of an increased frequency of adverse drug reactions compared with the general population.[2] Trial participants are less likely than non-selected patients to be receiving potentially interacting medications; they may also be monitored more carefully than in real-life situations. Moreover, RCTs do not always measure all potential side-effects.[3]

Two studies illustrate these points. Mann observed that the safety database on newly licensed drugs is limited by the number and characteristics of the patients involved.[4] In the UK, successful applications for product licences for medicines containing new active substances have in the past included safety data derived from a median of 1480 (range 129-9400) patients.[5] Most of these participants will have been carefully selected to exclude comorbidities, and few will be typical of the patients likely to receive the drug once it has been marketed.[4] It is unlikely that uncommon adverse reactions will be identified from such a small number of highly selected patients, and it is therefore necessary to use post-marketing surveillance techniques such as spontaneous adverse drug reaction reporting and prescription-event monitoring to survey the results of the normal clinical use of newly marketed drugs in large populations.[4] With specific reference to osteoporosis, Dowd et al undertooken a retrospective chart review of all new female patients with osteoporosis seen in the osteoporosis clinic of a US academic medical centre from March 1995 to June 1998 who met clinical criteria for treatment with an antiosteoporotic agent, and for whom sufficient data were available to determine whether they would have been eligible for inclusion in four large multicentre trials in which the centre was involved.[6] Even ignoring study exclusion criteria relating to the prior use of oestrogen or antiosteoporotic agents, at most only 21% of the 120 patients would have been eligible for inclusion in any of the four studies, and three studies would have excluded over 90%. Comorbidity was the major reason for exclusion (60%). However, the authors admit that their sample may not have been typical of all osteoporotic patients because it was limited to women who had been referred

to an academic centre, and because some patients might have been skimmed off by the trials which were taking place in the centre.

In this report, therefore, we will not undertake a systematic review of randomised trials in order to include the adverse event data which they report, although for comparison with observational studies we will refer to the adverse event data from the placebo-controlled studies identified in our systematic reviews of RCTs which report fracture outcomes in postmenopausal[7] and steroid-induced osteoporosis. However, we will discuss the results of randomised controlled trials designed specifically to look at adverse effects in osteoporotic patients. We will not discuss tolerance studies in healthy volunteers: these frequently take the form of endoscopy studies designed to assess the effect of bisphosphonates on the upper gastrointestinal tract, and such studies represent a weak form of evidence because of important limitations which make extrapolation to clinical practice difficult.[8]

We also draw on other study types which are important in identifying drug-related adverse events. These include:

- retrospective analyses of large databases (eg prescription-event monitoring studies)
- cohort studies, including post-marketing surveillance studies
- case-control studies
- cross-sectional surveys
- case reports.

The non-randomised studies on which we will draw monitor the safety of medicines under their usual conditions of use. However, they too have limitations. Retrospective analyses, while useful for examining the frequency of uncommon adverse events, may be open to bias.[9] Probably the most comprehensive and rigorous of such studies are prescription-event monitoring (PEM) studies. These are non-interventional cohort studies designed to monitor the safety in everyday general clinical practice of new drugs intended for widespread, general practitioner use. In England, the UK Drug Safety Research Unit (DSRU) is provided with copies of all prescriptions for selected new drugs dispensed throughout England over a period long enough to allow exposure data to be collected for 20-30,000 patients. After an interval of 3-12 months from the first prescription for each patient, the DSRU sends each prescriber a questionnaire seeking information on any ‘events’ (new diagnoses, reasons for referral to a consultant or admission to hospital, unexpected deterioration (or improvement) in a concurrent illness, suspected drug reaction etc) which may have occurred since the drug was first prescribed. Medically qualified staff at the DSRU then assess the likelihood of a causal relationship between the drug and each adverse event.[4] Prescription-event monitoring is therefore is superior to post-marketing surveillance systems which rely on the spontaneous reporting of suspected adverse drug reactions by health professionals: these may under-report adverse events, and the quality of submitted reports may be poor.[10] PEM is more comprehensive than spontaneous reporting systems as the questionnaires prompt the clinicians to respond, and does not rely on the

individual clinician's assessment of causality to identify an adverse drug reaction. However, on average, only 58% of the questionnaires are returned, and only 52% provide clinically useful data. This is a potential source of bias as it is not known whether the patients whose doctors complete and return the questionnaires differ from those whose doctors do not. Additionally, PEM only monitors drug use in general practice, and does not include any drugs which are started in hospital. It also includes no measure of compliance other than that the prescriptions have been dispensed.[4] As there may also be other, unidentified, confounders.[4] in both PEM and spontaneous post-marketing surveillance the presence of confounders prohibits the definitive attribution of causality to drug exposure.[10]

Some uncommon, unexpected, or long-term adverse effects, which are often different from those detected in clinical trials, may only be published in case reports. It may be difficult to establish causality in such cases, although some assess this using criteria such as the response to discontinuation of, and rechallenge with, the drug.[9] Moreover, case reports of unusual adverse effects are often subsequently supported by the findings of further studies such as retrospective analyses and postmarketing surveillance. Consequently, we will include case reports in our review, but only when they relate to adverse effects for which more robust evidence is not available.

Adverse effects associated with oral bisphosphonates

Oral bisphosphonates have been associated with adverse effects affecting a number of body systems. These effects are listed by the manufacturers in the relevant Summaries of Product Characteristics (see Appendix 1). The most common adverse effects relate to the gastrointestinal tract, the most clinically important of these being oesophagitis and oesophageal ulceration. Postmarketing reports identified cases of oesophagitis and oesophageal ulceration with alendronate some of which were more severe than had been seen in clinical trials. As oesophagitis was rare when alendronate was administered intravenously, it seemed likely that it was caused by direct contact of the drug with the local mucosa.[11] Contributory factors were thought to include taking alendronate with less than 6 fluid ounces (180 ml) of water, taking the tablet while in a supine position or lying down after taking it, continuing to take alendronate after the onset of symptoms suggestive of oesophagitis, and having pre-existing oesophageal disorders which would prolong mucosal exposure to the drug.[12] Consequently, on 15th March 1996, Merck & Co, the manufacturers of alendronate, issued a letter warning physicians that alendronate could irritate the oesophagus, but that such side effects could be reduced by careful adherence to the dosing instructions.[13] At the same time, the Summary of Product Characteristics was revised to clarify those instructions, emphasising that alendronate should be taken with at least 6 fluid ounces of water, that the tablet should not be chewed or sucked, and that the patient should remain upright for at least 30 minutes after taking the medication.[14] subsequently, in April 1996, the Committee on Safety of Medicines also issued a document emphasising the importance of adhering to the new dosing recommendations and of monitoring patients for possible signs of oesophagitis.

SYSTEMATIC REVIEW OF ADVERSE EFFECTS ASSOCIATED WITH ORAL ALENDRONATE, ETIDRONATE OR RISEDRONATE

METHODS FOR REVIEWING ADVERSE EFFECTS

Search strategy

The literature searches aimed to identify all literature relating to adverse effects associated with oral alendronate, etidronate or risedronate used in the prevention and treatment of osteoporosis. The searches were conducted in April 2006.

Sources searched

Seven electronic bibliographic databases were searched (Medline, Embase, Cinahl, Biosis, Cochrane Central Register of Controlled Trials, Science Citation Index, Social Sciences Citation Index) (for search strategy, see Appendix 2). No language, date or study-type restrictions were applied to the searches. The reference lists of relevant articles were handsearched.

Inclusion criteria

- Population: adults requiring therapy for the primary or secondary prevention of osteoporotic fracture
- Intervention: oral alendronate, etidronate or risedronate
- Reported outcomes: clinical adverse events

Exclusion criteria

- Population: children and adolescents, adults taking bisphosphonates secondary to cancer or transplantation, healthy adults with normal bone mineral density
- Intervention: oral alendronate, etidronate or risedronate taken in conjunction with other antiosteoporotic drugs such as fluoride
- Study type: randomised trials of effectiveness, endoscopy studies.

Sifting

The references identified by the literature searches were sifted in three stages. They were screened for relevance first by title and then by abstract; all studies which appeared from their abstracts to be relevant were then read in full.

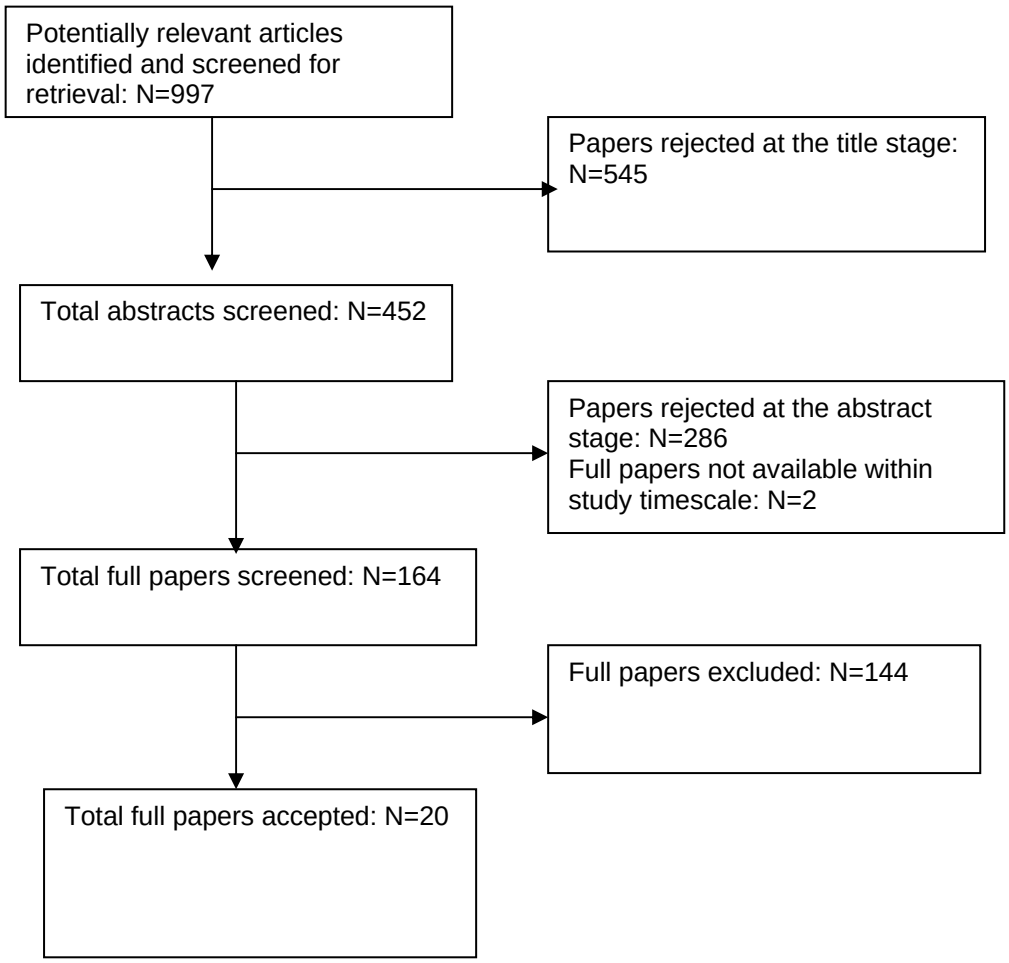
RESULTS

QUANTITY OF RELEVANT RESEARCH

Number of relevant studies identified

The electronic literature searches identified 997 potentially relevant articles. Of these, 20 were identified as relevant for inclusion in the systematic review[15,16,12,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33] (see Figure 1). A further two apparently relevant studies[34,35] were not available within the study timescale.

Figure 1 Adverse effects: summary of study selection and exclusion: electronic literature searches



A further 14 included studies were identified from citations.[36,37,38,39,40,41,42,43,44,45,46,47,48,49] This large number reflects both the recognised difficulty of devising appropriate search strategies for systematic reviews of adverse effects and also the limited time available for this review, as a result of which it was not possible to refine the search strategy and rerun the searches. Consequently, it is possible that some relevant studies may not

have been identified either by the electronic searches or subsequently from citations.

