Your patient, a 68-year-old woman, has been taking alendronic acid for five and a half years. She has responded well to the treatment and manages the side effects fairly well. She has not had her therapy reviewed recently and you believe it might be time for a drug holiday. What is the next step?

This is the kind of scenario that the metabolic bone clinic at Newcastle upon Tyne Hospitals NHS Foundation Trust began to receive enquiries about after the Medicines and Healthcare products Regulatory Agency issued a safety alert on the long-term use of bisphosphonates in 2011.

The advice followed reports of atypical femoral fractures associated with bisphosphonate use. It recommended that patients should have their bisphosphonate treatment re-evaluated periodically, particularly those who had been taking bisphosphonates for more than five years (see Box 1).

A pilot project was set up to develop a review pathway to be used in primary care for patients who are on long-term bisphosphonate therapy and who could benefit from a drug holiday.

During the review, patients were assessed for their risk of having a fracture using an established fracture risk assessment tool (FRAX) alongside clinical judgement. Medicines were reviewed by the pharmacist — who at the time was undertaking an independent prescribing qualification — and bisphosphonates stopped if appropriate. The risks and benefits of bisphosphonate treatment were discussed with patients and any questions they had about their therapy were answered.

A trust-approved information leaflet on drug holidays, developed by the secondary care specialist team in liaison with primary care colleagues, was given to each patient. Records were updated to indicate that the patient had undergone a review and, if applicable, whether their treatment had been stopped and why. Review dates and recall alerts were added to records to ensure the consultation was followed up appropriately.

Data were collected on the reasons each patient started bisphosphonate therapy, his or her FRAX score, fracture history, level of adherence, mobility and relevant lifestyle factors, eg, dietary calcium intake.

A multidisciplinary secondary care team analysed the data and discovered that there were more patients (70%) with high fracture risk than they had expected. This provided a better picture of fracture risk in primary care. They agreed on the outcomes of each review and put together a draft common pathway.

The final review pathway (see Box 2, p295), which was to be used in primary care to manage patients who are on drug holidays from bisphosphonates to prevent fractures...

**Box 1: Bisphosphonates**

Bisphosphonates are used to reduce fracture risk in osteoporosis. They work by reducing bone loss through the inhibition of osteoclast activity, which results in a net gain of bone mineral density. Clinical trial data have shown benefits of taking bisphosphonates for five years. However, the optimal treatment duration remains unknown and there have been concerns over the long-term impact of bisphosphonate use on bone quality.

It is thought that, in some cases, prolonged use of bisphosphonates may lead to a substantial reduction in bone remodelling and the development of micro-cracks and increased bone fragility, resulting in atypical fractures.

**Pilot clinic**

All patients from a local GP practice who had been taking bisphosphonates for at least five years were invited to have their therapy reviewed by the specialist secondary care pharmacist. Patients who were unable to attend the clinic were offered a telephone consultation or home visit appointment.

During the review, patients were assessed for their risk of having a fracture using an established fracture risk assessment tool (FRAX) alongside clinical judgement. Medicines were reviewed by the pharmacist — who at the time was undertaking an independent prescribing qualification — and bisphosphonates stopped if appropriate. The risks and benefits of bisphosphonate treatment were discussed with patients and any questions they had about their therapy were answered.

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in this way was a useful learning exercise for all involved. It was apparent that there was a need for better education on this therapeutic area in primary care.

Whereas the specialist team was accustomed to using just one system for recording consultations and planning follow-up reviews, there were numerous different systems used by the GP practices and the review pathway had to be applicable to all.

A high non-attendance rate (15%) among patients attending the GP clinic and difficulties keeping to the required frequency of blood tests for C-terminal telopeptide (CTX) meant that the original pathway — which measured CTX at 0, 4 and 12 months — had to be altered to include 12-month review only.

Outcomes
The project increased awareness and knowledge of drug holidays in primary care and helped to address concerns around long-term bisphosphonate use that had been raised by the MHRA.

More patients than expected were found to be at high risk of fracture; this highlighted the need for further research into this area.

Anecdotally, patients were reported to be pleased with the way the reviews were conducted and the information that was given.

Next steps
The National Osteoporosis Guideline Group has since produced its own information on drug holidays that maps well into the project.

A unified approach to using drug holidays across the wider region is needed. However, there are certain challenges that have limited further implementation of the project. For example, not all areas have access to bone turnover marker blood tests.

Although DEXA scanning can be used as an alternative, not all areas within the region have open access to this and there are cost and resource implications associated with this approach.

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Box 2: The bisphosphonate review pathway

There is limited evidence to support the long-term use of bisphosphonates and patients who have been on treatment for more than five years should be reviewed. Advice for further monitoring and treatment differs for each patient and depends on:

- The patient’s risk of having a fracture
- The age of the patient
- The bisphosphonate the patient was taking
- The patient’s fracture history
- Adherence to treatment

The specialist secondary care bone team at Newcastle upon Tyne Hospitals NHS Foundation Trust developed a bisphosphonate treatment review pathway to help GPs manage patients appropriately.

An established fracture risk assessment tool is used to estimate a patient’s 10-year fracture risk — something GPs have been increasingly using in primary care. This is plotted against his or her age on intervention threshold charts produced by the National Osteoporosis Guideline Group. There are two charts: one estimates the risk of hip fracture and the other the risk of major osteoporotic fracture in the next 10 years.

Patients below the NOGG recommended treatment threshold are deemed to be at low fracture risk and do not need to continue bisphosphonate treatment at this stage. They are then reviewed 24 months after stopping treatment. At review, if the 10-year risk of having a fracture is still beneath the NOGG threshold, then no further treatment is needed. If a patient is above the threshold he or she should be restarted on a bisphosphonate.

Patients whose risk of a fracture falls above the NOGG treatment threshold at baseline should also stop therapy but need to be reviewed after 12 months. Patients who were taking risendronate should restart at this stage.

For patients previously established on alendronic acid therapy, the decision to restart treatment depends on their level of C-terminal telopeptide (CTX) — a marker of bone turnover. The effect of alendronic acid wears off gradually over a period of two to five years. Therefore, although CTX will start to increase, it would not be expected to be in the “high” osteoporosis range at 12 months. A higher than normal CTX (>0.5 μg/L) would indicate that alendronic acid is not having a sustained effect and should be restarted. If the level is within range (ie, <0.5 μg/L), the drug holiday continues for a further 12 months.

There are no published data on how patients on ibandronic acid should be managed and these patients should be reviewed on an individual basis. Complex patients should be referred to specialist centres.