ANNALS OF INQUIRY

BITTER PILL

Dying patients wanted access to a new drug of uncertain benefit. But hasty approval comes at a cost.

BY GIDEON LEWIS-KRAUS

The wild success of the Ice Bucket Challenge, one of the past decade's feel-good social-media sensations, obscured its origins as a form of extortion. Its source, though murky, might be traced to Norway, where early nominees were pressured to choose between jumping into a frigid body of water and taking care of the weekend's bar tab. By early 2014, the moral ante had been upped: the penalty for noncompliance became, rather more nobly, a contribution to medical research. This structure—which incentivized bravado at the expense of charity—persisted until the spring, when American firefighters helped repackage the experience. Now a high-pressure hosing was the *reward* for a donation to a colleague's cause of choice. That July, a golfer decanted water on his own head in an effort to cheer up his cousin's husband, who had amyotrophic lateral sclerosis, or A.L.S., and invited others to donate to the "A.L.S. Foundation." By the end of the month, the idea, now connected to one disease, had taken on a life of its own. Bill Gates engineered an elaborate self-soaking contraption, posted high-definition footage, and challenged Elon Musk. The taunt was at once socially contagious, righteous, and fun. But there were still some disposed to see it as a threat. President Barack Obama, when drafted by Ethel Kennedy, Justin Bieber, and Donald Trump, declined in favor of a hundred-dollar contribution to A.L.S. research.

Organizations dedicated to A.L.S., unaccustomed to such largesse, were dumbfounded. At any given time, some thirty thousand Americans have the disease, which is characterized by a continuous loss of motor neurons until muscle function stills. Sustained patient-advocacy campaigns are limited by the fact that no one survives. As Gwen Petersen, a thirty-seven-year-old patient, told me, "There were the usual fund-raising walks, but asking an A.L.S. patient to walk is kind of tone-deaf." Merit Cudkowicz, the chair of neurology at Massachusetts General Hospital, said, "Patients are generally so overwhelmed with the day-to-day of their lives that the patient voice and advocacy were missing. And then it happened, and it's been very powerful, in mostly a really good way." In the pre-Challenge era, research was largely fruitless; the only drug on the market had been approved in 1995. But the viral campaign generated two hundred million dollars in aggregate donations, and one clinician hailed a "new era" in which she could "talk to patients with more hope." There was, in fact, no such thing as the "A.L.S. Foundation," but the assets of the A.L.S. Association, the top search result, grew fivefold, to a hundred and thirty million dollars. The group tripled its allocation to research.

One company working on the problem was a Cambridge-based startup called Amylyx, which traced its origins to a frat house at Brown University. In early 2013, Josh Cohen, an appealingly dishevelled junior, had an idea for a mechanism to slow the progression of degenerative diseases such as Alzheimer's and Parkinson's. Reading around in the literature, he struck upon studies of two known compounds that seemed to suit his notion. One was a generic drug for urea-cycle disorders. The other was an acid found in bear bile, which is a mainstay of Chinese medicine; it can be bought on Amazon for thirty-seven cents a pill. Late one evening, Cohen ran into a fraternity brother named Justin Klee, who asked him why he looked so unwell. Cohen told Klee that he'd been spending his nights researching whether these two molecules might, in combination, prevent neuron death. Within a day or two, they'd decided to start a company.

The pair had almost no idea what they were doing, but a prominent Alzheimer's researcher agreed to collaborate—if only to show two endearing college kids how difficult research really was. To his surprise, initial experiments returned positive results. Potential investors, however, were skittish. As Cohen told me, "There had recently been a long spate of failures in Alzheimer's, and we were just these two young guys." As the Ice Bucket Challenge became ubiquitous, they chanced to get a meeting with Cudkowicz. She had recently run her own trial with one of the compounds, but there is little commercial incentive to study generics, and she couldn't secure the funding to continue. Cohen and Klee, however, had already obtained a patent for their two-drug combination, which they called AMX0035. Cudkowicz persuaded them to pivot to A.L.S.

Their decision was in part emotional. Klee told me that they were struck by the selflessness of A.L.S. patients in trials: "You hear so often, 'I know this may not help me, but I'm doing this for the people who get the diagnosis after me.'" But the new focus also made practical sense. Alzheimer's trials each involve thousands of patients, but those for A.L.S., which is rarer, might enroll only a few hundred. Cudkowicz co-chaired a research organization that offered Amylyx a ready-made trial infrastructure. Advocacy groups were looking to distribute their Ice Bucket money, and Amylyx collected a grant from the A.L.S. Association and A.L.S. Finding a Cure. Substantial investor capital followed. One of the company's largest funders was a Dutch biotech entrepreneur named Henri Termeer, who demonstrated that rare diseases could be rendered profitable—as long as payers would tolerate high prices. Amylyx began a Phase II study that followed a hundred and thirty-seven patients for six months, with a subsequent "open-label extension," during which all trial participants could receive the drug for free. When the results came back, Cohen and Klee called the Alzheimer's researcher, after midnight, and



"Are we selling hope?" the clinician Jonathan Glass said. "Or are we selling things that we know really work?"

ILLUSTRATION BY MARIA CHIMISHKYAN

told him to pour himself a drink. "They didn't say anything about money," he has said. "They told me, 'Guess what: Amylyx is going to help A.L.S. patients.'"

According to a study published in 2020, AMX0035 seemed to slow patients' decline by about twenty-five per cent during the trial period. A later finding gave even greater reason for optimism: in the trial's extension, those who never got the placebo in the first place survived an average of five months longer. The drug had few side effects, apart from some gastrointestinal distress. Cudkowicz told me, "You get so used to things not working out that you try to shield yourself from disappointment, and it was just amazing that their idea worked." Still, the results were not unambiguous. In an editorial, two outside researchers advised that the "tantalizing preliminary data" be interpreted with restraint: the effect was "modest," and a larger trial would be needed as confirmation. Cudkowicz concurred. "We did not design this study to be the single study for F.D.A. approval," she said.

Historically, the F.D.A. has required two "adequate" trials before it approves a drug. In Amylyx's case, a subsequent trial was likely to take three more years. The A.L.S. community, however, felt that there was no time to waste. The majority of current patients would be incapacitated or dead if they had to wait that long. Dr. Neil Thakur, the A.L.S. Association's chief mission officer, observed on the organization's podcast that the study's results were "not a slam dunk." "The findings aren't as strong as what the F.D.A. typically does to skip a Phase III trial," he said. "So I think they're going to need some help to make that decision." Advocacy groups began to mobilize. Brian Wallach, a forty-two-year-old who had co-founded a young organization called I AM A.L.S., believed that his life and those of thousands of fellow-sufferers hung in the balance. "Please do not let another generation of A.L.S. patients die in pursuit of the perfect," he later told regulators. "We want to live. You have the power to make that possible."

