asked me if I might administer a much larger than usual dose of morphine to kill him. I spoke with him about code status and comfort care (evidence suggests that having such a conversation can reduce ICU admissions and even help alleviate suffering), feeling somewhat disingenuous, since I knew what would happen: our social worker would talk with him, take down a working phone number, and promise to call if a hospice spot opened up. He asked to be discharged.

Cifuentes, however, asked for something different. He asked to go home. So instead of calling the social worker, our medical team called the Guatemalan consulate. With Cifuentes's permission (he also gave me permission to use his name in this article), we described his diagnosis and prognosis and told them what we considered the best — and perhaps the only — medical plan: to send Cifuentes home.

Sending dying patients to their homeland is nothing new. In fact, many palliative care teams in immigrant-heavy areas have started to provide this service as something tantamount to granting a dying wish. Sometimes patients themselves pay, but often funding comes through the patient's home government, such as Mexico's Protección Civil department. Palliative care teams that routinely send patients home have built strong relationships with consulates, which are essential for the travel arrangements and for establishing medical care near the patient's home. If arranged properly, sending a dying patient home can be a win–win solution: it provides a dying patient a means of palliation without using county or emergency Medicaid funding.

At first glance, sending dying patients home at their request may appear to be an approach that would please advocates on both sides of the debate over illegal immigration. But it does raise some concerns. Would helping a dying immigrant to get home lead to the use of emergency Medicaid funds for palliative purposes? (If so, evidence suggests that hospice services for undocumented immigrants, as with all health care services, would cost significantly less than those for the native born.) Are we, by not providing dying patients the standard of care, coercing immigrants to return home? These are valid concerns, but they should not detract from the principal issue: in a system in which emergency care for immigrants is being limited and adequate palliation for dying patients is not possible — a system in which dying people feel compelled to return to the hospital immediately after discharge — sending the right patients home may be ethically necessary.

Two weeks after I discharged him — not to his apartment, not back to the emergency department, but to his home — I received a message: Cifuentes had died. The woman from the consulate sounded sad when she gave me this news, and it wasn't difficult to know why. She had accompanied our patient from the hospital through the airport and onto the plane. She'd arranged for a doctor to see him in Guatemala. She had delivered him to his ranchito near the Caribbean coast, where friends and his daughter gathered to help Mauricio Cifuentes die peacefully.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Bisphosphonates for Osteoporosis — Where Do We Go from Here?

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Osteoporosis, a disease characterized by reduced bone mass and increased skeletal fragility, affects 10 million Americans; another 34 million are at risk for it. Bisphosphonates are widely prescribed for osteoporosis; more than 150 million prescriptions were dispensed to outpatients between 2005 and 2009. All the bisphosphonates that have been approved for the treatment of osteoporosis have shown robust efficacy in preventing fractures in registration trials lasting 3 to 4 years. Recently, however, data on safety have raised concern regarding the optimal du-
ration of use for achieving and maintaining protection against fractures.

Normal bone growth and remodeling entail a tightly coupled process of bone resorption and new bone formation. Osteoporosis-related bone loss occurs when bone resorption exceeds bone formation; bisphosphonates decrease bone resorption, thereby slowing bone loss. The pharmacology of bisphosphonates is complex. During therapy, bisphosphonates are incorporated into newly formed bone and can persist there for years, through multiple cycles of bone resorption and deposition. Thus, patients continue to be exposed to the pharmacologic effects of bisphosphonate activity long after they stop taking the medication.

The long-term safety and efficacy of bisphosphonate therapy for osteoporosis are important concerns for the Food and Drug Administration (FDA). In response to postmarketing reports of rare but serious adverse events associated with bisphosphonates, such as atypical femur fractures, osteonecrosis of the jaw, and esophageal cancer, the FDA performed a systematic review of long-term bisphosphonate efficacy. The findings, summarized here, were presented at a joint meeting of the FDA Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Committee.4 The committees jointly recommended that bisphosphonate labeling be updated, although there was consensus that the data did not support a regulatory restriction on the duration of drug use.

