No price too high?

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Accessibility
NO PRICE TOO HIGH?

AGLUCERASE offers the first real hope of reversing the glycolipid deposition responsible for the painful and sometimes life-threatening complications of Gaucher’s disease. Because it is both uniquely promising and remarkably expensive, it poses stark dilemmas for patients, legislators, and physicians. Many patients treated with aglucerase risk the loss of their private health insurance coverage because they are likely to exceed its limits. Congress, which passed the Orphan Drug Act to encourage the development of treatments for uncommon conditions like Gaucher’s disease, is now debating whether the act goes too far to protect the profits of pharmaceutical companies. Policy makers and physicians who believe that cost should not be a consideration in deciding whether to approve or administer a promising treatment face a severe test of their conviction.

The standard regimen of aglucerase, devised by researchers at the National Institutes of Health (NIH),1 can cost hundreds of thousands of dollars annually per patient during the first phase of treatment. This phase, which usually lasts from 6 to 24 months, is followed by a lifelong maintenance phase at a lower dosage. NIH researchers hope to reduce the maintenance dosage to as little as 7.5 U per kilogram of body weight every two weeks6 — well below the dosages reported in the literature. At this low dose, the treatment still costs tens of thousands of dollars each year. Even bone marrow transplantation, once regarded as the most aggressive treatment for seriously ill patients with Gaucher’s disease, costs less.

Few patients pay these costs directly. Most have private health insurance policies that cover all but a fraction of the costs.2 But these policies usually specify a lifetime ceiling on health benefits (most commonly $1 million), and those who receive high-dose aglucerase regimens can reach the ceiling in two or three years. Thus, the costs of aglucerase therapy will frequently exhaust insurance benefits, and because nearly all private insurance plans either exclude coverage

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for preexisting conditions or refuse to enroll persons who have a serious disease, patients who lose their insurance usually remain uninsured.

Alglerase could be administered at lower cost if the price were lower or if less of it were used in treatment. In a study reported in this issue of the *Journal*, Figueroa and his colleagues at the Scripps Clinic tested the latter approach. In an ingenious application of their hypothesis that high-affinity receptors for glucocerebrosidase are rapidly saturated at the doses used in previous studies, the Scripps group tested a high-frequency ("fractionated") alglerase-sparring regimen. Their regimen appears to be as effective as the NIH regimen. Because the dosing schedule for the Scripps regimen is much less convenient than the leading alternatives and adds at least $6,500 to the annual costs of intravenous infusion, in other circumstances it would be a mere curiosity. But for a 70-kg adult, it can save $300,000 in drug costs in the first year.

The published studies do not definitively establish the therapeutic equivalence of the NIH and Scripps regimens. The NIH patients may have had larger loads of accumulated glycolipid than the Scripps patients. Subtle differences in the effectiveness of alternative modes of administering alglerase could have escaped detection. Larger and longer-term studies that carefully control for patients' characteristics will be needed to learn more about the effectiveness of each regimen. But without compelling evidence that an alternative regimen is superior, perhaps the regimen that costs hundreds of thousands of dollars less should be considered the new standard.

Even with the Scripps regimen, outlays for a 70-kg patient exceed $70,000 annually, about as much as for the lowest-dosage maintenance regimens proposed by the NIH researchers. Why is the price so high? The costs of research and development for new drugs, though difficult to measure, are usually substantial. According to industry spokespersons, pharmaceutical companies spend an average of $231 million (in 1987 dollars) to bring a "new clinical entity" to market. In the treatment of a rare condition, these costs must be recovered from few patients, making a low price infeasible. The pharmaceutical manufacturer must also recover production costs. Manufacturing usually accounts for a small share of the cost of producing a drug, but alglerase may be an exception. Currently, alglerase is derived from placental extracts, and Genzyme, the manufacturer, claims that its production costs are extremely high.