In this report, we first review the evidence relating to the overall prevalence of adverse effects in patients taking oral alendronate, etidronate or risedronate, and then summarise the evidence for specific categories of adverse effect.

General adverse effects: the evidence from randomised controlled trials specifically designed to assess adverse effects

Four randomised trials were identified which were designed specifically to assess bisphosphonate tolerability. These were:

- Two 12-week studies of weekly alendronate (70 mg) in ambulatory, community-dwelling men and postmenopausal women with osteoporosis[19,22]
- One 8-week study of daily alendronate (10 mg) in women who had discontinued alendronate therapy at least 30 days prior to study entry because of gastrointestinal symptoms judged by the investigator to be treatment-related[27]
- One 12-week study of daily risedronate (5 mg) in postmenopausal women who had discontinued daily alendronate (10 mg) in the first 12 weeks of treatment because of upper gastrointestinal symptoms, but who had been free of those symptoms for at least two weeks.[50]

Eisman et al excluded from their study patients with a history of severe oesophagitis or oesophageal ulcer due to previous bisphosphonate use; however, they did not exclude patients with other gastrointestinal disorders, and permitted the use of NSAIDs. They considered their study population to be representative of patients who might be prescribed alendronate in clinical practice. They found no statistically significant differences between the alendronate and placebo groups in relation to adverse events or discontinuations for upper GI adverse events. Two patients experienced an upper GI event which was considered serious: one in the alendronate group (nausea and vomiting) and one in the placebo group (oesophageal ulcer).[19]

To be representative of patients who would be considered for once-weekly alendronate in normal clinical practice, Greenspan et al included approximately equal numbers of prior users of daily oral bisphosphonates and patients who were bisphosphonate-naïve, stratifying randomisation by prior bisphosphonate use. In line with the product label, they excluded patients with severe oesophagitis, oesophageal ulcer, stricture, or achalasia, for whom oral bisphosphonates were contraindicated; however, they did not exclude patients with a history of other upper GI tract disorders or who had previously been intolerant of daily bisphosphonates. They permitted prior or current use of NSAIDs, proton pump inhibitors, histamine receptor antagonists, aspirin, or glucocorticoids. At study entry, approximately 55% of patients were using NSAIDs or aspirin, and approximately 15% were using either proton pump inhibitors or histamine receptor antagonists. Again, there were no statistically significant differences in the incidence of upper gastrointestinal adverse events between the alendronate and placebo groups either as a whole or in

the bisphosphonate-naïve or prior bisphosphonate subgroups.[22] A post-hoc subgroup analysis found that alendronate was not associated with an increased risk of upper GI adverse events in the 222 patients who received study medication and also used an NSAID or aspirin for at least 7 consecutive days during the study period.[51]

Miller et al rechallenged women who had discontinued alendronate therapy because of drug-related GI symptoms. 29.5% of alendronate group and 30.1% of the placebo group used either a proton pump inhibitor or a H2-receptor blocker during the study; in most patients (alendronate 18/26, placebo 24/26), use of these agents had begun before enrollment and continued unchanged throughout the study period. During the study, 33.0% of the alendronate group and 29.8% of the placebo group used aspirin or an NSAID. 24 patients in each group (alendronate 27.3%, placebo 28.6%) experienced an upper GI adverse event within 8 weeks; only one of these (gastritis in a placebo recipient) was serious. 15% (13/88) of patients in the alendronate group and 17% (14/84) in the placebo group discontinued treatment because of upper GI adverse events.[27]

In the study by Adachi et al, rates of discontinuation due to upper GI adverse events and the distribution of adverse events was said to be similar in the risedronate and placebo arms. One serious adverse event occurred in each arm, but both were considered unrelated to study treatment. 80% of the risedronate group completed 12 weeks of therapy and took at least 80% of the study medication during that period. Completion rates were similar among patients with a history of gastrointestinal disease at study entry, prior use of acid suppressant drugs, and concomitant use of NSAIDs.[50]

Arguably, none of these studies was long enough for a full assessment of adverse events. However, Eisman et al argued that a 12-week study was adequate since prior clinical experience suggested that most upper GI adverse events occurred within the first three months of alendronate therapy,[19] while Greenspan et al decided to undertake a 12-week study because, in the 12-month study by Pols et al,[52] approximately 50% of the upper GI adverse events observed at 12 months had been reported by three months.[22] On the other hand, Miller et al admitted that their study was flawed because of its brevity: although the median time from first taking alendronate to the onset of previous upper GI complaints in the study participants was 31 days, the median time to discontinuation in the first exposure was 91 days (13 weeks), and therefore, had the study continued for longer than 8 weeks, more discontinuations might have occurred. Moreover, they enrolled women who were willing to attempt rechallenge with alendronate despite an earlier upper GI adverse event, but it is likely that those women who had suffered the most severe initial reactions would have been unwilling to volunteer for the trial. [27] Finally, the study by Adachi et al of risedronate in women intolerant of alendronate[50] was very small (67 patients were randomised), and no power calculation was mentioned. It therefore seems likely that the study was underpowered in relation to its primary outcome measure, rates of discontinuation due to upper gastrointestinal adverse events.

General adverse effects: the evidence from unrandomised studies

Prescription-event monitoring studies

Prescription-event monitoring studies have been carried out in England for alendronate[12,26] and risedronate.[16] Usable data were gathered on 11,916 of 22,131 patients prescribed alendronate, primarily for osteoporosis, by their general practitioners between October 1995 and January 1997,[12] and on 13,643 of 26,247 patients prescribed risedronate for osteoporosis by their GPs between September 2000 and June 2002.[16] 336 patients (2.8%) were reported to have had suspected adverse reactions to alendronate[12] and 405 (3.1%) to risedronate.[16] Of the 457 suspected adverse reactions to alendronate reported by the GPs, only 75 (16.4%) were said to have been reported to the Committee on Safety of Medicines.[12]

The incidence of the most commonly reported conditions is set out in Table 1. It is implicit in both studies that conditions are likely to be drug-related if the incidence in the first month of treatment is significantly greater than that in months 2 to 6. On this basis, both alendronate and risedronate appear to be associated with gastrointestinal complaints (including dyspepsia, nausea and vomiting, abdominal pain, diarrhea, constipation) and more general complaints (malaise/lassitude, headache/migraine, rash, dizziness). Alendronate also appears to be associated with dysphagia and asthma/wheezing, and risedronate with myalgia, anorexia, visual defects and oedema. However, in the absence of a placebo arm, there is inevitably some degree of uncertainty.

Table 1: Alendronate[12] and risedronate[16]: incidence of most commonly reported conditions, by treatment period

Condition	Events per 1000 patient-months				ID_1 significantly greater than ID_2	
	First month of treatment (ID_1)		2^{nd} to 6^{th} months of treatment (ID_2)			
	Alend	Rised	Alend	Rised	Alend	Rised
Dyspeptic conditions	32.2	26.9	10.9	8.1	✓	✓
Nausea/vomiting	20.8	20.3	4.7	4.7	✓	✓
Abdominal pain	13.8	8.9	4.1	2.7	✓	✓
Respiratory tract infection	8.6	-	8.7	-		
Respiratory tract infection, lower	-	5.1	-	4.7		
Respiratory tract infection, higher	-	3.7	-	2.6		
Diarrhoea	8.3	9.0	3.1	3.2	✓	✓
Malaise/ lassitude	6.5	6.9	2.5	1.8	✓	✓
Intolerance	6.0	14.3	1.3	2.8	✓	✓
Headache/ migraine	4.9	7.4	2.0	1.9	✓	✓
Gastrointestinal unspecified	4.8	8.9	1.3	1.7	✓	✓
Back pain	4.7	-	3.1	-		
Joint pain	-	4.2	-	2.5		
Myalgia	-	3.7	-	1.6		✓
Constipation	4.0	4.2	1.4	1.8	✓	✓
Rash	3.5	3.7	1.6	1.8	✓	✓
Dysphagia	3.5		1.3		✓	
Urinary tract infection	3.3		2.4			
Asthma/ wheezing	Not stated	-	Not stated	-	✓	
Dizziness	Not stated	-	Not stated	-	✓	✓
Anorexia	-	Not stated	-	Not stated		✓
Visual defect	-	Not stated	-	Not stated		✓
Unspecified side effects	-	6.3	-	1.6		✓
Hospital referral, no admission	-	4.8	-	3.4		
Oedema	-	4.4	-	1.6		✓

Rare events considered possibly related to alendronate included hypercalcaemia and dyspnoea (two reports each) and angioedema, erythema multiforme, hypocalcaemia, and chronic obstructive airway disease (one report of each). Four reports of renal failure and three of renal function test abnormalities were also considered possibly to be related to alendronate use.[12] The more common conditions will be discussed below.

Post-marketing surveillance studies

Van Staa undertook a key post-marketing surveillance study of significant suspected adverse drug reactions associated with the use of cyclic etidronate (400 mg/day for 14 days followed by 76 days of calcium supplementation). He drew on world-wide reports either submitted by health professionals to the

manufacturer or published as case reports between 1990, when marketing of the drug began, and September 1997, and estimated reporting rates by dividing the number of spontaneous reports by the number of cycles dispensed, as a proxy for the cumulative world-wide exposure to this etidronate regimen.[31] Van Staa also drew on published peer-reviewed clinical studies[31] and on a large epidemiological study which he and his colleagues undertook comparing 7977 patients taking cyclical etidronate in routine UK clinical practice with age-, gender- and practice-matched controls.[53] The findings of both of Van Staa's studies are reported below by category of adverse event.

Other cohort studies

Four studies were identified which studied cohorts of women commencing treatment with daily alendronate:

- women members of the Kaiser Permanente Medical Care Program who had begun treatment with daily alendronate (10 mg), with or without recent or concomitant NSAIDs or oral glucocorticoid agents, between October 1995 and October 1996[54]
- consecutive women treated with daily alendronate (10 mg) in a hospital department[23]
- women receiving daily alendronate (10 mg) for primary osteoporosis in the USA[25]
- women enrolled in the Kaiser Foundation Health Plan in Northern California who agreed to participate in a telephone survey 4 to 12 months after they had initiated alendronate therapy for osteoporosis.[30]

A retrospective review of the medical records of patients aged 65-89 who had been prescribed oral bisphosphonates for a diagnosis of osteoporosis or osteopenia at a US university hospital between January 1999 and March 2003[55] was excluded because only 114 of the 181 patients initiated bisphosphonate treatment during the study period; the remaining patients (37%) had been on bisphosphonate therapy for some time and were presumably therefore known to tolerate it.

The key findings of these studies are summarised in Table 2.

Table 2: Cohort studies of women receiving alendronate: key findings

Study	Country	Number in cohort	Duration of follow-up	Number reporting side effects	Number reporting GI side effects	Number discontinuing therapy because of side effects
Ettinger et al 1998[54]	USA	812	mean 8 months (range 2.0-15.3 months	not reported	32.7%	Self-report: 28.5% Prescription records: 34.9%
Kelly & Taggart 1997[23]	Northern Ireland	77	9-66 weeks	24 (31%)	not clear	20 (26%)
Kyriakidou-Himonas 1997[25]	USA	157	1 year	32 (20%)	15%	19 (12%)
Tosteson 2003[30]	USA	366	4-12 months	86 (24%)	50 (14%)	70 (19%)

The study by Ettinger et al[54] revealed the highest incidence of gastrointestinal adverse events which alendronate users attributed to therapy, and the highest proportion of women discontinuing that therapy because of those adverse events. All of the women who took part in the survey used some concomitant medications, and 60% did not comply with at least one of the alendronate dosing instructions. However, surprisingly, compliance with all the safety instructions did not affect the risk of experiencing new GI symptoms, although compliance with absorption instructions was associated with a significantly increased risk of such symptoms.

