



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Osteoporosis: ‘real-world’ adherence and persistence with oral bisphosphonates

A systematic review of worldwide observational studies, including studies from the UK, suggests that persistence and adherence rates with oral bisphosphonates are wide ranging, relatively low and reduce over time. Several factors were found to affect this, with higher persistence rates seen in people taking fewer medicines and those taking weekly bisphosphonates rather than daily. This ‘real-world evidence’ emphasises the need to support people in their medicines choices to agree a plan that is based on their own circumstances, values and preferences. The NICE [decision support tool on bisphosphonates for treating osteoporosis](#) can help inform this discussion. Also of note is that the NICE guideline on [multimorbidity](#) recommends discussing stopping bisphosphonates after 3 years.

Overview and current advice

NICE recommends [oral bisphosphonates](#) (alendronic acid, ibandronic acid and risedronate sodium), and intravenous bisphosphonates (ibandronic acid and zoledronic acid) as options for treating osteoporosis in adults:

- who are eligible for risk assessment as defined in the NICE guideline on [osteoporosis](#) (recommendations 1.1 and 1.2) and the NICE quality standard on [osteoporosis](#) and
- who have been assessed as being at higher risk of osteoporotic fragility fracture using the methods recommended in the NICE guideline on [osteoporosis](#) (recommendations 1.3 to 1.12) and the NICE quality standard on [osteoporosis](#) and
- when bisphosphonate treatment is appropriate, taking into account their risk of fracture, their risk of adverse effects from bisphosphonates, and their clinical circumstances and preferences.

NICE recommends that the choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatments available. NICE has produced a [decision support tool](#) which provides information to help people with osteoporosis and their health professionals discuss the options.

The NICE guideline on [multimorbidity](#) recommends telling people who have been taking a bisphosphonate for osteoporosis for at least 3 years that there is no consistent evidence of:

- further benefit from continuing bisphosphonate for another 3 years
- harms from stopping bisphosphonate after 3 years of treatment.

The guideline also recommends discussing stopping bisphosphonates after 3 years and including patient choice, fracture risk and life expectancy in the discussion.

A systematic review of observational studies ([Fatoye et al. 2019](#)) aimed to summarise adults' persistence and adherence with oral bisphosphonates in real-world settings, and to identify factors that may affect these.

New evidence

The systematic review ([Fatoye et al. 2019](#)) included 89 prospective and retrospective observational studies from the US, Canada, Europe (including the UK), Australia and Asia. Adherence and persistence with oral bisphosphonates (including alendronic acid, risedronate sodium and ibandronic acid) was measured using prescription claims data. Persistence was measured based on the length of treatment without a gap (mostly 30 days but ranging up to 90 days in some studies) in prescription refills. Adherence was measured by calculating the medication possession ratio (the number of days' supply of medication received divided by the length of the follow-up period) and the proportion of days covered. It was not possible to carry out a full meta-analysis because there was heterogeneity between studies in reporting and calculations of adherence and persistence.

The mean age of people in the studies ranged from 53.0 years to 80.8 years and the length of follow-up in the studies ranged from 3 months to 14 years. A total of 60 studies including 4,070,739 people were identified that measured persistence. The overall mean **persistence** with oral bisphosphonates tended to reduce over time and ranged from:

- 34.8% to 71.3% at 6 months
- 17.7% to 74.8% at 1 year
- 12.9% to 60.6% at 2 years
- 21.0% to 40.0% at 3 years.

Out of 19 studies that reported 2-year persistence with oral bisphosphonates, more than 70% found that the proportion of people persistent with bisphosphonates was less than 30%.

A total of 55 studies including 4,033,731 people were identified that measured **adherence**. The proportion of people adhering to bisphosphonates at 1 year ranged from 31.7% to 72.0% across 31 studies. At 2 years the proportion of people adhering to bisphosphonates reduced and ranged from 34.5% to 47.9% across 6 studies. One study with 3-month follow-up that assessed adherence rates with risedronate sodium and alendronic acid found that the proportion of people adhering to daily medication was lower than the proportion adhering to weekly medication (72.8% compared with 80%). Overall, adherence rates with bisphosphonates tended to decrease over time both within and across studies.

Determinants of persistence and adherence to bisphosphonates were found to include:

- prior bone mineral density (BMD) test: people who had received a prior BMD had higher persistence and adherence compared with those who did not
- frequency of medication dosing: people who took bisphosphonates weekly had higher mean persistence rates than people who took them daily
- age: older people up to age 80 had higher rates of persistence and adherence to bisphosphonates than younger people. Adherence rates decreased at age 80 and older
- number of other medicines taken at baseline: people taking more medicines at baseline had a slightly greater risk of discontinuing bisphosphonates
- gender: compared with men, women had a lower likelihood of adhering to oral bisphosphonate medicines.

Commentary

Commentary provided by NICE

This systematic review used 'real-world' data from countries across the world to try and understand if people continue taking oral bisphosphonates after they have been initiated. The results suggest that overall, persistence and adherence with these medicines is relatively poor and reduces over time.

Some interesting factors that may affect adherence and persistence were noted from the studies. In line with findings from a previous systematic review ([Cramer et al. 2007](#)), people who were prescribed weekly bisphosphonates had higher mean persistence rates than people who were prescribed the daily regimen. The number of concomitant medicines taken was also an important factor with people taking more medicines at baseline having a slightly greater risk of discontinuing bisphosphonates. Overall, adherence rates with bisphosphonates tended to decrease over time both within and across studies.

The review had some limitations including reliance on only observational data. Excluding other study designs such as open-label extension studies could have led to publication bias. Adherence and persistence data were obtained only from prescription claims data and do not guarantee that the medicines were actually taken by the person. It is also difficult to determine from prescription data, the reason why a medicine may have been discontinued or not taken regularly. Further studies examining patient-derived data would be useful to investigate reasons for poor adherence and persistence.

Overall, the findings from this review support the need for healthcare professionals to encourage informed, shared decision making when people are considering taking an oral bisphosphonate. Decision aids such as the NICE [decision support tool on bisphosphonates for treating osteoporosis](#) can help to explain the material risks and benefits of taking a bisphosphate to reduce the risk of fractures in people with osteoporosis. Importantly, people who are at risk of falling and their carers should be offered information orally and writing in line with the NICE guideline on [falls in older people](#).

The NICE key therapeutic topic on [shared decision making](#) provides an overview of shared decision making, the drivers and barriers to this, and approaches to overcome them. Prescribers are also reminded that the NICE guideline on [multimorbidity](#) recommends discussing stopping bisphosphonates after 3 years and including patient choice, fracture risk and life expectancy in the discussion.

Study sponsorship

The systematic review received no specific funding.

References

- Cramer JA, Gold DT, Silverman SL et al. 2007. [A systematic review of persistence and compliance with bisphosphonates for osteoporosis](#). *Osteoporosis International* 18:1023–31
- Fatoye F, Smith P, Gebrye T et al. 2019. [Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review](#). *BMJ Open* 9:e027049. doi:10.1136/bmjopen-2018-027049

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