The price can be high, however, even if the costs of research, development, and manufacturing are not. Every American pharmaceutical company has an obligation to its shareholders to maximize profits, just as it has a mission to make safe and effective treatments available to patients. By greatly weakening the forces that ordinarily restrain the sellers of goods and products from charging high prices, our health care system sometimes awards manufacturers higher profits when they charge higher prices. If an automobile manufac-
and providers, decisions about the value of health care techniques are often implicit and fragmented. The United States has no coordinated strategy for controlling the availability of safe and effective techniques, regulating their prices, or capping health care expenditures. Consequently, medical innovations flourish in the marketplace, enabling American manufacturers to lead in the development of new drugs and devices, and Americans spend far more on medical care than the citizens of any other country. Dramatic advances in molecular biology promise to make both these features of American health care more prominent. Because major technological advances coincide with unprecedented public distress at rising health expenditures, policy makers, payers, and physicians face increasingly difficult choices.

Providing access to new and established forms of technology and health care while controlling expenditures is the paramount challenge facing American medicine. Sometimes scientific advances, like those of the Scripps group, make the task easier by lowering the cost of effective care. But we cannot expect advances in biomedical science to spare us from hard decisions. The need to make choices will compel us to weigh the costs and benefits of technological innovations and sometimes to conclude that a promising or effective treatment is just too expensive. Drawing such conclusions can be difficult, and acting on them painful. But if patients and payers never say no, we cannot blame the producers of medical advances for inferring that no price is too high.

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REFERENCES

SOUNDING BOARD
BARBITURATES IN THE CARE OF THE TERMINALLY ILL

Barbiturates are well known for their capacity to cause death reliably and painlessly and for their efficacy in producing unconsciousness before the administration of other lethal drugs. Barbiturates are used in the execution of prisoners by lethal injection, are commonly employed by Dutch physicians in performing euthanasia, and have played a part in reported cases of assisted suicide in the United States. A recent best-selling book recommends barbiturates as a reliable method of suicide for the terminally ill.

Physicians also administer barbiturates to the terminally ill without intending that they be used to cause the death of the patient. Even in these circumstances, however, the unavoidable side effects of the drugs may hasten the patient’s death, and caregivers may be uncertain about whether their actions will be viewed as killing or caring. In this article, we review situations in which the nonlethal use of barbiturates may be indicated and discuss situations in which their administration can be morally justified. We also provide practical advice for the use of these agents.

CASE REPORTS

Patient 1 was a 28-year-old woman with a retroperitoneal soft-tissue sarcoma that arose as a second cancer after she had been successfully treated for a rhabdomyosarcoma of the cervix and vagina at the age of 14. Despite surgical excision and chemotherapy, her second tumor spread locally, metastasized to her spine and lungs, and eventually invaded her spinal canal from T11 to L3. The intensity of her pain increased steadily. Maximal-dose radiation therapy had already been administered, and decompressive surgery was not feasible because of the size of the tumor. Trials of phenytoin and lorazepam were without benefit. A fentanyl infusion produced only partial relief.

A subarachnoid catheter was placed below the site of the tumor, and an infusion of bupivacaine diminished her leg spasms, but did not result in sensory analgesia in dermatomes above T11 because of a near-complete spinal block at approximately L1. A subarachnoid injection of phenol at T7–T8 also failed to provide adequate pain relief.

Her pain became so severe that she relinquished most decision making to her mother, with the understanding that she desired pain control even if it could only be achieved at the cost of sedation. She was then kept in a state of light sedation (with intermittent arousability to voice) with a fentanyl infusion (at a rate roughly corresponding to 5000 mg of morphine per hour), nitrous oxide (50 percent in oxygen) by face mask, and a methohexitol infusion (loading dose, 2 mg per kilogram of body weight; infusion, 4 to 5 mg per kilogram per hour) until she died of progressive hypoxemia two days later.

Patient 2 was a 19-year-old woman who for nine years had had an astrocytoma that now involved her brain stem and cervical spinal cord. As her tumor...