Kelly & Taggart stated that 24 women in their study reported side effects: two had rashes, and the remainder mainly had upper GI problems, especially problems suggesting gastro-oesophageal reflux (dyspepsia 16, heartburn 14, retrosternal pain 9, dysphagia 5, nausea 8, vomiting 3); one developed an oesophageal stricture which required dilatation. Upper GI symptoms developed in seven of the 16 women who lay down after taking alendronate (44%), and six of the 21 (29%) with a history of upper GI disease, two of whom also lay down after taking alendronate.[23] 51 of the 77 women included in this study had previously been treated with cyclical etidronate for a minimum of two years and had tolerated it well. Of this 51, 18 (35%) developed significant side effects with alendronate, compared with six of the 26 women (23%) who had not previously been treated with etidronate. They suffered severe gastrointestinal effects, which resolved when alendronate treatment was stopped.[47]

The population of Kyriakidou-Himonas's cohort study was said to resemble the average woman with osteoporosis and other comorbidities rather than a carefully selected study population. All side effects were considered mild, with the exception of one patient who developed severe heartburn and was found to have an acute oesophageal ulcer after 1 month of alendronate; this patient used to lie down immediately after taking the medication. Gastrointestinal side effects were the most common, heartburn being the major complaint (7%). Other side effects were muscle aches (1.2%), joint pain (1.2%), cough (0.6%), bad taste (0.6%) and itching (0.6%). Although 19 patients discontinued alendronate because of side effects, two then restarted therapy after 6-8

weeks and reported no side effects thereafter. The average period of alendronate use before discontinuation was 3 months.[25]

Tosteson noted that half of the 24% of women receiving daily alendronate who reported side effects, reported that these were very or extremely bothersome.[30]

Thus, these studies suggest that, in a population representative of women likely to be prescribed bisphosphonates for osteoporosis, at least 20% of those prescribed alendronate are likely to suffer adverse events which they attribute to therapy, and the number suffering gastrointestinal adverse events may rise to over 30%.

General adverse effects: the evidence from randomised controlled trials of effectiveness

In the placebo-controlled randomised trials included in our systematic reviews of postmenopausal[7] and steroid-induced osteoporosis, the prevalence of adverse events was generally similar in the bisphosphonate and placebo groups (see Appendix 3). Only one trial, Saag et al's study of alendronate in patients requiring long-term steroid therapy, found a statistically significant excess of patients with upper gastrointestinal adverse events in the bisphosphonate arm at 48 weeks.[56] Most studies reported high levels of upper gastrointestinal adverse events in their placebo arms, reaching 47% in women without prior fracture enrolled in the Fracture Intervention Trial even though women with recent peptic ulcers or dyspepsia requiring daily therapy had been excluded.[57]

Two authors subsequently undertook further analysis of pooled data from a number of placebo-controlled trials of risedronate. Taggart et al pooled data from nine phase 3 clinical trials which compared risedronate 5mg/day with placebo for the prevention or treatment of postmenopausal or steroid-induced osteoporosis,[58] while Steinbuch et al[59] undertook a retrospective cohort study of the intention-to-treat population of three studies of risedronate in postmenopausal osteoporosis or osteopenia.[60,61,62] None of the trials reviewed in these studies excluded patients because of previous or active GI tract disease, and all permitted the use of medications such as aspirin and NSAIDs which have the potential to irritate the gastrointestinal tract.

Taggart et al's analysis included 10,068 patients who received at least one dose of placebo or 5 mg risedronate. 61.0% had a history of GI tract disease, and 38.7% had active GI tract disease such as heartburn, oesophagitis, or oesophageal, gastric, or duodenal ulcers. Approximately 56% were using aspirin or NSAIDs at study entry, and 21.9% of the placebo group and 20.8% of the risedronate group used them on three or more days each week during the study. Despite this, no excess of upper GI tract adverse events, or of withdrawals because of such events, was seen in patients taking risedronate (upper GI tract events: risedronate group 29.8%, placebo group 29.6%, RR 1.01, 95% CI 0.94-1.09, p=0.77; withdrawal because of upper GI adverse events: risedronate group 3.3%, placebo group 3.0%). In both groups, the risk

of an upper GI tract adverse event was increased by the presence of active GI tract disease, the need for antisecretory therapy, and the use of aspirin or NSAIDs. However, in patients who had active oesophageal disorders or peptic ulcers at study entry, risedronate did not result in a worsening of these conditions or an increase in the frequency of upper GI tract adverse events.[58]

Steinbuch et al[59] limited their cohort study to the North American participants in the three studies because of the availability of national death indices in the US and Canada. They found no difference between the risedronate and placebo groups in all-cause mortality, cancer mortality, or mortality from cancer of the lung or gastrointestinal tract. A statistically non-significant reduction in deaths from cardiovascular causes in the risedronate group was largely due to a statistically significant reduction in stroke mortality in the combined risedronate groups (p=0.015).

Gastrointestinal disorders

The evidence summarized above demonstrates that gastrointestinal disorders are the adverse events most commonly reported in connection with alendronate and risedronate therapy. In the PEM study of alendronate, 150 patients (1.3% of the cohort) were reported to have discontinued treatment as a result of oesophagitis. Other reported serious upper GI events included gastric, duodenal and peptic ulceration, gastritis, and duodenitis. However, only nine of the 502 reported deaths for which the cause of death was established were attributed to gastrointestinal causes.[12] The incidence of dyspepsia found in the PEM studies of alendronate and risedronate during the first month of treatment is high compared with prescription monitoring data relating to women aged over 60 prescribed non-gastrointestinal drugs: these show an incidence of dyspeptic symptoms of only 6.0 events per 1000 patient-months in the first month of treatment.[12]

Although the PEM studies found a lower incidence of dyspepsia in month 1, at 26.9 events per 1000 patient-months of exposure, with risedronate than with alendronate (32.3 events per 1000 patient-months of exposure), the investigators suggest that this may be due at least in part to a greater awareness of the need to adhere to the dosing instructions at the time when risedronate was introduced, together with a selection bias towards patients able to follow those instructions, and is not necessarily simply due to a difference in the way the two drugs act on the gastric mucosa.[16] However, a retrospective cohort study carried out by Worley et al suggests that alendronate may be more harmful than risedronate. The investigators compared the occurrence of gastrointestinal events in women aged 65 and older in a US managed care medical and pharmacy claims database who initiated therapy with daily or weekly alendronate (10 mg/d n=1,146; 70 mg/w n=3,221) or daily risedronate (5 mg n=802) between November 2000 and May 2002. After adjusting for age and GI-related events in the 6 months preceding initiation of therapy, alendronate users had a 42% higher risk of incurring a GI event than risedronate users (p=0.016). There was no significant difference between patients taking daily and weekly alendronate.[33]

De Groen et al[17] reviewed computerised databases of postmarketing surveillance, including all reports received by Merck up to 5th March 1996, for "reports of adverse oesophageal reports associated with the use of alendronate in which there were terms suggestive of esophageal irritation". At that date, an estimated 470,000 patients worldwide had been prescribed alendronate for osteoporosis, and 5,000 for Paget's disease. Merck had received 1213 spontaneous reports of adverse effects, of which 199 related to the oesophagus, and 51 patients had suffered oesophageal adverse events classified as serious (ie requiring hospitalisation) (n=34) or severe (n=17). The most common terms used in the reports on these 51 patients were oesophageal ulcer, oesophagitis and erosive oesophagitis. Of the 43 patients for whom information on the timing of symptoms was available, 42 had symptoms within 2 months, and 19 within one week, of starting treatment. It is not clear how many of the patients with oesophageal adverse events were taking a 40 mg daily dose of alendronate for Paget's disease rather than a 10 mg dose for osteoporosis.

Merck subsequently funded a retrospective cohort study to compare the incidence of hospitalisations for gastric or duodenal perforations, ulcers and bleeding among 6432 patients aged 35 years or over in the USA who had been dispensed 10 mg/day alendronate between 1st October 1995 and 30th September 1997, and in two unexposed cohorts, one of 33,176 people matched by age, sex, and health maintenancy organisation, and the other of 9,776 women aged 60 or over who had suffered an osteoporotic fracture. The crude incidence rate of gastroduodenal perforation, ulcer, or bleeding in the alendronate cohort (3.4 per 1000 person-years) was three times that in the non-fracture unexposed cohort (1.1 per 1000 person-years). However, there was no statistically significant difference between the two groups (RR alendronate vs control 1.8, 95% CI 0.8-3.9) after adjustment for age, sex, chronic disease score, recent exposure to prescription NSAIDs or oral corticosteroids, and number of hospitalisations in the year preceding alendronate prescription (or the referent date for the non-exposed group). Ten of the 14 gastroduodenal perforations, ulcers, or bleeding events in the alendronate cohort occurred in the 3863 women aged 60 or over, and 58 similar events occurred in the 9,776 women in the fracture cohort, a relative risk for alendronate of 1.1 (95% CI 0.6-2.3) which remained unchanged after controlling for other factors.[42]

Aki et al undertook a retrospective study in Turkey of 759 postmenopausal women aged under 80 who had taken daily alendronate 10 mg continuously for at least 6 months.[15] 158 (20.8%) had an upper gastrointestinal tract complaint which was thought to be due to alendronate; of these, 32 (20.2%) had to discontinue alendronate therapy, and 47 (29.7%) required additional medication to deal with the gastrointestinal complaints. Although noncompliance with at least one of the safety rules was not associated with a statistically significant difference in the incidence of upper gastrointestinal complaints, such complaints were significantly more common in patients taking antacids, proton pump inhibitors or H2R blockers than in patients who were not (24.8% vs 16.5%). In a one-year post-marketing study summarised

by Graham,[63] Daoud and Licata[41] found that 35% of 128 patients receiving alendronate had gastrointestinal side effects.

Van Staa's studies suggest that cyclical etidronate is associated with much lower risk of gastrointestinal events. Although mild gastrointestinal disturbances such as dyspepsia, nausea, diarrhoea, and constipation have been reported during treatment, the number of spontaneous reports of oesophagitis or oesophageal ulcer is very low at 1 report per 0.9 million prescriptions.[31] The highest quality evidence comes from a retrospective cohort study undertaken by van Staa et al as part of a post-marketing surveillance study of data from June 1987 to June 1995 evaluating the effects of etidronate in clinical practice.[48] They compared the incidence of upper gastrointestinal adverse events in 7977 patients in England and Wales who received one or more prescriptions for cyclical etidronate and two control groups:

- osteoporosis controls: patients with a diagnosis of osteoporosis who were not bisphosphonate users, matched by age, gender and, where possible, medical practice
- non-osteoporosis controls: patients without a diagnosis of osteoporosis, also matched by age, gender and, where possible, medical practice.

The cohorts were not perfectly matched: patients in the etidronate cohort were more likely than those in the other cohorts to have a diagnosis of rheumatoid arthritis, use NSAIDs or corticosteroids during the follow-up period, use H2 antagonists or antacids in the year before study initiation, and visit the GP more frequently in the year before study initiation; these differences were more pronounced between the etidronate cohort and the non-osteoporosis controls. About 44% of the etidronate group were prescribed NSAIDs or aspirin during the follow-up period. There were no statistically significant differences between etidronate takers and osteoporosis controls in the crude incidence of all upper gastrointestinal events (relative rate 0.92, 95% CI 0.78-1.09) or of oesphagitis/oesophageal ulcers, peptic ulcers, and gastritis/duodenitis separately, and the incidence of abdominal pain was significantly lower in the etidronate group (see Table 3). Moreover, after adjustment for risk factors, there were no significant differences between the etidronate and the non-osteoporosis group in terms of the incidence either of all upper gastrointestinal I events together (relative rate 1.12, 95% CI 0.91-1.37) or of oesophagitis/oesophageal ulcers, gastritis/duodenitis, peptic ulceration, or gastrointestinal haemorrhage separately. The incidence of upper gastrointestinal events during NSAID, aspirin, or corticosteroid use was similar in all three groups. Finally, there was no evidence that the rate of gastrointestinal events in etidronate users was higher during the 14 days when etidronate was taken than in the rest of the 90-day cycle.