Drug regulation in America has been driven by public calamity. In 1937, a company in Tennessee sold Elixir Sulfanilamide as a remedy for streptococcal infections. The active ingredient had been dissolved in a chemical used in antifreeze, and a hundred people died, many of them children. The Food and Drug Administration, which had been feeble since its founding decades earlier, was empowered to insure that drugs weren't needlessly harmful before they could be sold. Nevertheless, useless potions proliferated. In 1961, at the National Congress on Medical Quackery, the U.S. Secretary of Health, Education, and Welfare pointed out that, along with actual snake oils and other nostrums, bottled seawater was being sold for up to twenty dollars a gallon as a "panacea for virtually all human ailments." Soon after, the antiemetic thalidomide was determined to cause severe birth defects overseas. One F.D.A. official had steadfastly resisted corporate pressure to approve it, and public confidence in the institution swelled. Congress radically expanded the agency's mandate, granting it authority over not only safety but also efficacy.

In the next decade, though, free-market pundits and economists increasingly saw the F.D.A. as an example of excessive regulation. The average development times for drugs had grown considerably, and fewer were coming on the market. Some critics attributed this decline in pharmaceutical dynamism to the perverse incentives of the career bureaucrat. There were, they pointed out, two primary kinds of errors that regulators might make. They might approve a product that turned out to be unsafe—as they did in 1976, when they signed off on a swine-flu vaccine that, in some cases, led to paralysis—and face the public's wrath. Or they might fail to act quickly on a drug that later proved effective—as in the case of beta-blockers, which were available in Europe years before they were deemed fit for consumption in the U.S. The first kind of error, a so-called Type I error, was conspicuous, and thus likely to be corrected. But the second kind, a Type II error, had no natural constituency to demand redress. The libertarian economist Alex Tabarrok came to describe these victims as interred in the "invisible graveyard."

On October 11, 1988, members of ACT UP, a newly formed coalition of AIDS activists, stormed the F.D.A.'s headquarters, then in Rockville, Maryland. In the midst of the H.I.V. epidemic, a lengthy drug-approval process seemed unconscionable. Gregg Gonsalves, a former member of ACT UP, told me, "People came up to me in ACT UP meetings and asked if there was a drug that could help with one opportunistic infection or another. There was nothing for them. And to say that out loud is hard." The group's members didn't want to be told what risks they could take. Richard Klein, a retired F.D.A. official, told me, "A guy

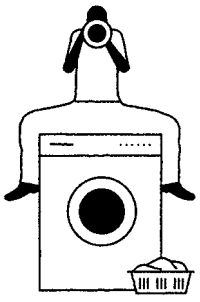


called me up, and he was really angry that he couldn't use whatever H.I.V. therapy from Mexico he wanted to get. He said, 'I can go to Vegas and gamble away my last nickel and nobody would say anything about that, but this is my life—why can't I gamble with it?'"

As the historian Lewis A. Grossman notes in his excellent book "Choose Your Medicine," previous generations of activists had focussed on a patient's right to have a say in her care. In one study in the nineteen-sixties, about half of doctors surveyed thought that it was medically acceptable to perform a mastectomy on an unconscious woman without her explicit consent. In a 1970 Senate hearing on the safety of oral contraceptives, every member of the proceedings was a man. The women's-health movement changed all of this.

For some activists, the emphasis on autonomy included promoting unorthodox treatments—rejecting chemotherapy in favor of, say, apricot kernels. What distinguished ACT UP was its longing for access to the products of the "government-industrial-academic biomedical complex." Protesters outside the F.D.A. building wore white lab coats stained with fake blood; others held a die-in, with cardboard gravestones bearing epitaphs like "I Died for the Sins of FDA." This sentiment brought AIDS activists into uneasy alignment with the right. Grossman describes a surreal episode of "Crossfire" that aired just hours after the protest. The guests were the AIDS activist Peter Staley, who had worn a "Karate Kid" bandanna and scaled the F.D.A. building's façade to hang a "Silence = Death" banner, and Pat Buchanan, whose recent memoir had described Gay Pride Week as a "celebration of sodomy." Buchanan said, "Mr. Staley, this is going to astonish you, but I agree with you a hundred per cent. I think if someone's got AIDS and someone wants to take a drug, it's their life, and if it gives him hope he ought to be able to take it."

After the ACT UP occupation, Grossman writes, the F.D.A. "never really resumed business as usual." In 1992, it introduced a pathway called "accelerated approval," which could be granted to drugs that showed an impact on a biomarker associated with a given disease (H.I.V. viral load, for example), even if they hadn't yet demonstrated a clear clinical benefit. The agency had also formalized its commitment to "expanded access," a way for patients with serious or life-threatening diseases who had no other options to get investigational drugs. In 1997, Congress allowed the F.D.A. to approve drugs on the basis of a single trial, as long as the evidence was persuasive enough. The entire orientation of the agency changed. It was no longer chiefly protecting patients from drugs that might hurt; it was now trying to facilitate consumer access to drugs that might help.



Brian Wallach grew up in Washington, D.C., the grandson of the last U.S. Ambassador to Iran and the son of establishment lawyers. He served as a political director on the first Obama campaign, where he met his wife, Sandra Abrevaya, a communications director. He then got a job in the White House counsel's office, and later served as a federal prosecutor in Chicago. In 2017, while he was working on a gun-trafficking case, his left hand started to cramp. He dropped his pen, then dropped it again. A few months later, on the same day that the couple brought their second daughter home from the hospital, he was given his diagnosis and told that he had perhaps six months to live. In March, I spoke with Wallach and Abrevaya, as they were preparing for a ski trip to Colorado. Wallach has curly graying hair and sensible blue-rimmed glasses. He spoke into a small marshmallow of a microphone, and wore around his neck a voice amplifier that resembles a camera, giving him the look of an unapologetic tourist. A varsity-style banner on his wall reads, "Joy is an act of resistance." When he first told friends about his diagnosis, he said, he often found himself doing the consoling. "My family never knew if the vacations we were on would be the last," he told me. "I'm someone who's stubborn and optimistic, so it was my job to say, 'This is awful, but we will find a way forward.'"

Wallach and Abrevaya founded I AM A.L.S. as a "patient-centric, patient-led" organization. One of his goals, as a proper Obama disciple, was to "change the narrative" around the disease. He and Abrevaya remember turning off a "60 Minutes" segment about A.L.S. because it was so depressing. "We knew this was not the whole story," he told me. Researchers felt that the Ice Bucket Challenge had put them in a position to make great advances, but they needed influential allies. "The fuller story was one of hope, and the only question was when that hope would be realized," Wallach said. He read every book he could about AIDS activism, and learned that only a "sustained advocacy presence" in D.C. could make A.L.S. a priority. The group hired a lobbying firm and helped form an A.L.S. congressional caucus, which worked to pass legislation that directs a hundred million dollars a year to research. Wallach hand-delivered an open letter to the F.D.A. inquiring after treatments that were "stuck in the pipeline." In a short film circulated by the Obama Foundation, Abrevaya describes the couple as "back in campaign mode. We spend our date nights editing Web-site copy and coming up with awareness strategies."