The FDA review of the data focused on studies in which bisphosphonate drugs had been administered for at least 3 years and that had captured fracture data systematically and completely. We therefore focused on three long-term extension trials — the Fosamax Fracture Intervention Trial Long-Term Extension (FLEX), the Reclast Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly—Pivotal Fracture Trial (HORIZON-PFT) extension, and the Actonel Vertebral Efficacy with Risedronate Therapy—Multinational Trial (VERT-MN) extension — in which the duration of treatment ranged from 6 to 10 years (see table). All three studies were extensions of the initial fracture registration trials that had enrolled postmenopausal women with baseline fractures, low bone mineral density T scores (−1.5 or less), or both. The FLEX and HORIZON-PFT trials used a randomized withdrawal design in which patients who had previously been receiving bisphosphonate treatment were enrolled in the extension periods and underwent repeated randomization to receive either placebo or continued bisphosphonate treatment. Unlike the registration trials, the extension studies used bone mineral density as the primary outcome measure. Our analyses of the extension studies include both bone mineral density and fracture outcomes (which are limited to vertebral and nonvertebral osteoporotic fractures).

Overall, findings with respect to all three bisphosphonates were remarkably similar in terms of mean treatment-related increases in bone mineral density through 5 years.1 Continuation of treatment beyond 5 years resulted in maintenance of bone mineral density in the femoral neck and further increases in bone mineral density at the lumbar spine. In patients who were switched to placebo, bone mineral density in the femoral neck decreased modestly during the first 1 to 2 years and then stabilized, whereas bone mineral density in the lumbar spine continued to increase despite discontinuation of bisphosphonate therapy.

The data regarding responses in bone mineral density are similar to those in published analyses.4–4 In the FDA’s opinion, however, the more meaningful end point for osteoporosis therapies is the rate of fracture. Each bisphosphonate registration trial enrolled 3000 to 7500 patients and was powered for the demonstration of fracture efficacy, whereas the long-term extension studies, with enrollments ranging from only 164 to 1233 patients, were not. Because the question is one of long-term efficacy, the FLEX trial, with 10 years of bisphosphonate exposure, became central to the FDA review.

In the FDA analysis of vertebral fractures — both morphometric (also called asymptomatic or radiographic) and clinical or symptomatic fractures — occurring in the two randomized extension trials, the benefit in terms of fracture protection from continued bisphosphonate therapy was inconsistent. In the FLEX trial, the rate of clinical vertebral fractures, but not the rate of morphometric vertebral fractures, was reduced. In HORIZON-PFT, improvement was demonstrated in morphometric vertebral fractures but not in clinical vertebral fractures. An independent post hoc analysis of FLEX showed a benefit in terms of nonvertebral fractures in a very specific subgroup of patients — those without vertebral fractures at baseline who also had a femoral-neck T score of less than −2.5.5

According to the FDA analysis of the FLEX trial, the rates of
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Vertebral and nonvertebral osteoporotic fractures were similar whether participants continued to receive alendronate (Fosamax) for up to 10 years (a rate of 17.7%) or were switched to placebo for the extension period (16.9%). In the time-to-fracture analyses, fracture rates were consistent across treatment groups (Fosamax 5 mg, Fosamax 10 mg, and placebo) and all subgroups of bone mineral density through year 3 (approximately 8 years of continuous treatment, including the registration period). When all data on vertebral and nonvertebral osteoporotic fractures with long-term therapy are pooled across the three extension trials (2496 patients), fracture rates are shown to be relatively constant over time. Pooled data pertaining to patients who received continuous bisphosphonate treatment for 6 or more years result in fracture rates ranging from 9.3 to 10.6%, whereas the rate for patients switched to placebo is 8.0 to 8.8%. These data raise the question of whether continued bisphosphonate therapy imparts additional fracture-prevention benefit, relative to cessation of therapy after 5 years. Statistical limitations preclude inferring any meaningful association between long-term treatment and increased risk of fracture.