Table 3: UK retrospective cohort study: crude incidence of upper gastrointestinal adverse events[48]

	Number of cases (rate)		
Event	**Etidronate cohort (n=7977)**	**Osteoporosis controls (n=7977)**	**Non-osteoporosis controls (n=7977)**
All upper GI events	303 (3.0%)	256 (2.8%)	173 (1.8%)
Oesophagitis/ oesophageal ulcers	126 (1.2%)	112 (1.2%)	78 (0.8%)
Peptic ulcers	72 (0.7%)	61 (0.7%)	38 (0.4%)
Gastritis/ duodenitis	125 (1.2%)	99 (1.1%)	64 (0.7%)
Abdominal pain	609 (6.2%)	586 (6.7%)	370 (3.9%)
GI haemorrhage	49 (0.5%)	56 (0.6%)	31 (0.3%)

Delaney et al undertook a retrospective study of the gastrointestinal tolerability of weekly risedronate in all postmenopausal women treated at Brigham and Women's Hospital, Boston, USA, with a 30 mg dose between February 1998 and March 2001 (n=150).[18] Despite the fact that some patients were prescribed weekly risedronate because they had discontinued oral alendronate or etidronate because of gastrointestinal symptoms, or had suffered gastrointestinal symptoms either in the past or at the onset of treatment, only five patients (3%) reported gastrointestinal symptoms over a follow-up period of apparently approximately one year; four of the five discontinued therapy.

Two studies set out to assess the association between bisphosphonate use and gastrointestinal complaints as measured by the uptake of relevant medical care. Roughead et al undertook a case-control study in Australia comparing new users prescribed bisphosphonates (primarily alendronate) in general practice who had no recent histamine 2 receptor antagonist or proton pump inhibitor use (n=1753) with matched controls who were prescribed other medications (n=3341). They found that, after controlling for previous NSAID use, new bisphosphonate users were significantly more likely than controls to require acid suppression agents (histamine 2 receptor antagonists, proton pump inhibitors or antacids) within 6 weeks of their prescription (odds ratio 3.21, 95% CI 2.02-5.11).[28]

As part of Ettinger et al's study, mentioned above, of women members of the Kaiser Permanente Medical Care Program, the investigators studied the rate of acid-related upper gastrointestinal disorders (ARD) (peptic ulcer, gastric ulcer, gastro-oesophageal reflux disease, gastritis, oesophagitis, dyspepsia, nausea, vomiting and abdominal pain) in this population.[20] 812 women (median age 70) were followed for a mean of 10 months following prescription of alendronate. During this period, 100 women (12.3%) received medical care for 135 ARD events, 19 of which required hospital admission. ARD was diagnosed at a rate of 28.5 events per 100 person-years. Use of NSAIDs was associated with a significantly increased risk of ARD. Alendronate users had 1.6 times as many ARD events as women aged 50 or older in the general health plan population (95% CI 1.1-2.3). Alendronate users who took NSAIDs (34% of the total) were at 70% higher risk of ARD than those who did not take NSAIDs (RR 1.7, 95% CI 1.1-2.6), and the 10% who had a prior ARD diagnosis were also at substantially increased risk of ARD compared with

those who had not had a prior ARD event (RR 3.0, 95% CI 1.9-4.9).[20] Despite previous claims that oesophageal symptoms were associated with failure to adhere to the patient safety dosing instructions,[17] Ettinger et al found that such failure did not increase the risk of ARD.[20]

In conclusion, the most reliable evidence relating to the incidence of gastrointestinal side effects associated with oral bisphosphonate use is probably that from the UK PEM studies. These studies report a higher rate of oesophageal events than identified by post-marketing surveillance. This is not surprising since PEM prompts physicians to report possible adverse effects, while surveillance which relies on spontaneous reporting is recognised to under-report the events of interest. Moreover, while individual PEM studies do not have a control group, the incidence of gastrointestinal effects in the first month of alendronate or risedronate therapy is approximately five times that seen in comparable patients in other PEM studies receiving other prescriptions. This is consistent with the finding of the case-control study by Roughead et al that new bisphosphonate users are three times as likely as controls to require prescribed acid suppression agents. The incidence of gastrointestinal side effects appears to be highest with alendronate and lowest with etidronate.

Musculoskeletal and connective tissue disorders

Reports of musculoskeletal and connective tissue disorders are rare in connection with bisphosphonate use. Worldwide, generalised osteomalacia has been reported in patients treated with cyclic etidronate at a rate of 1 report per 3.6 million treatment cycles; in all cases, the patients had received fewer than four cycles of etidronate and there were alternative possible aetiologies.[31] The UK epidemiological study conducted by van Staa et al found a very low incidence of osteomalacia which was similar in etidronate-takers and controls.[53] Worldwide reports of lower extremity stress fractures associated with cyclical etidronate are similarly low, at 1 per 2.2 million treatment cycles, and again the UK epidemiological study found comparable rates in etidronate-takers and controls.[31]

Osteonecrosis of the jaws has been reported in patients taking daily alendronate (10 mg) for osteoporosis, although 94% of cases of such osteonecrosis associated with bisphosphonate use have occurred in patients receiving intravenous pamidronate or zolendronic acid, generally in connection with multiple myeloma or metastatic breast cancer. The risk of such osteonecrosis generally increases with length of bisphosphonate treatment, but one case occurred in an osteoporosis patient who had taken alendronate for only two years.[49]

Aki et al's retrospective study found that three of 759 postmenopausal women aged under 80 who had taken daily alendronate 10 mg continuously for at least 6 months suffered diffuse bone and joint pain which appeared to be attributed to alendronate use.[15]

A case of a woman with postmenopausal osteoporosis who suffered severe diffuse myalgia and symmetrical polyarthritis 12 hours after each intake of once-weekly alendronate appears to be the first such case reported.[21] In this context, it may be relevant that the PEM study of risedronate found a significantly higher rate of myalgia in the first month of treatment compared with months 2-6.[16]

Neurological disorders

Neurological disorders have very occasionally been reported in connection with bisphosphonate therapy. There have been rare spontaneous reports of hallucinations, generally beginning shortly after starting treatment with cyclic etidronate and disappearing after discontinuation. So, for instance, Burnet and Petrie reported confusion and olfactory, auditory and visual hallucinations in a 74-year old woman after one week of therapy; the hallucinations ceased within 48 hours of discontinuation of etidronate and recurred on rechallenge.[38] Such hallucinations have been reported at a rate of one per 825,000 treatment cycles.[31]

Coleman et al also reported auditory hallucinations and visual disturbances in a 79-year old woman following a change from daily alendronate, which she had been taking for over 2 years, to weekly alendronate. These hallucinations and visual disturbances, which occurred on numerous occasions a few hours after taking the weekly dose, ceased on discontinuation of alendronate therapy, and seemed to be directly related to the once-weekly alendronate formulation.[40]

Wolffenbuttel and van der Klauw reported that three patients being treated with cyclical etidronate for osteoporosis developed mood, concentration and memory problems after some months or years; these problems diminished within several weeks of drug withdrawal, and reappeared after rechallenge. One of the patients had similar complaints with pamidronate and another with alendronate.[32]

Skin and subcutaneous tissue disorders

The UK epidemiological study did not find an increased risk of erythematous skin conditions among patients taking cyclic etidronate compared with controls.[31] However, the PEM studies found that both alendronate and risedronate were associated with significantly higher rates of rash in the first month of treatment compared with months 2-6.[12,16] Kelly & Taggart noted that two of 77 women starting alendronate therapy developed rashes which resolved when they stopped taking the drug.[23]

Ocular disorders

Bisphosphonates have been associated with ocular disorders, some of which are potentially sight-threatening.[46,43] Following reports of ocular adverse events associated with intravenous pamidronate,[64] Fraunfelder and Fraunfelder collected data on bisphosphonates and adverse ocular events

from the spontaneous reporting systems of the United States National Registry of Drug-Induced Ocular Side Effects and Food and Drug Administration, and from the World Health Organisation (see Table 4).[44] These data suggest that alendronate and risedronate are, rarely, associated with serious adverse ocular events (in particular, uveitis, scleritis and episcleritis). It is not clear to what extent the events overlap with those reported to Health Canada[46] or to the Australian Adverse Drug Reactions Advisory Committee.[36]

Table 4: Adverse ocular events associated with bisphosphonates reported to United States National Registry of Drug-Induced Ocular Side Effects and the Food and Drug Administration, and the World Health Organisation[44]

Adverse event	Alendronate	Clodronate	Etidronate	Pamidronate	Risedronate
Abnormal or blurred vision	94	5	18	24	2
Ocular pain	33	-	-	16	-
Nonspecific conjunctivitis	30	-	3	72	7
Uveitis	19	-	-	66	-
Scleritis	4*	-	-	19	1
Photophobia	-	1	-	-	14
Episcleritis	-	-	-	-	10

* including 3 cases reported by Mbekeani et al[65]

In the UK epidemiological study of Van Staa et al,[53] iritis, uveitis or scleritis were recorded in 27/7977 (0.3%) of the etidronate cohort. Although only two patients had no possible aetiology other than etidronate use, scleritis was significantly more common in the etidronate cohort than in the osteoporosis cohort (adjusted RR 12.04, $p<0.05$).

The alendronate PEM study noted that 391 eye events were reported in a cohort of 11,916 patients, but that follow-up information was not obtained to allow the assessment of causality.[12] In the risedronate PEM study, however, 313 patients (2.3%) were reported to have suffered 359 ophthalmological events during the study period, 265 of them (1.9%) whilst undergoing risedronate treatment.[37] 30 patients (0.2%) reported such events as a reason for stopping risedronate. For 181 events, sufficient information was reported to exclude an association with risedronate, but further information was sought on the remaining 178 events. 118/178 questionnaires were returned with enough information to enable causality assessment, enabling 19 events in 19 patients to be assessed as possibly (n=17) or probably (n=2) related to risedronate therapy. In most cases, onset was over 1 month after treatment initiation (median 42 days). With the exception of one case of episcleritis, all ophthalmological adverse events resolved completely after discontinuing risedronate.[16] Although the incidence of ophthalmological events identified by this PEM study was said to be lower than that seen in clinical trials, this may be due, at least in part, to the fact that causality could only be assessed for 66% of the events: for the remainder, either the questionnaire was not returned or the information supplied was inadequate.[37]

Respiratory disorders

Respiratory disorders have occasionally been associated with bisphosphonate therapy. In patients taking cyclical etidronate, asthma has been spontaneously reported at a rate of one report per 350,000 treatment cycles, typically relating to the exacerbation (mostly mild) of existing asthma, usually in the first 14 days (ie the etidronate phase) of the first treatment cycle. The UK epidemiological study did not find an increased risk of asthma or chronic airway disease among patients taking cyclic etidronate compared with controls.[31] However, the alendronate PEM study noted that reports of asthma or wheezing were significantly greater in the first month of therapy than in months 2-6.[12]

Hypersensitivity disorders

Kimura et al reported one instance of red papules and petechiae associated with daily alendronate,[24] and Kontoleon et al published the only reported case of urticaria associated with alendronate.[45] Delaney et al reported, in postmenopausal women taking weekly risedronate, one case of skin rash with hives over both forearms which resolved once risedronate was discontinued, and one case of moderate flu-like symptoms which resolved after one month on therapy.[18]

One case has also been reported of fatal toxic epidermal necrolysis with associated pancytopenia in a patient with a history of autoimmune disorders 7 days after starting cyclic etidronate therapy. The patient had been admitted to hospital with severe anaemia which required a blood transfusion at around the same time as starting etidronate therapy. In addition, one case of pancytopenia associated with etidronate, and one case of aplastic anaemia associated with etidronate plus calcium, have been reported to the Committee on Safety of Medicines.[39]

Adverse events: discussion

The majority of adverse events associated with oral bisphosphonate therapy relate to the gastrointestinal tract. Although clinical trials indicated that alendronate had a gastrointestinal tract safety profile similar to placebo, in post-marketing experience it has been associated with a higher than expected occurrence of gastrointestinal tract adverse events which in some cases (for instance, oesophageal ulceration) were more severe than in clinical trials. This difference is likely to be due, at least in part, to the fact that the alendronate clinical trials generally excluded patients with a history of upper gastrointestinal disease (see Appendix 3), whereas the contraindications for the normal clinical use of alendronate only include achalasia and other motility disorders of the oesophagus, oesophageal stricture, or pre-existing severe reflux oesophagitis.[66]

It is also notable that the high level of reporting of gastrointestinal adverse events both in patients taking oral bisphosphonates in real life and in the placebo arms of the clinical trials may be due to reporting bias attributable in

part to a heightened awareness of the potential for gastrointestinal adverse events with such medication (a nocebo effect[67])because of the dosing instructions and product information leaflet. Cryer and Bauer cite in support of this theory two one-year trials which randomised patients to oral alendronate, matching placebo, or nasal calcitonin. In these trials, around 17% of both the alendronate and the placebo groups reported drug-related upper gastrointestinal tract adverse events, compared with only 1% of the calcitonin group.[8] Plausibly, therefore, the high numbers of gastrointestinal adverse events reported in the placebo as well as the intervention arm of the bisphosphonate trials reflects the combination of a relatively high background incidence of upper gastrointestinal tract complaints in osteoporotic patients with an increased sensitivity to such complaints and an increased likelihood that they will be reported to a healthcare professional, rather than a straightforward causal relationship to bisphosphonate therapy.