One of the ways I AM A.L.S. differentiated itself was its relentless pursuit of *any* treatment that seemed promising. Wallach told me that modest gains could add up: "When you're dealing with a terminal illness, you piece together the therapies that keep people alive longer until more curative therapies come on the market." The F.D.A. had made it clear that Amylyx was expected to complete another trial, but Wallach knew that the agency could approve the drug immediately. Scientific certainty was a luxury that only the healthy could afford. He and other patients were already buying a version of the product from compounding pharmacies, for about seven thousand dollars a year. "I will give credit to those drugs for me being here well past the point when I should have passed away," he said. The A.L.S. Association, which some patients had criticized for failing to advocate more aggressively for other experimental medicines, launched an e-mail campaign. Members met with regulators, including the acting director of the F.D.A. "I saw on the campaign and in the White House how important it was for people

in Congress to know who you are," Wallach said. "When we announced my diagnosis, everyone reached out and said, 'How can I help?'"

In late May of 2021, the A.L.S. Association convened an event called the We Can't Wait Action Meeting. A patient named Troy Fields expressed frustration that a purported survival benefit of several months, in patients who live only a few years, had been described as "modest." "For me, this could mean walking my daughter down the aisle at her wedding, or witnessing my grandson's birth," he said. Sandy Morris, a well-known A.L.S. activist, told a story about a friend, Cory, who had surveyed the community and determined that patients had a "sky-high acceptance" of the potential risks. "Cory died waiting," she said. "I am here today to say that I am dying waiting."

Wallach called for a congressional hearing, and his wish was swiftly granted. At the hearing, Representative Anna Eshoo referred specifically to Amylyx's drug as she interrogated an F.D.A. official about agency sluggishness, a rare congressional endorsement of an investigational treatment. Representative Jan Schakowsky, who beforehand had met with Wallach, a constituent, thanks to Abrevaya's connections, told a story about a friend with A.L.S. who had chosen assisted suicide. "If I sound upset—because my constituents are here—I have been getting calls from their friends all over the country, who are begging for a bit of hope," she said. Wallach, in his testimony, noted that thousands of patients were watching. "Some of them have waited and postponed their decision for suicide to see this hearing," he said. "When you are diagnosed with A.L.S., you are told you have two to five years to live. So if this won't be on the market for four years, every single A.L.S. patient, including us, will be dead." Two months later, the F.D.A. reversed its position, and invited Amylyx to submit its application.

Contemporary patient advocacy might owe its energy and ambition to AIDS activists, but the radical theatricality of the eighties and nineties—wrapping Jesse Helms's home in a giant condom, scattering victims' ashes on the White House lawn—has largely given way to a shrewd professionalism. The A.L.S. Association's office, in Rosslyn, Virginia, could be confused with the glossy sanctuary of a mid-size lobbying firm. When I visited, in March, Calaneet Balas, the C.E.O., told me that the group's goal is "making A.L.S. livable"—an objective that means different things to different people. What we now call A.L.S. might ultimately be understood to encompass several different diseases. For ten per cent of patients, the disease is linked to known genetic mutations. For the remaining cases, environmental and behavioral factors are presumably relevant. There are unexplained clusters, for example, in Ohio and Michigan, and veterans are more than twice as likely to contract the disease. At the A.L.S. Association's urging, the V.A. has designated the disease as connected to military service, which has unlocked additional benefits. Before Amylyx's drug, the Association hadn't involved itself in an approval process—not that it had many opportunities to do so. But the group was invested in this drug, both literally—it stood to make a return of a million dollars on its original grant, which it planned to dedicate to future research—and symbolically: approval would pleasingly close the loop on the Ice Bucket Challenge. Still, Thakur, the chief mission officer, told me that the organization was ultimately convinced by the evidence: "We don't want to be confused with a group that's not scientific."

AIDS advocacy—which drafted on previous movements—helped adapt the health-care system to the desires of patients. Today, they are consulted at every stage of the drug-development and approval process: they help shape funding strategies at the National Institutes of Health and contribute to technical debates over trial design, study criteria, and the relevance of particular metrics to their own experiences. As an F.D.A. representative put it, patients come to the table with their own Ph.D.—"personal history of disease." Patient-advocacy organizations have flourished, and some have been extremely fortunate in their strategic decisions: the Cystic Fibrosis Foundation funded research into drugs that have proved nothing short of magical for some patients, transforming a death sentence into a manageable condition.

Investments in basic research, however, are generally long-term bets, and people with terminal diagnoses are understandably impatient. They have come to see drug-approval decisions as their moments of maximum leverage. As Grossman put it to me, advisory-committee meetings, in which outside experts advise the F.D.A. on particularly vexing cases, "used to be snorefests, just a group of green-eyeshade people sitting around running numbers. Now, depending on the drug, they've turned into fora for public advocacy." Many patient-advocacy groups are lushly funded: last year, the Alzheimer's Association's revenue was about half a billion dollars. A study in *The New England Journal of Medicine* found that at least eighty-three per cent of the largest groups receive money from pharmaceutical companies. "H.I.V. activism was a true grassroots movement, not one funded by drug companies," Daniel Carpenter, the author of "Reputation and Power," a colossal history of the F.D.A., told me. "I don't want to say everything since then has been astroturfed. But companies do learn the lesson of 'Oh, that's how you get a drug through the F.D.A.'"

Groups that are wealthier and better coördinated have significant advantages: breast-cancer advocacy organizations have been particularly potent, and Carpenter has shown that they enjoy much faster approval times than groups dedicated to prostate cancer, which is similarly prevalent, or to lung cancer, which is deadlier. In 2002, lung-cancer patients coalesced in support of Iressa, a drug that faced considerable F.D.A. doubt; the drug was approved, and is still prescribed to a subset of patients. In 2016, parents of children with Duchenne muscular dystrophy pressured the F.D.A. to green-light a drug that had been studied in a single uncontrolled trial of only twelve boys. Hundreds of supporters flocked to an F.D.A. committee meeting, including several children in wheelchairs, and the approval camp prevailed.