It should be noted that all fracture data discussed here are post hoc and are limited by statistical power, selection bias, sample size, and timing issues that vary among studies. Thus, the available data on long-term efficacy do not clearly identify subgroups of patients who are more likely to benefit from drug therapy beyond 3 to 5 years. Nevertheless, the emergence of safety concerns warrants consideration of new treatment algorithms for patients with osteoporosis. The available data do suggest that bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains, but no adequate clinical trials have yet delineated how long the drugs’ benefits are maintained after cessation. Additional data are needed to determine whether markers of bone turnover or bone mineral density can reliably aid in decisions concerning duration or interruption of bisphosphonate treatments.

All labeling for bisphosphonates that are currently approved for treatment of osteoporosis contains an “Important Limitation of Use” statement: “The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.” To optimize the efficacy of bisphosphonates in reducing fracture risk, decisions to continue treatment must be based on individual assessment of risks and benefits and on patient preference. In this regard, patients at low risk for fracture (e.g., younger patients without a fracture history and with a bone mineral density approaching normal) may

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**Long-Term Efficacy against Fracture for Three Bisphosphonates in Core Registration and Extension Studies.**

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Alendronate (Fosamax)</th>
<th>Risedronate (Actonel)</th>
<th>Zoledronic Acid (Reclast)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core registration study†</td>
<td>0–4 Placebo, 21.0%; alendronate, 10.6%</td>
<td>0–3 Placebo, 32.1%; risedronate, 20.5%</td>
<td>0–3 Placebo, 20.0%; zoledronic acid, 9.8%</td>
</tr>
<tr>
<td>Extension study</td>
<td>5–10 Alendronate/zoledronic/ placebo, 17.7%; alendronate/placebo, 16.9%</td>
<td>4–5 Placebo, 32.1%; risedronate/risedronate, 19.3%;</td>
<td>4–6 Zoledronic acid/zoledronic acid/placebo, 8.6%; zoledronic acid/ placebo, 12.0%</td>
</tr>
<tr>
<td>6–7</td>
<td>Risedronate/risedronate/ risedronate, 13.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† For purposes of comparison, proportions of patients with fractures in the core registration study are based on enrollment in the extension studies.

* Osteoporotic fracture was defined as a morphometric vertebral or a clinical vertebral or nonvertebral fracture, excluding fractures of the fingers, toes, hands, feet, and skull; traumatic fractures; or pathologic fractures. Data for the placebo groups in the core registration studies of alendronate and zoledronic acid are estimates. Alendronate data are from FLEX, involving 1099 patients with a maximum enrollment of 10 years. In the extension study, the patients received either continuous alendronate (alendronate/alendronate) or alendronate for 5 years followed by placebo for 5 years (alendronate/placebo). Risedronate data are from VERT-MN, involving 164 patients with a maximum enrollment of 7 years. In the extension study, the patients received either continuous risedronate for 5 or 7 years (risedronate/risedronate or risedronate/risedronate/risedronate) or continuous placebo for 5 years (placebo). Zoledronic acid data are from HORIZON-PFT, involving 1233 patients with a maximum enrollment of 6 years. In the extension study, the patients received either continuous zoledronic acid for 6 years (zoledronic acid/zoledronic acid) or zoledronic acid for 3 years followed by placebo for 3 years (zoledronic acid/placebo).
prove to be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years, whereas patients at increased risk for fracture (e.g., older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy.

Clearly, given the potential for cumulative risk, caution should be exercised in switching between bisphosphonates and other potent antiresorptive medications. Further investigation into the benefits and risks of long-term therapy, as well as surveillance of fracture risk after discontinuation of bisphosphonate therapy, will be crucial for determining the best regimen of treatment for individual patients with osteoporosis.

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