The part played by non-compliance with the dosing instructions in the development of gastrointestinal adverse events is not entirely clear. Some case reports suggest a direct connection between failure to follow the safety instructions and adverse events, but other patients have suffered very similar symptoms despite compliance.[63] In their post-marketing surveys of alendronate, de Groen[17] and Ettinger et al[54] found that, of the patients who developed new gastrointestinal symptoms and for whom information was available on both water intake and posture, 39% in de Groen's study and 44% in the study by Ettinger et al[63] did so despite compliance with the safety instructions. Moreover, Ettinger et al found that compliance with absorption instructions was associated with a significantly higher incidence of new gastrointestinal symptoms.[54]

PERSISTENCE WITH ORAL BISPHOSPHONATE THERAPY

INTRODUCTION

Definition of persistence

Persistence refers to the length of time for which a patient continues to take a prescribed medication.[68] It is often defined as the percentage of patients still on medication at a given time without any gap in medication-taking of 30 days or longer.[69] Persistence is generally measured indirectly, using methods such as patient self-reporting, pill counts, or review of prescription records and claims. None of these methods are ideal, as they depend on the reliability of self-reporting, or on the assumption that dispensed medication has been used by the patient.[70]

Persistence is distinct from both compliance, which is defined as taking the drug consistently as prescribed by the clinician[69] (in the case of oral bisphosphonates, at the right time, with the right amount of water, in the correct posture etc), and adherence, which has been defined as a combination of compliance and persistence.[69] It is recognised that, for a number of reasons, persistence is likely to be substantially better in clinical trials than in community settings.

The decision to persist with prescribed medication is multifactorial. Factors which influence the decision include:

- perception of benefits
- perception of risks
- inconvenience
- economic burden.

The weight carried by each of these factors in the final decision varies from person to person. However, persistence has been found to be lower:

- if the medical regimen is complex
- if the disorder being treated is asymptomatic (as in osteopenic and some osteoporotic patients)
- if the treatment is long-term
- if there are several troublesome side effects.[29]

Persistence with prescribed medication: hierarchies of evidence

As with adverse events, the traditional hierarchy of clinical evidence used in the evaluation of clinical efficacy is not the most appropriate for the study of persistence, not least because clinical trials often involve selection and screening processes which exclude those potential participants who are perceived to be less likely to persist with the study medication. We wished to identify studies which assessed persistence with oral alendronate, etidronate or risedronate in normal clinical use. Consequently, although this report briefly summarises the persistence data relating to the placebo-controlled studies identified in our systematic reviews of RCTs which report fracture outcomes in postmenopausal[7] and steroid-induced osteoporosis, it will also draw on other study types.

Persistence may be influenced by different healthcare systems, as they may affect factors such as the cost of the medication to the patient. The most relevant evidence is therefore that drawn from UK studies. We have excluded studies, such as that by Liel et al,[71] which focus on the effect on persistence of changing the financial context.

SYSTEMATIC REVIEW OF PERSISTENCE WITH ORAL ALENDRONATE, ETIDRONATE OR RISEDRONATE THERAPY

METHODS FOR REVIEWING PERSISTENCE WITH ORAL ALENDRONATE, ETIDRONATE OR RISEDRONATE THERAPY

Search strategy

The search aimed to identify all literature relating to persistence with medication in patients prescribed oral alendronate, etidronate or risedronate for the prevention or treatment of osteoporosis. The search was conducted in May 2006.

Sources searched

It was only possible to search one electronic bibliographic database (Medline) within the study timescale (for the search strategy, see Appendix 4). No language, date or study-type restrictions were applied to the search. The reference lists of relevant articles were handsearched.

Inclusion criteria

- Population: adults requiring therapy for the primary or secondary prevention of osteoporotic fracture
- Intervention: oral alendronate, etidronate or risedronate
- Reported outcomes: persistence

Exclusion criteria

- Population: children and adolescents, adults taking bisphosphonates secondary to cancer or transplantation, healthy adults with normal bone mineral density
- Intervention: oral alendronate, etidronate or risedronate taken in conjunction with other antiosteoporotic drugs such as fluoride
- Study type: RCTs of effectiveness, endoscopy studies.

Sifting

The references identified by the literature searches were sifted in three stages, being screened for relevance first by title and then by abstract; studies which appeared from their abstracts to be relevant were then read in full.

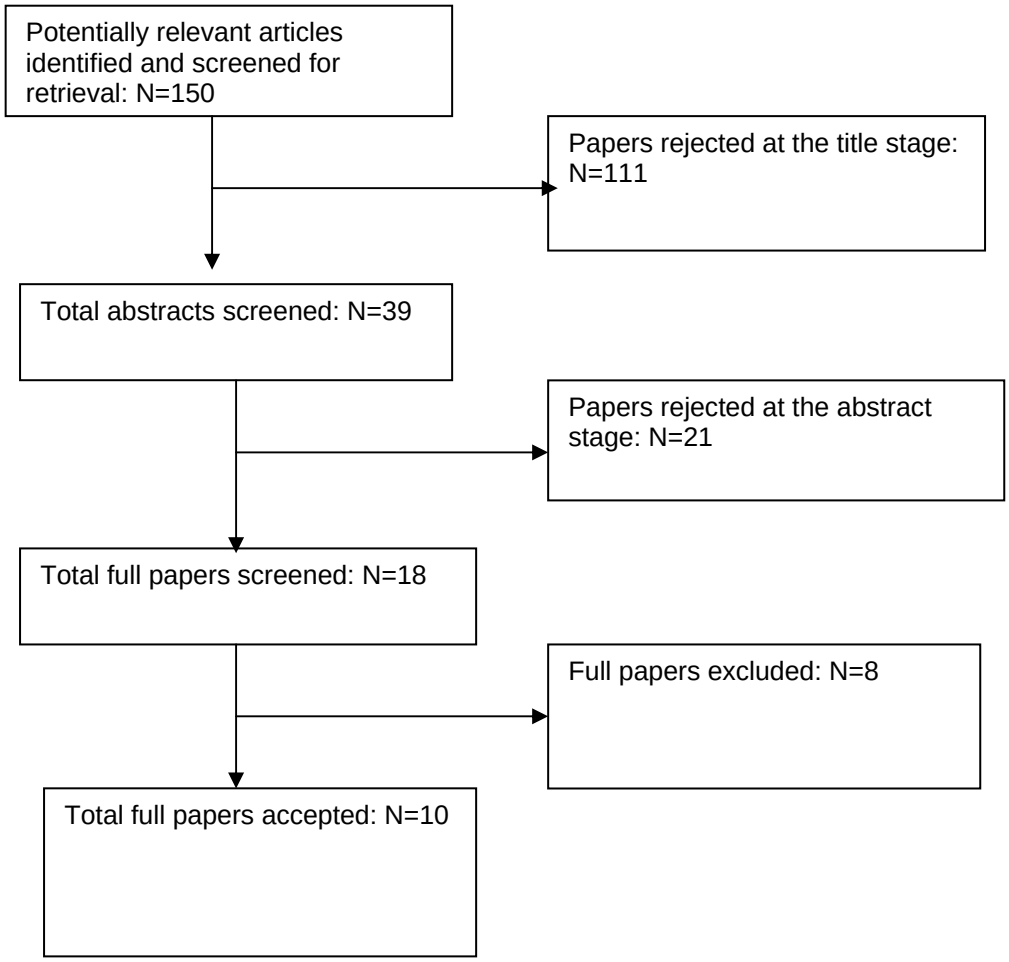
RESULTS

QUANTITY OF RELEVANT RESEARCH

Number of relevant studies identified

The electronic literature searches identified 150 potentially relevant articles. Of these, ten articles were identified as relevant for inclusion in the review[72,73,74,75,76,29,77,30,78,79] (see Figure 2).

Figure 2 Persistence with oral bisphosphonates: summary of study selection and exclusion: electronic literature searches



A further five relevant studies[16,12,80,81,82] were identified by the adverse events search reported above, and two studies[83,84] were identified from citations.

Two further studies[85,86] which were identified from citations could not be included as they were not available within study timescale. The study by Yood et al[87] was excluded as it was not clear at what time point persistence was assessed in patients taking bisphosphonates.

Persistence with oral bisphosphonate therapy: the evidence from randomised controlled trials of effectiveness

Table 5 summarises the evidence on persistence from the placebo-controlled studies identified in our systematic reviews of RCTs which report fracture outcomes in postmenopausal[7] and steroid-induced osteoporosis. It is clear from this table that, even in randomised trials, persistence with therapy declines over time.

Table 5: RCTS reporting persistence: percentage of patients in bisphosphonate group still taking bisphosphonate therapy, by year

Study	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Daily alendronate for postmenopausal osteoporosis						
AOPS[88]	~89	~72	~70			
Bone 2000[89]	NR	74				
EPIC Study[90]	NR	NR	NR	NR	NR	50
Fracture Intervention Trial: women with pre-existing fractures[91]	NR	NR	89			
Fracture Intervention Trial: women without pre-existing fractures[57]	NR	NR	NR	81		
Liberman 1995[92,93]	92	89	84			
Lindsay 1999[94]	95					
Pols 1999[52]	88					
Rossini 1994[95]	100					
Cyclical etidronate for postmenopausal osteoporosis						
Herd 1997[96]	NR	85				
Meunier [97]	NR	89				
Montessori[98]	NR	NR	87			
Pouilles 1997[99]	NR	83				
Storm[100]	NR	NR	61			
Watts 1990[101]	NR	83				
Cyclical etidronate for steroid-induced osteoporosis						
Adachi 1997[102]	82					
Cortet 1999[103]	98					
Geusens 1998[104]	NR	72				
Jenkins 1999[105]	87					
Pitt 1998[106]	NR	85				
Roux 1998[107]	88					
Daily risedronate for postmenopausal osteoporosis						
Brown[108] (5 mg dose)	84					
Clemmesen 1997[109] (2.5 mg dose)	NR	66				
Fogelman 2000[110] (5 mg dose)	NR	78				
Harris 1999[60] (5 mg dose)	NR	NR	60			
McClung 2001[62] (2.5 or 5 mg dose)	NR	NR	51			
Mortensen 1998[111] (5 mg dose)	86	46				
Reginster 2000[112] (5 mg dose)	82	NR	62			
Weekly risedronate 35 mg for postmenopausal osteoporosis						
Brown[108]	81					
Daily risedronate for steroid-induced osteoporosis						
Cohen 1999[113] (5 mg dose)	82					

NR - not reported

The FIT trial found that discontinuation of the study medication was greatest in the first month post-randomisation: 4.8% of participants had withdrawn at 3 months, and 11.1% at 12 months.[114]

Persistence with oral bisphosphonate therapy: the evidence from unrandomised studies

Prescription-event monitoring studies

The most relevant evidence for persistence with oral bisphosphonate therapy comes from the UK PEM studies of alendronate and risedronate. 2920 of the 11,916 patients prescribed alendronate by general practitioners (24.5%) appeared to have discontinued therapy within a year. The two most common reasons for stopping treatment were dyspeptic conditions (756, 6.3% of the total cohort) and noncompliance (365, 3.0% of the total cohort).[12] 8,245 of 11,742 patients (70.3%) whose treatment status was recorded were still being prescribed risedronate after 6 months.[16]