It wasn't until recently that the role of advocacy groups provoked public scrutiny. In June, 2021, the F.D.A. announced the accelerated approval of Aduhelm, the first new treatment for Alzheimer's in eighteen years. Aduhelm reduced levels of amyloid plaques in the brain, a biomarker that tracks with cognitive decline. But the drug seemed to do little, if anything, to arrest or reverse the course of the disease. It also carried the risk of

serious adverse effects, including brain bleeding. Nevertheless, many enrollees felt sure that their progression had been slowed. The Alzheimer's Association—which had collected about half a million dollars that year from the drug's sponsor, Biogen—exhorted its members to plead the drug's case. (The Association's C.E.O. at the time said that its actions were not affected by pharmaceutical funding.) An F.D.A. advisory committee voted against the drug's approval, but the committee was overruled by the F.D.A.

The drug was put on the market at a cost of fifty-six thousand dollars a year. Three members of the committee resigned, among them Aaron Kesselheim, a professor at Harvard Medical School, who declared the ruling perhaps "the worst approval decision that the F.D.A. has made that I can remember." Kesselheim saw it as part of a long war of attrition. "In recent years, under steady pressure from the pharmaceutical industry and the patient groups it funds, the F.D.A. has progressively lowered its standards," he wrote. (Biogen stands by the drug, and maintains that it satisfied the requirements for accelerated approval.) Some patients felt as though they'd been sold a bill of goods; a retired neurologist in the early stages of the disease told the *Times* that he found the Alzheimer's Association's campaign "shocking and irresponsible." But perhaps no one was as crestfallen as A.L.S. advocates, who lamented only that the F.D.A. had not yet shown them the same generosity.



"Oh, great. Pumpernickel Pete is here."

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In March, 2022, the F.D.A. gathered an advisory committee to discuss Amylyx's application. Members would be asked to vote on whether the results so far "establish a conclusion" that the drug is "effective." Agency officials, in their briefing documents, were polite, respectful, and unequivocal: the answer, as far as they were concerned, was no. One of the members of the committee was Caleb Alexander, a soft-spoken pharmacoepidemiologist at Johns Hopkins, who spoke with me from a sabbatical in Munich. He told me he wished that the evidence had been more persuasive. "Too bad but I suppose this is why one has advisory committees," he wrote in his notes.

As the agency saw it, there were a number of problems with the trial. Recruits had been told that they might experience gastrointestinal side effects, so they could have guessed if they were getting the real thing or a placebo—a salient issue for a trial that relied on self-reported measures. Trickier still were potential "baseline imbalances," especially during the trial's extension: those who switched from the placebo to the drug were, on average, healthier than those who had dropped out along the way, which might have exaggerated the ostensible effects. Some outcomes were also compared with "external" controls—that is, data from patients in previous decades, when the general standard of care was lower. Most important, the F.D.A. had proposed one method of statistical analysis, but Amylyx had elected to use an alternative. When the F.D.A. subjected the data to its own test, the results were no longer statistically significant. (Administrators defended their analysis, and argued that the other apparent issues were either negligible or addressed.) Alexander told me, "It was like fourth down in football, where you have to bring out the measurement tape to see if you got a first down or not."

The agency was reluctant to accept the apparent five-month survival benefit, which it regarded as the result of a statistical fishing expedition. Alexander told me, "I was mindful of the old Texas sharpshooter fallacy—you shoot holes in a barn and draw bull's-eyes around those holes." The agency did not rule out the possibility that the drug might do *something*. But the standard for approval is not "promising"; it is "substantial evidence of effectiveness." Cudkowicz said, "In the end, we just didn't know who was right. This was a really small study that was never designed to do what it was being asked to do."

The patients, for their part, seemed unable to believe that this discussion was happening at all. They felt as though they were being buried alive by the disease while the F.D.A. was making a fuss about confidence intervals and P values. Wallach told me that the agency's position had been pushed primarily by its biostatistician—the last defender of a retrograde regime that sought "one-hundred-per-cent certainty that a drug works." Patients recruited by the advocacy groups told agonizing stories. When Jeff Derby was diagnosed, in 2018, his neurologists told him to get his affairs in order and to eat whatever he wanted. He believed that his presence at the

meeting was due to Amylyx's drug. "I have seen six A.L.S. patients in my social circle over the past two years pass away without it, and yet their timeline was similar to mine," he said. He asked committee members to imagine having a loved one with A.L.S.: "Even if it is only six and a half months, would you not want that for them?" Sandy Morris, the patient activist who had commanded the room during the We Can't Wait meeting, now spoke mostly through her daughter. "My apologies for my compromised voice," she said on her own, at the end. "Maybe if I had been allowed to take AMX0035 you would be able to hear me more clearly."

Alexander told me, "Those clips from the meeting are very compelling. But they're not talking about the scientific merits at hand. Some of the patients just assume the five-month purported benefit is real. Didn't they realize just how large the probability was that the drug won't work? That this might not be a one-per-cent chance it won't work but a *good* chance?" As Jonathan Glass, an Emory University researcher and physician with three decades of experience treating A.L.S. patients, told me, "What are we selling to patients? Are we selling hope? Is that what we should be selling? Or are we selling things that we know really work?"

In the end, the committee voted against the drug, 6–4. One skeptical patient, who has been affiliated with I AM A.L.S., told me that he had been asked to testify at the meeting but refused. "I didn't see the evidence," he said. "It's very easy to beat the statistics to death until you get a finding you like." He continued, "It's possible that the A.L.S. Association has been driven into positions of public support for a quote-unquote promising therapy that it might privately question, because I AM A.L.S. is taking that position. But I AM A.L.S. itself is being pushed into that position by this super-hard-line crowd, and no one can afford to be anything less than the most strident."

More than two decades after he first joined ACT UP, Gregg Gonsalves, now a professor of epidemiology at Yale and a MacArthur Fellow, fretted that AIDS activists had made a "devil's bargain." The Alzheimer's Association's "activist shtick" on behalf of Aduhelm, he said, reminded him of a story from the AIDS era. One night, Larry Kramer arrived at an ACT UP meeting hollering that people were dancing in the streets of San Francisco because something called Compound Q, a Chinese cucumber extract, was going to alleviate AIDS symptoms. As it turned out, the extract didn't alleviate anything. "It sounds ridiculous in retrospect, but every few months you'd hear about something like Compound Q," Gonsalves told me. "At a certain point, we realized, Oh, shit, we're just getting dud after dud after dud." Gonsalves has worked with A.L.S. advocates, guiding them on how best to make headway. But he has also reminded them that AIDS activists "got lucky"—an effective cocktail was developed about a decade after the virus was identified. A.L.S. was first described a hundred and fifty years ago, but we still have a lot to learn about the underlying physiopathology. Gonsalves's father recently died after a long descent into dementia. "We need better drugs for neurodegenerative diseases," he told me. "But the way to do it is not to say, 'Open the floodgates of the F.D.A.'" In the AIDS era, Gonsalves learned a lesson that each new patient community has had to learn for itself. "Access was only as good as the answers that came with the pills," he has written. "Hope in the absence of data was astrology."