Table 6: Persistence with bisphosphonate use in new users

Study	No of patients for whom data available	Country	Bisphosphonate used	Persistence			
				6 months	1 year	2 years	3 years
Biswas 2003[12]	11,916	England	Alendronate		75%		
Barrera 2005[16]	11,742	England	Risedronate	70%			
Hamilton 2003[80]	219	Northern Ireland	Risedronate		78% at 24-60 weeks		
Papaioannou 2003[76]	477	Canada	Alendronate		77%	70%	64%
Papaioannou 2003[76]	1196	Canada	Etidronate		90%	81%	72%
Sebalt 2000[84]	1003	Canada	Alendronate	86%	80%		
Sebalt 2000[84]	1176	Canada	Etidronate	94%	88%		
Hejdova 2005 [74]	40	Czech Republic	Daily alendronate		80%		
Ringe 2002[82]	9188	Germany	Daily risedronate	88%			
Segal 2003[29]	115	Israel	Daily alendronate	82%			
Penning-van Beest 2006[81]	946	Netherlands	Daily alendronate		35%		
Penning-van Beest 2006[81]	339	Netherlands	Weekly alendronate		52%		
Penning-van Beest 2006[81]	678	Netherlands	Etidronate		30%		
Penning-van Beest 2006[81]	161	Netherlands	Daily risedronate		42%		
Turbi 2004[78]	426	Spain	Daily alendronate		74%		
Cramer 2005[73]	2010	USA	Daily alendronate or risedronate		32%		
Cramer 2005[73]	731	USA	Weekly alendronate		44%		
Ettinger 1998[54,20]	812	USA	Daily alendronate	65%	54%		
Ettinger & Gallagher 2004[115]	not stated	USA	Daily bisphosphonate; new users only		16%		
Ettinger & Gallagher	not stated	USA	Weekly bisphosphonate; new		33%		

2004[115]			users only				
McCombs 2004[75]	3720	USA	Bisphosphonates		24%		
Tosteson 2003[30]	366	USA	Daily alendronate		81% at 4-12 months		
Daoud 1997[41] summarised by Graham 2002[63]	128	Not specified	Alendronate		62%		

The studies by Barrera, Biswas, Cramer, Ettinger, Ettinger & Gallagher, McCombs, Papaioannou, Penning-van Beest, and Sebaldt et al summarised in Table 6 above used prescription records as the measure of persistence. They are therefore likely to overestimate persistence with therapy as this method does not allow for any interval between discontinuation of therapy and failure to refill a prescription. Although in many cases this period will be less than that covered by the last prescription, it cannot take into account patients who, for whatever reason, continue to refill the prescription even though they do not intend to take the medication.

The apparent preference for etidronate rather than alendronate seen in the Canadian studies[76,84] may have been unduly influenced by reasons of cost: etidronate, but not alendronate, was covered for seniors by the provincial reimbursement plan. However, Sebaldt et al found that, beyond 6 months after initiation of therapy, the rate of discontinuation was the same for both drugs, at 1% per month.[84]

A number of studies suggest that the use of weekly rather than daily bisphosphonates regimens may improve persistence. Two short crossover randomised trials [83,77] identified that postmenopausal women with osteoporosis preferred weekly to daily alendronate therapy and felt they would be more willing to take it long-term. In an uncontrolled Israeli patient preference study, 3710 postmenopausal women who had previously been treated with daily alendronate were treated for 12 weeks with weekly alendronate.[79] At 12 weeks, 99% preferred weekly to daily alendronate, and 98% of the 3428 patients who completed the study wanted to continue with weekly alendronate, including 173 of the 223 patients (77.6%) who had previously discontinued daily alendronate due to intolerance. Finally, two unpublished surveys of a total of 690 patients apparently found that 79% of those taking daily bisphosphonates felt that once-weekly dosing would increase their likelihood of complying with treatment.[116]

The evidence of these studies is consistent with that of the observational studies summarised in Table 6. In the study by Segal et al, 6 of the 21 patients who discontinued daily alendronate continued with weekly alendronate.[29] Penning-van Beest [81] found that persistence at one year was similar with daily alendronate, etidronate and risedronate, but significantly higher with weekly than with daily alendronate (52% vs 35%, RR 1.56, 95% CI 1.32-1.85). Similarly, Ettinger and Gallagher[115] found that, in both old and new users, persistence at one year was significantly more likely with weekly than with daily bisphosphonates (new users 33,4% vs 15.7%, $p<0.0001$; continuing users 58.5% vs 39.0%, $p<0.0001$).

Persistence with oral alendronate, etidronate and risedronate therapy: discussion

The evidence from randomised trials suggests that persistence with oral alendronate, etidronate and risedronate therapy is over 80% at one year, but may fall as low as 50% at three years (see Table 5). However, the UK PEM studies, whose findings are likely to be more representative of normal clinical

practice, found that persistence with daily risedronate was only 70% at six months[16] and with daily alendronate was 75% at one year.[12] Moreover, these figures only relate to patients for whom the prescribed bisphosphonates were actually dispensed. Cole et al found that, in the USA, only 64 (82%) of 78 women recommended alendronate by their physician following a BMD scan accepted that recommendation.[72] Whilst the proportion may be higher in the UK, it is unlikely to be 100%, and therefore the proportion of patients prescribed bisphosphonates who are persistent with therapy is likely to be somewhat lower than the persistence rates seen in the PEM studies.

There is no UK evidence, and very little evidence worldwide, for longer-term persistence with oral bisphosphonate therapy (see Table 6). However, the short-term study by Ettinger et al suggests that many patients who discontinue oral bisphosphonate therapy do so soon after commencing therapy. Of 812 women prescribed alendronate and followed for a mean of ten months, 20.8% had discontinued at two months, and 46.1% by ten months.[20] This, in combination with the data relating to alendronate presented by Papaioannou et al,[76] suggests that the risk of discontinuation diminishes after completing one year of therapy.

Appendix 1: Alendronate, etidronate and risedronate for the prevention and treatment of osteoporosis: licensed application, contraindications and clinical undesirable effects (common effects in bold)

	Alendronate	**Etidronate**	**Risedronate**
Licensed application (ref BNF)	• Treatment of postmenopausal osteoporosis: 10 mg/d or 70 mg/week • Prevention of postmenopausal osteoporosis: 5 mg/d • Treatment of osteoporosis in men: 10 mg/d • Prevention and treatment of corticosteroid-induced osteoporosis: 5 mg/d (10 mg/d in postmenopausal women not receiving HRT)	• Treatment of osteoporosis • Prevention of bone loss in postmenopausal women • Prevention and treatment of corticosteroid-induced osteoporosis In all cases given in 90-day cycle of etidronate 400 mg/d for 14 days followed by calcium carbonate 1.25 g/d for 76 days	• Treatment of postmenopausal osteoporosis: 5 mg/d or 35 mg/week • Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women: 5 mg/d
Contraindications	• Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity to any component of the product • Hypocalcaemia • Renal impairment where GFR is less than 35 ml/min	• Known hypersensitivity to any of the ingredients • Severe renal impairment • Hypercalcaemia or hypercalcuria • Clinically overt osteomalacia • Pregnancy and lactation	• Known hypersensitivity to risedronate sodium or any of its excipients • Hypocalcaemia • Pregnancy and lactation • Severe renal impairment (creatinine clearance <30 ml/min)
Undesirable effects			
Gastro-intestinal disorders	**Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distension, acid**	**Diarrhoea, nausea, flatulence, dyspepsia, abdominal pain, gastritis, constipation, vomiting**; rarely, exacerbation of peptic ulcer with	**Constipation, dyspepsia, nausea, abdominal pain, diarrhoea,** gastritis, oesophagitis, dysphagia, duodenitis, oesophageal ulcer; rarely glossitis,

	regurgitation, nausea, vomiting, gastritis, oesophagitis, oesophageal erosions, melaena; rarely, oesophageal stricture, oropharyngeal ulceration, upper GI perforation, ulcers and bleeding, localised osteonecrosis of the jaw	complications, burning of the tongue	oesophageal stricture
Musculoskeletal and connective tissue disorders	**Musculoskeletal (bone, muscle or joint) pain**; rarely, severe musculoskeletal (bone, muscle or joint) pain	Arthropathies (arthralgia and arthritis), occasional mild leg cramps	**Musculoskeletal pain**
Neurological disorders	**Headache**	**Headache**; rarely, paraesthesia, peripheral neuropathy, confusion	**Headache**
Skin and subcutaneous tissue disorders	Rash, pruritus, erythema; rarely rash with photosensitivity; very rarely, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis		
Eye disorders	Rarely, uveitis, scleritis, episcleritis		Iritis
Hypersensitivity reactions	Hypersensitivity reactions including urticaria and angiodema, transient symptoms as in an acute-phase response (myalgia, malaise, and rarely, fever), typically in association with initiation of treatment	Rarely, hypersensitivity reactions including angio-oedema, urticaria, rash and/or pruritus	Very rarely, hypersensitivity and skin reactions, including angio-oedema, generalised rash, and bullous skin reactions, some severe
Respiratory problems		Rarely, exacerbation of asthma	
Blood disorders	Rarely, symptomatic hypocalcaemia, occasionally severe	Rarely, leucopenia, agranulocytosis and pancytopenia	
Miscellaneous		Rarely, alopecia, erythema multiforme	

APPENDIX 2: Adverse effects search: Medline search strategy

1 Diphosphonates/
2 bisphosphonate$.tw.
3 Alendronate/
4 alendronate$.tw.
5 risedronate$.tw.
6 1 or 2 or 3 or 4 or 5
7 Osteoporosis/
8 osteoporosis.tw.
9 7 or 8
10 6 and 9
11 gastrointestinal$.tw.
12 Nausea/
13 nause$.tw.
14 Dyspepsia/
15 dyspepsia$.tw.
16 oesophagitis$.tw.
17 Gastritis/
18 gastritis.tw.
19 Abdominal Pain/
20 abdominal pain$.tw.
21 Deglutition Disorders/
22 dysphagia.tw.
23 Vomiting/
24 vomit$.tw.
25 Diarrhea/
26 diarrh?ea.tw.
27 Headache/
28 headache$.tw.
29 muscle pain$.tw.
30 Exanthema/
31 skin rash$.tw.
32 or/11-31
33 10 and 32
34 (ae or po or to or co or de).fs.
35 adverse event$.tw.
36 adverse effect$.tw.
37 side effect$.tw.
38 safe$.tw.
39 34 or 35 or 36 or 37 or 38
40 33 and 39

APPENDIX 3

Placebo-controlled studies of bisphosphonates for the treatment and prevention of postmenopausal or steroid-induced osteoporosis: toxicity

Study	Population	Exclusion criteria related to GI disease	Upper GI adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Alendronate					
Adami 1995[117]	Postmenopausal women with osteoporosis or osteopenia (lumbar T-score -2 or below), 5% of whom had vertebral fracture at entry	"any associated health problems that could affect their participation in the study"	13% of women taking alendronate and 14% of the placebo group, but only 5% of the arm taking intranasal calcitonin, had at least one upper GI adverse event. There was only 1 case of gastritis, in the placebo group; no oesophagitis or gastro-oesophageal mucosal erosion were reported	Similar in alendronate and placebo groups	Alendronate 10mg: 3% Alendronate 20 mg: 8% Placebo: 6%
AOPS[88]	Healthy, recently postmenopausal, women aged 40-59 without osteoporosis	Major upper GI diseases (eg peptic ulcer, oesophageal disease, malabsorption) within 1 year of study entry	Clinically significant upper GI AEs were seen in 26% of the 1 and 5 mg groups, 30% of the 10 mg group, 32% of the 290 mg group and 29% of the placebo group. Of these, only flatulence and odynophagia showed dose-related increases	Clinical AEs (including mild common symptoms such as headache and upper respiratory infection) occurred in more than 90% of each group	Alendronate 1 mg: 7% Alendronate 5 mg: 7% Alendronate 10 mg: 7% Alendronate 20/5mg: 10% Placebo: 7%
Bone 1997[118]	Postmenopausal women with osteopenia or osteoporosis (T-score <-2, but no more than 1 lumbar crush fracture), 37% of whom had vertebral fracture at entry	History of recent major GI disease (eg peptic ulcer, oesophageal disorder, malabsorption, or recent use for more than 2 weeks of a drug to inhibit gastric acid secretion	No significant difference between treatment groups	Suspected drug-related AEs: Alendronate 1mg: 20% Alendronate 2.5 mg: 26% Alendronate 5 mg: 17% Placebo: 23%	Alendronate 1mg: 9% Alendronate 2.5 mg: 9% Alendronate 5 mg: 14% Placebo: 10%
Bone 2000[89]	Hysterectomised postmenopausal women with lumbar spine BMD below 0.862 g/cm^2 (Hologic) (mean T-score -2.5±0.2)	History of recent major upper GI mucosal erosive disease (including significant upper GI bleeding, recurrent peptic ulcer, oesophageal or gastric	Occurred in 27% of women receiving alendronate and 22% of the placebo group (no significant difference between groups)	None attributed to alendronate.	Alendronate: 6% Alendronate + oestrogen: 9% Placebo: 10%

		varices			
Carfora 1998[119]	Postmenopausal women with osteoporosis (lumbar spine T-score <-2.5)	Active peptic ulcer disease	Episodes of nausea, dyspepsia, mild gastro-oesophagitis and abdominal pain appeared during the first 15 months of treatment with 20 mg of alendronate (no indication given of number of women affected)	Cutaneous rash was associated with alendronate (no indication given of number of women affected)	Not specified
Chesnut 1995[120]	Postmenopausal women with osteopenia (lumbar spine BMD $\leq$0.88 g/cm$_2$) but no vertebral or hip fractures attributable to osteoporosis	None stated	GI side effects, including nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain, occurred mainly in the first year of treatment with 40 mg alendronate. 9 women receiving alendronate withdrew because of upper GI adverse events: 7 of these were receiving 40 mg/day, and only 1 less than 20 mg/day	The only non-GI side effect associated with alendronate was skin rash. 1 woman withdrew from the 20 mg group because of a rash which was believed to be alendronate-related	Alendronate: 6% Placebo: 29%
Dursun 2001[121]	Postmenopausal women with osteoporosis or osteopenia (lumbar spine T-score of -2 SD or below)	Active gastrointestinal disease	States only that no side effects were serious enough to discontinue medication	States only that no side effects were serious enough to discontinue medication	None
EPIC Study[90]	Healthy postmenopausal women aged 45-59 no more than 10% of whom had a lumbar spine BMD below 0.8g/cm^2	History of peptic ulcer or oesophageal disease requiring prescription medication within the previous 5 years	At 4 years, the number of women suffering upper GI adverse events was similar in all groups, ranging between 37-46%	At 4 years, drug-related adverse events (including upper GI adverse events) had occurred in 11% of women in the 5 mg group, 16% in the 5 mg/placebo group, 15% in the 2.5 mg group and 9% in the 2.5 mg/placebo group, compared with 13% in the placebo group	Number not specified but said to be similar in the alendronate and placebo groups
Fracture Intervention Trial: women with pre-existing fractures[91]	Postmenopausal women with severe osteoporosis (at least 1 existing vertebral fracture)	Peptic ulcer disease or dyspepsia requiring daily treatment	41% of women in the treatment group and 40% in the placebo group experienced upper GI problems (p=0.67). The rate of events did not increase after the dose was increased to 10 mg	Not specified	Alendronate: 8% Placebo: 10%
Fracture Intervention Trial: women without	Postmenopausal women with osteoporosis or	Recent peptic ulcers or ulcers requiring hospitalisation,	48% of women in the treatment group and 47% of women in the placebo group experienced upper GI problems	Not specified	Alendronate: 10% Placebo: 10%

pre-existing fractures[57]	osteopenia (femoral neck BMD 0.68 g/cm$_2$) but no vertebral fractures	dyspepsia requiring daily treatment			
Greenspan 2002[122]	Elderly women living in residential care with osteoporosis or osteopenia (lumbar or total hip BMD <-2)	Recent major upper GI mucosal erosive disease	33% of women in the alendronate group and 35% in the placebo group reported upper GI adverse events; 0.6% and 1.9% respectively reported serious upper GI adverse events	93% of women in each group reported clinical adverse experiences (including upper GI adverse events).	Not specified
Liberman 1995[92, 93]	Postmenopausal women with osteoporosis (lumbar T-score <-2.5) but no vertebral fractures	Active peptic ulcer disease	Adverse upper GI events:[123] Alendronate 5 mg: 37% Alendronate 10 mg: 42% Alendronate 20/5mg: 40% Placebo: 39% Probably or possibly drug-related adverse events:[123] Alendronate 5 mg: 17% Alendronate 10 mg: 15% Alendronate 20/5mg: 19% Placebo: 15% Withdrawal due to upper GI AE: Alendronate 5 mg: 3.5% Alendronate 10 mg: 1.0% Alendronate 20/5mg: 2.0% Placebo: 2.0%	Any clinical adverse event: Alendronate 5 mg: 90% Alendronate 10 mg: 89% Alendronate 20/5mg: 89% Placebo: 90% Probably or possibly drug-related adverse events: Alendronate 5 mg: 28% Alendronate 10 mg: 27% Alendronate 20/5mg: 31% Placebo: 25%	Alendronate 5 mg: 5% Alendronate 10 mg: 4% Alendronate 20/5mg: 8% Placebo: 6%
Lindsay 1999[94]	Postmenopausal women with osteoporosis or osteopenia already receiving HRT (T-score at lumbar spine or femoral neck <-2 and at the other site <1.5), 57% of whom had a previous fracture	Conditions that affect oesophageal emptying	10.7% of women in each group suffered potentially drug-related GI AEs	Adverse effects were evenly distributed between the 2 groups. Back pain was the only adverse effect which was significantly more common in the intervention group (10% vs 3%)	Alendronate: 4% Placebo: 7%
Pols 1999[52]	Postmenopausal	Major GI disease (eg	The groups were comparable in the	There were no statistically	Not specified

	women with osteoporosis or osteopenia (lumbar T-score <-2)	peptic ulcer disease) in previous year, or use of drug to inhibit gastric acid secretion for >2 weeks in previous 3 months	overall incidence of upper GI adverse events (alendronate 21.3%, placebo 19.3%, NS), and of specific upper GI adverse events such as abdominal pain, dyspepsia, nausea etc	significant differences between groups in the overall incidence of adverse effects (alendronate 67.1%, placebo 69.7%), adverse events considered by the investigator to be possibly, probably or definitely drug-related (19.1% versus 18.0%), adverse events resulting in permanent discontinuation of study medication (6.4% versus 5.6%) or serious adverse events (alendronate 6.5%, placebo 6.3%)	
Rossini 1994[95]	Postmenopausal women with osteoporosis or osteopenia (spinal BMD >2 SD below adult mean without vertebral fractures)	None reported	No adverse events were experienced during the 6 months of alendronate treatment	No adverse events were experienced during the 6 months of alendronate treatment	None
Saag 1998,[56] Adachi 2001[124]	Men and women aged 17-83 with underlying rheumatologic, pulmonary, dermatologic, gastrointestinal or other diseases requiring long-term (at least 1 year) oral glucocorticoid therapy with at least 7.5 mg prednisone or its equivalent NB After 48 weeks, the extension study is not truly randomised	History of recent (within 1 year) major upper GI disease; use of NSAIDs was not restricted except that patients with a history of GI side effects from NSAIDs agreed not to take them during the study.	At 48 weeks: Alendronate 5 mg: 30/161 (19%) Alendronate 10 mg: 40/157 (25%) Placebo: 26/159 (16%) (P<0.05) At 2 years: Alendronate 2.5/10 mg: 5/29 (17%) Alendronate 5 mg: 13/63 (21%) Alendronate 10 mg: 17/55 (31%) Placebo: 19/61 (31%)	At 48 weeks: Musculoskeletal pain: Alendronate 5 mg: 14% Alendronate 10 mg: 16% Placebo: 16% Upper respiratory infection: Alendronate 5 mg: 12% Alendronate 10 mg: 13% Placebo: 9% Headache: Alendronate 5 mg: 8% Alendronate 10 mg: 8% Placebo: 6% Urinary tract infection: Alendronate 5 mg: 10%	At 48 weeks: Alendronate 5 mg: 8/161 (5%) Alendronate 10 mg: 6/157 (4%) Placebo: 8/159 (5%) At 2 years: Alendronate 2.5/10 mg: 1/29 (3%) Alendronate 5 mg: 2/63 (3%) Alendronate 10 mg: 3/55 (6%) Placebo: 3/61 (5%)

				Alendronate 10 mg: 6% Placebo: 8% At 2 years: all AEs (including upper GI AEs): Alendronate 2.5/10 mg: 26/29 (90%) Alendronate 5 mg: 59/63 (94%) Alendronate 10 mg: 51/55 (93%) Placebo: 55/61 (90%)	
Etidronate					
Adachi 1997[102]	Ambulatory patients aged 18-90 who had started high-dose therapy with prednisone or its equivalent within the previous 100 days and were expected to continue treatment for at least 1 year at a mean daily dose of 7.5 mg/d or greater for 90 days, with subsequent ongoing treatment at a mean daily dose of 2.5 mg or more	None reported	All adverse events (mostly mild, transient GI events) Etidronate group: 12/74 (16%) Placebo group: 13/67 (19%)	None specified	None
Cortet 1999[103]	Patients receiving long-term glucocorticoid therapy for an anticipated duration of more than 1 year for inflammatory rheumatic diseases (rheumatoid arthritis, polymyalgia rheumatica or giant	None reported	Etidronate group: 32% Placebo group: 31%	All adverse events: Etidronate group: 84% Placebo group: 87%	5 – none treatment-related (sudden death n = 2, MI n = 1, congestive heart failure n = 1, lung cancer n = 1)

	cell arteritis)				
Geusens 1998[104]	Postmenopausal women receiving long-term corticosteroid treatment mainly for rheumatological conditions	None reported	Etidronate group: 4/18 (22%) Placebo group: 3/19 (16%)	Said to be comparable in both groups	Etidronate group: 1/18 (ruptured aortic aneurysm) Placebo group: 2/19 (anaphylactic shock, shoulder fracture)
Herd 1997[96]	Ambulatory white women at least 1 but no more than 10 years postmenopausal with BMD between 0 and –2 SD of normal values for a 50-year-old woman measured in the local population	None reported	Nausea, dyspepsia and diarrhoea were reported by 22% of subjects in the placebo group and 12% in the etidronate group	The most frequently reported adverse events, infection (primarily respiratory tract infections) and back pain, occurred with similar frequency in both groups. 11% of the etidronate group and 7 (9%) in the placebo group reported serious adverse events	Etidronate: 7% Placebo: 0
Jenkins 1999[105]	Patients aged 18 years and over with either polymyalgia rheumatica or rheumatoid arthritis in whom there was a clinical indication to commence corticosteroids, at low to moderate doses, for the first time	None reported	No data	No data	1 death in the placebo group (not treatment-related)
Meunier 1997[97]	Early postmenopausal women with normal BMD (Z-score between +2 and -2) who had not undergone hysterectomy or bilateral oophorectomy	None reported	No severe GI adverse events were reported. 5 subjects, 4 in the etidronate and 1 in the placebo group, all of whom had a pre-study history of GI problems, reported mild abdominal pain; they were all intolerant of the calcium supplement	Overall, the majority of adverse events which were reported were mild in severity and comparable in incidence between the groups	Etidronate: 0 Placebo: 7%