By the early nineties, ACT UP was beginning to splinter. In 1988, when activists stormed the F.D.A. building, the agency was the enemy, and the goal was

THERAPY

Early snow. Garbage
trucks in the alley pushing
slush around, chewing.

Gnawed by a hundred
minor obligations, I draw
a bath, then sit on the toilet

fully clothed. I want
a therapist, I said to Meg,
smarter than me. You

charm them, she said. You
need a man, someone the age
your dad would be now.

How old would you be now?
I do the math and come up
with a number so low

I check again. Nothing
changes. I go out and drag
the bins back to the house,

then lower myself
into the lukewarm tub. I let half
the water out and turn

the tap, mixing the original
water with water that would
scald me if I touched it.

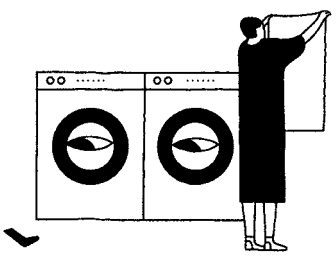
—Edgar Kunz

to get "drugs into bodies." During the next few years, however, a group of autodidactic "treatment activists" collaborated more closely with the scientific community, and their perspective changed. As many activists have since acknowledged, it wasn't entirely fair to blame the agency for the apathy shown by the Reagan Administration. F.D.A. officials had made AZT, the first antiretroviral to target H.I.V., available for "compassionate use" while still in trials, and it was approved with unusual alacrity. As Gonsalves told me, "There weren't hundreds of drugs hiding behind the curtain at the F.D.A. It was much more complex." In 1991, ACT UP called for a moratorium on close collaborations between activists and researchers. Gonsalves and some of his colleagues split off to form the Treatment Action Group, or TAG.

The accelerated-approval pathway, which was introduced the next year, was heralded by ACT UP as a major victory, but, in time, TAG activists grew apprehensive. In theory, accelerated approval was provisional: the drug could go on the market, but the drug's sponsor still had to prove that it worked. TAG activists worried that companies with an approval in hand were unlikely to follow through. In 1992, a new antiretroviral was the first candidate for the process. Mark Harrington, a TAG founder and the F.D.A. advisory committee's patient representative, was unconvinced that the drug would do much. But the AIDS community was largely in favor of the drug, and he felt honor-bound to vote yes. His suspicions eventually proved correct. Harrington later wrote that "the AIDS community, in its understandable desperation, was being manipulated by industry to demand the expeditious approval of inadequately tested drugs."

Two years later, Gonsalves, who replaced Harrington on the committee, was asked to consider another antiretroviral. He felt that the confirmatory trial planned for the drug was too small. When he voted no, ACT UP activists described the decision as "self-hating and GENOCIDAL." Later that year, the F.D.A. evaluated a new protease inhibitor that was still in early-stage trials. Gonsalves and other TAG members wrote a letter to the F.D.A. commissioner, imploring him not to grant accelerated approval. Many members of ACT UP were horrified. As it turned out, the drug worked, but it was soon overtaken by others in its class; had it been hastily approved on flimsy evidence, a generation of patients might have been treated with an inferior product. If the crusade for access wasn't accompanied by a commensurately spirited campaign for answers, the chief beneficiaries would be the pharmaceutical companies.

Such episodes prefigured a broader turn in the case for exacting drug regulation. For the past fifty years, the standard criticism of the F.D.A.—one common among conservatives and patients—has been that it treats those who are ill as too muddleheaded and desperate to think for themselves. The agency might otherwise publicize its opinions without making them coercive: just as customers in search of a budget-pick vacuum might consult Wirecutter, those curious about a drug could turn to the F.D.A. Patients would be allowed to experiment, and their doctors could be trusted to guide them. But the TAG activists argued that an empowered F.D.A. was essential to generate the information necessary to make rational choices. Amy Kapczynski, who worked with ACT UP and is now a law professor at Yale, has pointed out that pharmaceutical knowledge is a public good, one that no market actor has an incentive to produce. Companies tend to publish positive data; insurance companies, conversely, interpret results to restrict coverage. The F.D.A.'s premarket



review process is likely the *only* means by which we can get a reliable sense of whether a drug works.

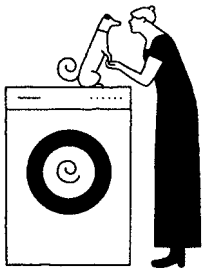
This might seem counterintuitive, but drugs are not like other consumer products. Carpenter told me that the Wirecutter scenario would benefit only the companies with the largest marketing budgets: "You can't go out and drive a drug. You can't feel a drug working. So if I can get into the market and persuade people with advertising that something is superior, I can advertise my way to a position of profitability." It is often impossible even for clinicians to tell whether a medication—especially one that purports to slow a disease's progression rather than cure it—is helping people. As Joseph Ross, a professor at the Yale School of Medicine, told me, "People want to wave their hands and say, 'Somehow we'll find out whether it works,' and it's just not the case."

The accelerated-approval pathway is supposed to split the difference by making drugs available while confirmatory trials are pending. Once a drug is on the market, however, it can be difficult to recruit participants for placebo-controlled trials. (Why would anyone risk getting a sugar pill when she could get the real thing?) The remaining option—a process of trial and error—sounds more plausible in theory than it is in practice. Alison Bateman-House, a bioethicist at N.Y.U.'s medical school, raised the example of convalescent plasma, which was indiscriminately used to treat COVID patients at the beginning of the pandemic. "People were, like, 'Wow, ninety thousand people are using this, so we'll get real-world data,' but, as it turns out, we still have no idea," she said. Even when drug sponsors manage to complete confirmatory trials, the results can remain up for grabs. Kesselheim, the Harvard professor, recently looked at the past two decades of accelerated approvals in oncology—a field often touted by advocates as an excellent model of "regulatory flexibility"—and found that only about a fifth of approved drugs ever showed a meaningful impact on survival. Cancer patients now have their choice among an array of very expensive options that might or might not do anything for them.

The F.D.A. has the power to rescind drug approvals, but the process is burdensome and protracted. In 2011, the agency gave accelerated approval to Makena, the only F.D.A.-approved drug for preterm birth, a condition that disproportionately affects women of color. A large follow-up study, which was completed eight years later, showed no benefits. But the manufacturer drew on the support of doctors and patients—who don't appreciate having their only option taken away—to argue that the drug's availability was a matter of health equity. It was taken off the market only this past

spring, under extreme duress. (Makena's manufacturer did not respond to requests for comment.)

The most coherent argument against strict regulation is that it is simply immoral to withhold a potentially effective treatment from a person who wants it. Jessica Flanigan, a libertarian philosopher and the author of the book "Pharmaceutical Freedom," told me, "Patients who are suffering shouldn't be used as a means to generate public goods. It is wrong to hold patients hostage." But the reality is that, in most cases, the best way to know if a new drug works is to deny access to some people it might benefit. This is a wrenching but often necessary trade-off. To prioritize access over knowledge is to address the needs of current patients at the expense of future ones. Either way, it's the lives of patients all the way down.



The skeptical patient told me that he thinks about this all the time. "There are maybe twenty-five thousand of us now," he said. "But when you do the math the total number of people in the U.S. who will ever get A.L.S.—maybe five years from now, maybe seventy years—is well over half a million people, and we owe them actions and policies and principled behavior that maximize the odds of getting a therapy that stops or prevents this disease. Part of this, for me, is the clarifying effect when you're given a terminal diagnosis: How do I want to live the rest of my life? I try to live as best I can." He was willing to articulate this argument only anonymously, because it left him vulnerable to nasty mobs on social media: "When you mention our obligations to people who don't yet have A.L.S., you don't always get a positive reception."

Brian Wallach believed, after the first advisory committee, that the F.D.A. could still be persuaded to rise to the occasion. When we spoke, he and Abrevaya rejected the insinuation that they had mustered "soft anecdotes" against hard science. "The characterization of us as desperate and uneducated, pressuring government to do things they shouldn't do, is hurting our efforts to climb a mountain to save our own lives," Wallach said. He asked Jonathan Glass, who had administered one of the trial sites, to add his byline to an op-ed on the drug's merits, but Glass demurred. Glass told me, "I really like Brian, and I said to him, 'Brian, you're still going to die, whether you get this drug or not. It's the disease that's killing people, and it's nobody's fault.'" He added, "This black-and-white idea that if you approve the drug you're saving lives and if you don't there's blood on your hands—that's just a useless argument." The A.L.S. Association organized an open letter from clinicians, but Glass refused to sign it; for a trial administrator to weigh in on approval felt to him like a clear conflict of interest.

Glass wasn't alone in his misgivings, but it wasn't easy to argue with terminally ill patients without seeming monstrous. A respected bioethicist put forth, in a mild tweet, that she believed future patients also deserved consideration. An A.L.S. patient responded with a video in which the bioethicist's head had been superimposed on a woman forcibly stripped of her clothes and thrust into a wheelchair. "Do not speak on behalf of the A.L.S. community," the text reads. "You do not have a degree in 'dying from a brutal terminal disease.' At the same time, we will not comment on being a heartless robot that lacks human compassion, as we do not have a degree in cuntiness. Bodies are ravaged by ALS. We are powerless. The FDA is not, and yet the rape of every ALS body continues under their watch." The skeptical patient told me, "There are A.L.S. neurologists who have told me that they felt almost blackmailed into supporting some of these therapies because of the fear of being attacked on social media, and, if they're running trials, they can't afford to have patients walking away from their clinics."

In September, the F.D.A. took the exceptionally unusual step of reconvening the advisory committee. New analyses had been published, along with a paper by Cudkowicz that sought to rebut the F.D.A.'s criticisms of the trial. But Cudkowicz said that patients deserved as much credit: "There was a whole groundswell in the movement. People had gone from thinking approval wasn't even an option to the idea that it would be offensive not to approve it." Caleb Alexander, who had voted no initially, was stunned. "They gave the sponsor a second bite at the apple," he said. The F.D.A.'s summary documents looked as bleak as they had the first time. As Mark Weston, the committee's patient representative, put it, "It almost feels like this is a setup to say, 'Gee, we warned you.'"

But when the meeting began Billy Dunn, then the director of the F.D.A.'s neurology office and the official who oversaw Aduhelm's approval, opened by declaring that A.L.S. patients were entitled to the "maximum degree of regulatory flexibility." The worst thing that could happen was for the Phase III trial, which is required for European approval, to show that the drug didn't work, and Dunn asked Amylyx's C.E.O.s if, in that case, they would withdraw the drug. Justin Klee, now a thirty-one-year-old executive with shareholders, offered a pledge of sorts: "We will do what is right for patients, which includes voluntarily removing the product from the market." Kesselheim told me, "To highlight this unenforceable promise as an essential part of that meeting? I can empathize with somebody sitting on the committee and thinking it seemed like it was theatre."

The F.D.A.'s remit does not extend to drug pricing, but Kenneth Fischbeck, a committee member from the N.I.H., pushed to consider the issue. Amylyx had already made the drug freely available through an expanded-access program, though enrollment had been capped at a few hundred. "What we are basically doing, as I understand it, is helping to decide whether or not the company can charge for this drug," he said. "I don't think there's any limit on their ability to give it away for free."

The F.D.A. saw nothing new in Amylyx's presentation aside from more analytic sleight of hand; the company's supporters saw nothing new in the F.D.A.'s hesitation aside from what Wallach called "baseless, statistical arguments." If it seemed as though the participants were trapped in a looping existentialist play, it was because they were. They weren't really arguing over the data; they were agonizing about how to dwell, under conditions of pain and uncertainty, in proximity to death. The composition of the room, however, had changed. There were more cli-

nicians: Cudkowicz, who had helped run Amylyx's trials, told me that she spoke in favor of approval because she was confident that the executives would do the right thing. The patient side was marked by absences, including that of Sandy Morris, who, a week before, had chosen a death with dignity.

The crucial difference between the two meetings was the question put to the committee. Where it was initially asked to vote narrowly on effectiveness, it was now being asked to consider a fuzzier test: whether the drug, in light of the "unmet need in A.L.S.," could reasonably be prescribed. The committee voted in favor of approval, 7–2. The committee chair, Thomas Montine, switched his vote to yes. "To me, the challenge before the F.D.A. panel was the balance of compassion and certainty," he told me. "Compassion tells us to make this available to people who have nothing." Fischbeck cast a second no vote, a decision that he, too, said was motivated by compassion. "I have had friends who've died from A.L.S. over the years," he told me. "I've long thought it's the worst disease anyone can have. It is important for us as a field to be motivated by their desperation but not to take advantage of it." He related a story from early in his career: "One patient's family had gone to Florida to get a snake-venom extract that cost, like, forty thousand dollars, and they had sold their house in Philadelphia to pay for that. I found that so abhorrent."

Three weeks later, the F.D.A. announced the approval of the drug, which would carry the trade name Relyvrio. (Officials noted that they felt the drug was worth confirming, despite the uncertainty, "given the serious and life-threatening nature of A.L.S.") On a conference call with investors, Klee seemed to walk back the vow to withdraw the drug if it proved ineffective: "The Phase III trial is not a formal commitment." (Klee told me that the study's timelines would be met, and said, with the sincerity that had endeared him to clinicians, "If we have a drug that's not helping people, why in the world would we keep it on the market?" Cohen showed me a bracelet he was wearing that read, "What Would Sandy Do?") Glass, who was on the conference call, told me, "We kept asking him, 'How much is it going to cost? How much?'" He said that when Klee revealed the answer—a hundred and fifty-eight thousand dollars a year—"people were just flabbergasted. You did this for *patients*?"