Montessori[98]	Women aged <75, ambulant and active, postmenopausal for at least 1 year, with a lumbar spine Z-score of <-1.	Active GI disease	Common adverse events in both groups included heartburn, constipation, abdominal cramps and diarrhoea	Overall, adverse events were mostly mild and evenly distributed over both groups. The two cases of cancer in the control group were considered unrelated to study medication	Only 1 subject withdrew because of an adverse event (severe diarrhoea) almost immediately after enrolment. This subject's group was not given
Pitt 1998[106]	Ambulatory Caucasian patients aged 30 or over with normal BMD suffering from a variety of disorders and being treated with high-dose corticosteroids	Inflammatory bowel disease	Number of patients reporting mild to severe upper GI AEs: Etidronate group: 2/26 (8%) Placebo group: 0/23 (0%)	All adverse events: Etidronate group: 17/26 (65%) Placebo group: 19/23 (83%) The most common AEs were respiratory infections, back pain and accidental injury. Most AEs were mild or moderate in severity Serious adverse events: Etidronate group: 5/26 (19%) Placebo group: 8/23 (35%) None of these were thought to be related to study treatment	Etidronate group: 3/26 (12%) (MI, death due to respiratory failure, death due to adenocarcinoma of lung) Placebo group: 1/23 (4%) (death due to perforated bowel)
Pouilles 1997[99]	Postmenopausal, HRT-naïve, women aged 45-60	None reported	The adverse event profile of etidronate and placebo were said to be similar, although more digestive AEs occurred in the etidronate group	Overall, 92 women (84%) experienced 1 or more adverse events (46 in each group)	Etidronate: 2% Placebo: 0
Roux 1998[107]	Patients with a variety of conditions who had recently initiated high-dose oral corticosteroid therapy which was expected to continue for at least 12 months, with a mean daily dose, for the initial 90 days in the study, of at least 7.5 mg prednisone or its equivalent, and with subsequent ongoing treatment at a mean	None reported	Proportion of patients reporting upper GI AEs (all moderate in severity): Etidronate group: 12% Placebo group: 5% (P=0.32)	Proportion of patients reporting any AE: Etidronate group: 86% Placebo group: 88%	Etidronate group: 5/58 (9%) Placebo group: 1/59 (2%) None of the withdrawals were attributed to etidronate

	cumulative dose of at least 2.5 mg/d				
Storm 1990[100]	Postmenopausal women with severe osteoporosis (at least 1 but no more than 4 atraumatic vertebral crush fractures)	None reported	None reported	No significant side effects were observed related to etidronate	None
Watts 1990[101]	Postmenopausal women with severe osteoporosis (at least 1 but no more than 4 vertebral crush fractures)	Active gastrointestinal disease	5-6% in all groups suffered nausea during days 1-17 (the phosphate/placebo and etidronate/placebo phases of the cycle); however, during days 1-3 (the phosphate/placebo phase), 39% of subjects receiving phosphate suffered diarrhoea compared with 9% of those receiving placebo	Overall, adverse effects were mild, generally infrequent and comparably distributed between the treatment groups	Etidronate only: 3% Phosphate only: 1% Etidronate-phosphate: 1% Placebo: 2%
Risedronate					
Brown 2002[108]	Postmenopausal women with osteoporosis	None. Patients with previous or active upper GI disease were not excluded, and concomitant use of NSAIDs or aspirin was permitted.	Any upper GI tract event: 5 mg/d: 84/480 (17.5%) 35 mg/week: 89/485 (18.4%) 50 mg/week: 92/491 (18.7%) Moderate to severe upper GI tract event: 5 mg/d: 23/480 (4.8%) 35 mg/week: 22/485 (4.5%) 50 mg/week: 21/491 (4.3%)	Drug-related AEs: 5 mg/d: 114/480 (23.8%) 35 mg/week: 115/485 (23.7%) 50 mg/week: 99/491 (20.2%) Serious AEs: 5 mg/d: 34/480 (7.1%) 35 mg/week: 40/485 (8.2%) 50 mg/week: 45/491 (9.2%)	5 mg/d: 57/480 (11.9%) 35 mg/week: 56/485 (11.5%) 50 mg/week: 43/491 (8.8%)
Clemmesen 1997[109]	Postmenopausal women with severe osteoporosis (at least 1 but no more than 4 vertebral fractures)	None reported	3 women (7%) in each group reported upper GI adverse events that were moderate to severe. 3 women (7%) in the cyclic risedronate group and 1 (2%) in the continuous risedronate group reported GI AEs related to the oesophagus; all were judged to be mild to moderate in severity, and 3 of the 4 women had a previous medical history of oesophagitis	No serious adverse events (including GI AEs) were considered causally related to risedronate	14% overall (not attributed to groups)
Cohen 1999[113]	Ambulatory patients aged 18-85 with a variety of rheumatologic,	None. Patients with a history of upper GI disorders and patients taking drugs known to	Risedronate 2.5 mg: 15/73 (21%) Risedronate 5 mg: 11/75 (15%) Placebo: 13/76 (17%)	Serious AEs: Risedronate 2.5 mg: 15/73 (21%) Risedronate 5 mg: 17/75 (23%) Placebo: 20/76 (26%)	Risedronate 2.5 mg: 5/73 (7%) Risedronate 5 mg: 3/75 (4%) Placebo: 4/76 (5%)

	pulmonary and skin conditions, who had initiated moderate to high doses of corticosteroids (mean dose of prednisone or prednisone equivalent ≥7.5 mg/d) within the previous 3 months and were expected to continue treatment for another 12 months	be irritating to the GI tract were not excluded.		All musculoskeletal AEs: Risedronate 2.5 mg: 34/73 (47%) Risedronate 5 mg: 37/75 (49%) Placebo: 37/76 (49%) Back pain: Risedronate 2.5 mg: no data Risedronate 5 mg: 12% Placebo: 8% Arthralgia: Risedronate 2.5 mg: no data Risedronate 5 mg: 25% Placebo: 15% Back pain and arthralgia were mostly mild and were not considered drug-related; they did not cause any withdrawals	
Eastell 2000[125]	Postmenopausal women with rheumatoid arthritis who required long-term (>6 months) treatment with oral glucocorticoids at an average daily dose of at least 2.5 mg prednisolone	None reported	Daily risedronate: 15/40 (38%) Cyclical risedronate: 21/40 (53%) Placebo: 22/40 (55%)	Serious AEs: Daily risedronate: 25/40 (63%) Cyclical risedronate: 19/40 (48%) Placebo: 21/40 (53%)	Daily risedronate: 6/40 (15%) Cyclical risedronate: 9/40 (23%) Placebo: 6/40 (15%)
Fogelman 2000 [110]	Postmenopausal women with osteopenia or osteoporosis (lumbar T-score –2 or less)	None. Patients with previous or ongoing upper GI disease were not excluded, and prior or concomitant use of NSAIDs or aspirin was permitted.	30% in the 2.5 mg group, 23% in the 5 mg group and 26% in the placebo group suffered upper GI symptoms (most commonly abdominal pain, suffered by 11-13%, and dyspepsia, suffered by 8-14%). The various symptoms were evenly distributed among treatment groups	93% of the 2.5 mg group, 95% of the 5 mg group and 96% in the placebo group suffered adverse events (including upper GI AEs); 11% of the 2.5 mg group, and 15% each of the 5 mg and placebo groups suffered serious adverse events	Risedronate 2.5 mg: 10% Risedronate 5 mg: 11% Placebo: 8%
Harris 1999[60]	Postmenopausal	None. Patients with	30% of the 5 mg group and 27% of the	97% of the 5 mg group and 95%	Risedronate 5 mg: 17%

	women with severe osteoporosis (either at least 2 vertebral fractures or 1 vertebral fracture and lumbar-spine T-score of -2)	previous or ongoing upper GI disease were not excluded, and prior or concomitant use of NSAIDs or aspirin was permitted.	placebo group suffered upper GI adverse events (most commonly abdominal pain, suffered by 12-13%, and dyspepsia, suffered by 11-13%). Duodenitis was more common in the 5 mg group (1% vs 0.2%)	of the placebo group suffered adverse events (including upper GI AEs). 34% and 29% respectively suffered AEs which were thought to be drug-related, and 29% and 27% respectively suffered serious AEs.	Placebo: 17% Adverse events related to the digestive system accounted for 42% of withdrawals due to adverse events from the placebo group and 36% from the 5 mg risedronate group
McClung 1998[61]	Postmenopausal women with osteopenia (T-score at lumbar spine <-2)	None. Patients with active GI disease or on chronic NSAIDs were not excluded.	The incidence of mild to moderate upper GI adverse events was comparable between groups	No data	Risedronate: 8% Placebo: 11%
McClung 2001[62]	Women aged 70-79 with osteoporosis; women aged 80 or over with osteoporosis or at least one nonskeletal risk factor for hip fracture	None. Patients with previous or ongoing upper GI disease were not excluded, and prior or concomitant use of NSAIDs, aspirin, proton-pump inhibitors or antacids was permitted.	22% each of the 2.5 mg and placebo groups, and 21% of the 5 mg group suffered upper GI adverse events (most commonly abdominal pain, suffered by 8-9%, and dyspepsia, suffered by 8%). The various symptoms were evenly distributed among treatment groups	89% of the 2.5 mg group, and 90% each of the 5 mg and placebo groups suffered adverse events (including upper GI AEs); 30% of the 5 mg group and 31% each of the 2.5 mg and placebo groups suffered serious adverse events	Risedronate 2.5 mg: 18% Risedronate 5 mg: 18% Placebo: 18%
Mortensen 1998[111]	Early postmenopausal women with normal BMD (z-score within $\pm$ 2 SD) and no osteoporotic fracture	None	8% in the continous risedronate group, 13% in the cyclic group and 11% in the placebo group suffered abdominal pain, and 16%, 24% and 28% respectively suffered dyspepsia	There was no difference between treatment and placebo groups in the incidence of adverse events. Reports of arthralgia were low, and similar in the placebo and risedronate groups	Continuous risedronate: 5% Cyclic risedronate: 8% Placebo: 8% Only one of the adverse events (hip arthralgia in a subject receiving cyclic risedronate) was considered possibly drug-related
Reginster 2000[112]	Postmenopausal women with severe osteoporosis (at least 2 vertebral fractures)	None. Patients with previous or ongoing upper GI disease were not excluded, and prior or concomitant use of NSAIDs or aspirin was permitted.	23% of the 2.5 mg group, 27% of the 5 mg group, and 26% of the placebo group suffered upper GI adverse events (most commonly abdominal pain, suffered by 9-12%, and dyspepsia, suffered by 9-11%).	92% each of the 2.5 and 5 mg groups, and 91% each of the placebo group suffered adverse events (including upper GI AEs); 27% of the 2.5 mg group, 28% of the 5 mg group and 32% of the placebo group suffered AEs which were considered to be drug-related	Risedronate 2.5 mg: 13% Risedronate 5 mg: 15% Placebo: 20%
Reid 2000[126,127]	Ambulatory men and women aged 18-85 who had been	None. Patients were not excluded on the basis of prior or current GI	Risedronate 2.5 mg: 14/92 (15%) Risedronate 5 mg: 25/99 (25%) Placebo: 21/94 (22%)	Serious AEs: Risedronate 2.5 mg: 32/92 (35%) Risedronate 5 mg: 37/99 (37%)	Due to any AE: Risedronate 2.5 mg: 11/92 (12%)

	receiving moderate to high doses of oral corticosteroid therapy (≥7.5 mg/d prednisone or equivalent) for a range of diseases for at least 6 months and who were expected to continue corticosteroid therapy for at least 12 months. Premenopausal women had to be surgically sterile or using an acceptable form of birth control	disease or use of concomitant medications associated with GI symptoms.		Placebo: 37/94 (39%) Back pain: Risedronate 2.5 mg: no data Risedronate 5 mg: 23% Placebo: 10% Arthralgia: Risedronate 2.5 mg: no data Risedronate 5 mg: 24% Placebo: 16% Back pain and arthralgia were mostly mild and were generally not considered drug-related; they did not cause any withdrawals	Risedronate 5 mg: 11/99 (11%) Placebo: 11/94 (12%) Due to AEs possibly or probably related to the study drug: Risedronate 2.5 mg: 3/92 (3%) Risedronate 5 mg: 5/99 (5%) Placebo: 6/94 (6%)

APPENDIX 4: Compliance search strategy

1 compliance.mp. or Compliance/ or Patient Compliance/
2 continuance.mp.
3 adherence.mp.
4 1 or 2 or 3
5 bisphosphonates.mp. or Diphosphonates/
6 alendronate.mp. or Alendronate/
7 etidronate.mp. or Etidronic Acid/
8 risedronate.mp.
9 5 or 6 or 7 or 8
10 Osteoporosis/ or osteoporosis.mp.
11 4 and 9 and 10

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