Some patients saw the approval as a triumph. "It was very emotional," Wallach said. "Most of the people who were part of the trial are not here with us anymore." But others weren't sure how to feel. Recently, Gwen Petersen welcomed me to her light-filled, staircaseless home in Connecticut; she apologized for the scarcity of furniture, but one or two gratuitous end tables can make life with a walker feel like a steeplechase. She had been diagnosed as a thirty-two-year-old newlywed. (A psychiatrist she first saw thought that her balance issues were psychosomatic, and prescribed anti-anxiety medication.) She had participated in a trial for an investigational stem-cell treatment called NurOwn. "I had seven lumbar punctures with a fifty-fifty coin flip of getting a placebo, and I did it for the next generation," she said. "If these drugs truly work, and the evidence is there, then let people have them! But do we want a bunch of subpar therapies where the data has been sliced and diced three different ways from Sunday? And do we want to pay a hundred and sixty thousand dollars a year for a therapy that has 'eh' benefit?"

Klee told me that the company had tried to price the drug so that patients could get it "effectively, quickly, and affordably today," and pledged reinvestment in further research. He pointed out the company has a co-pay program that fully covers out-of-pocket expenses for privately insured patients. For those with government insurance, though, the situation is more complicated. Blaine Dangel, another patient, told me that her mother, who also has A.L.S., would incur a twenty-per-cent Medicare co-pay for Relyvrio, or about thirty thousand dollars a year, which is half of her fixed income. Dangel's wife, Lauren Broffman, who has a Ph.D. in health policy, said that the situation is excruciating for her as both a spouse and a scientist. "I wanted you to be able to take that medicine while waiting for the data to come through," she told Dangel. "I just wish there was a better mechanism than that circusy approval process."

The lingering uncertainty might be tolerable if drug prices were scaled in proportion to their benefit. In many countries, independent governmental bodies negotiate with manufacturers on that basis. In the United States, companies can charge whatever the market will bear. Last year, a nonprofit watchdog determined that a fair price for Relyvrio might be as little as nine thousand dollars a year. Steve Pearson, who leads the nonprofit, told me that our inattention to cost-effectiveness has cascading effects. When insurers refuse to cover an expensive drug of dubious benefit, as one payer did for Relyvrio this winter, only the wealthy can afford to take a flyer on it. But when companies do reimburse for such drugs, they pass on the cost to all of us, in the form of rising premiums. Taxpayers shoulder the burden of Medicare and Medicaid, and





"Hi—'Mom'? Going to Kayla's house? Thanks!"

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the underinsured are driven into bankruptcy. "It's really the lower-income people who are most hurt by it," Pearson said.

Cathy Collet, who lost her mother to A.L.S. and now watches over the community like a loving but stern librarian, told me she wishes that the advocacy organizations had the courage to oppose the industry on pricing. "They could say to the companies, 'If you're going to come in at six digits, you're not going to get our support,'" she said. But patients are easily extorted—as in, "Nice rare disease you have there. Wouldn't it be a shame if our research pipeline dried up?" As it turns out, an actual protection racket isn't even necessary. Many patients have become convinced that their interests and those of the drug companies are aligned: if companies see a congenial regulatory environment and a viable market for A.L.S. treatment, they might invest in further research. It's just as likely, however, that mediocre but profitable drugs sate the industry's desire to experiment. This has already been the case with Aduhelm, which set a precedent for several other similar treatments, one of which recently won accelerated approval. Seven years after the accelerated approval of the treatment for Duchenne muscular dystrophy, the manufacturer has had two similar drugs approved; confirmatory trials for all three remain incomplete.

Gonsalves has told the A.L.S. advocates he's worked with, including Collet, Sandy Morris, and Gwen Petersen, that using the sop of their "voice" on a panel to push for borderline approvals perpetuates a "cycle of defeat." He brokered introductions at the N.I.H.—the "first stop on the train," Gonsalves told them, rather than the last. In a meeting, he watched them press for more comprehensive research into the disease. "I felt like I'd found kindred spirits," he said. Still, Collet told me that a single-minded focus on drugs is something that only people of privilege can afford. She'd recently taken a Twitter poll: "I asked them, 'If you had a hundred thousand dollars, what would you want to spend it on? A new drug, home modifications, or quality home care?' Quality home care got sixty-one per cent of the votes." Jonathan Katz, an A.L.S. clinician and researcher in San Francisco, told me that he had just seen a patient, the father of three young kids, who lacked a home health aide but understandably wanted a Relyvrio prescription: "The wife told me, 'I don't have time for anything. When I have to get groceries, I have to put two newborn twins and my husband in a van.' How did we get the money to pay for this new drug and we don't have the money to help a family in this situation, which would be cheaper?"

This, of course, would require a complete overhaul of the health-care system. In the meantime, the existing regulatory apparatus has been steadily destabilized. The tactics of the AIDS era drew transformative attention to the "invisible graveyard," but the past three decades have seen an overcorrection, and the problem of paternalism has given way to the problem of benign neglect. The AIDS crisis also created the policy instruments to chart a middle path. Clinical trials could be made as inclusive as possible. Patients who cannot enroll in trials could have access, circumstances permitting, to investigational drugs through comprehensive expanded-access programs. Accelerated approvals could be subject to a tight timeline for confirmatory evidence, and there could be an enforcement mechanism for the rapid withdrawal of drugs that are not serving the sick. There is growing consensus on these points, but all are easier said than done. And no policy will ever fully resolve the tension between access and knowledge. The recognition that the system has a cost—that there is no deliverance from the purgatory of these trade-offs—does not make it any easier to conclude, in any individual case, that a patient should be barred from taking something she hopes will make her better. When I spoke to patients who wanted Relyvrio, I couldn't help but feel, in the moment, that they deserved the opportunity.

The existentialist play continues to loop. Wallach has long been a supporter of NurOwn, which was developed by an Israeli company called BrainStorm. The NurOwn trials failed, but many patients nonetheless believe that the F.D.A. is blocking their access to a miracle procedure. A highly active Facebook group called No More Excuses! has rallied support; posts repeat variations of the idea that NurOwn, which the F.D.A. keeps "locked up," delivers a "100% slowing of progression." In one campaign, patients posted photographs of themselves in shallow graves with their mouths covered in red tape. "As an ALS patient this makes me scream for access for all of us who are dying due to rampant systemic paternalism," Wallach wrote. "Neurologists and FDA dismiss this as 'anecdotes.' No. These

are our lives, our bodies and our evidence."

The F.D.A. has tried to de-escalate the situation: at one point, the agency issued an unconventional statement to combat the spread of misleading information, pointing out, for example, that there were actually *more* excess deaths among those who took the drug than among those who took the placebo. (BrainStorm has defended its drug, and a representative noted, "None of the deaths in the trial were deemed related to treatment by the principal investigators.") Collet told me a story about a patient who spoke at an F.D.A. meeting to describe a preternatural recovery. "He got up and talked about how before he took NurOwn he'd been having trouble walking, and then he ran around the conference-room table," she said. "In the back of my mind, I thought, A.L.S. has its ways of having ups and downs, and it's entirely possible that he was on the placebo. I suspect some of these miracle stories are the reason the company never unblinded the trial." She added, "It's easy for us to romanticize the H.I.V. history, but it wasn't all demonstrations that got things done—it was a lot of hard work figuring out what the science could and couldn't do. There's a tendency in A.L.S. to say, 'I am real-world evidence,' but that's not how it works." Except sometimes it is. In March, the F.D.A. announced that NurOwn would receive an advisory-committee meeting.

In 2018, Brooke Eby, a sportive goofball with strawberry-blond hair, started to feel as though her left foot couldn't keep up. She was a proud graduate of Lehigh University, and had a job at Salesforce that she loved. She told me, "I was a twenty-nine-year-old in New York City—what a place to have to limp slowly down the sidewalk!" At first, doctors didn't see anything obviously wrong, and even specialists were reluctant to make firm pronouncements. "I was not what they picture for A.L.S.," she told me. "After years of being poked and prodded, I was, like, 'Someone man up and say it. I'm sick of people dancing all around.'"

Recently, I met Eby for pastries—A.L.S. patients are encouraged not to lose weight—at a bakery near her apartment, in a prefabricated but lavishly A.D.A.-compliant neighborhood in North Bethesda, Maryland. Eby has a self-deprecating wit, and joked that she requires thirty-two turns to park her power chair. "Once it affects my speech and swallowing, it'll get serious, but for now it's like I got into a car accident and never recovered," she said. Because her diagnosis took so long—a common story—Eby was excluded from all clinical trials. She was prescribed two existing drugs, and, in November, she got her first dose of Relyvrio. She wasn't not going to take it. But, she told me, "none of the drugs are life-changing." Eby is in a group called Her A.L.S. Story, which includes Petersen, Dangel, and more than fifty other young women. She has observed that there's a fairly clear distinction in the group between those with means, who give money to fund drug research, and those who lack power chairs or basic support.

Eby had a bad case of COVID last summer, and in a hallucinatory fugue state she wrote down some ideas for TikTok videos. A few weeks later, she showed the ideas to a friend, who encouraged her to post. In the clips, which are often very funny, Eby assumes the character of a typically ditzy influencer to describe what life with A.L.S. is like. She became known primarily for videos that documented her attempts to discover the best way to mask the taste of Relyvrio, which comes in a small packet to be dissolved in water, like Emergen-C, and has an extremely astringent flavor. She has tried various aperitivi and digestifs, including peanut butter, picklebacks, Hershey's syrup, and taste-altering "miracle berries"; she's taken her Relyvrio through a straw, via a giant syringe, with a laundry clip on her nose, and out of a beer bong.

This February, I met up with her at an A.L.S. event in Washington, D.C., hosted by Collet, in a conference room with a view of the Capitol. During a coffee break, Eby took out a packet of Relyvrio and asked a dozen people to try it, later describing the activity, in voice-over, as a "Hunger Games for chasers." When I tasted the drug, it had a radioactive tartness, like pond water from Chernobyl; I tried to muffle the flavor with a Snickers bar, but it lingered for hours. Once we'd done our shots, Eby reminded us that we'd just consumed hundreds of dollars' worth of white powder.

Demand for Relyvrio remains high. Cudkowicz told me that her medical practice could scarcely keep up with the requests for prescriptions. Jonathan Katz, the clinician in San Francisco, said, "Since this drug came out, I feel like I'm the conduit to write prescriptions for drugs for a company to make a lot of money." Analysts predict that Amylyx's revenue this year will be almost four hundred million dollars. Katz added, "Nobody is saying, 'Stop cutting these things so close and sticking them on the market and charging a million dollars,' because then you get yelled at for telling the truth." Amylyx's Phase III trial is still under way in Europe, though regulators there recently indicated that the outlook for the company's first approval application is inauspicious. The results of the trial, which should be returned in 2024, may depend on how you squint at them. By that point, Relyvrio could be a billion-dollar drug. What will happen then? Klee promised to do "whatever is best for patients." And there will always be people who are convinced that something is working for them—either because, for some idiopathic reason, it actually is, or because it's lovely to think so.

A few months ago, Eby went off all three drugs. She told me, of Relyvrio, "I had no idea if it was doing anything. People were pooping their pants, and if you don't have a body that's working that can be an issue. It wasn't for me, but I felt like crap—my muscles were tired and achy." Still, she wasn't in bad spirits. "When I'm having a bad day, I just watch a lot of Harry Potter. The A.L.S. community is all about Harry Potter. It seems like there's no chance things are going to work out for him, and he ended up fine!"

Eby recently raised more than seventy thousand dollars for research in less than a week. "We just need to buy ourselves time—maybe there will be a medical miracle and we'll be around to see it and really benefit from it," she said. "I think things will work out for me." She knew that this made her a recognizable type on social media—the kind of person who speaks to the universe and expects gratification. "My friends say I have 'A.L.S. lucky-girl syndrome,'" she said. "I still feel like my life is pretty good. I have the best of the worst case, is how I frame it. If you're alive, you're lucky." She told me that she might re-start her Relyvrio regimen, but she seemed unenthusiastic. "The meds are intended to slow progression, but you're always getting worse," she said. "So how do you know?" ♦

WEB DISPLAY



“Are we selling hope?” the clinician Jonathan Glass said. “Or are we selling things that we know really work?”

Illustration by Maria Chimishkyan

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When Dying Patients Want Unproven Drugs

Patient-advocacy groups mobilized to demand access to a controversial new drug called Relyvrio. But hasty approval comes at a cost.

SOCIAL

When Dying Patients Want Unproven Drugs

Patient-advocacy groups mobilized to demand access to a controversial new drug called Relyvrio. But hasty approval comes at a cost.

SEO

When Dying Patients Want Unproven Drugs

Patient-advocacy groups mobilized to demand access to a controversial new A.L.S. drug called Relyvrio. But hasty approval comes at a cost, Gideon Lewis-Kraus writes.

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SOCIAL

“Therapy”

“Nothing / changes.”

SEO

“Therapy,” by Edgar Kunz

Poetry by Edgar Kunz: “Nothing / changes.”