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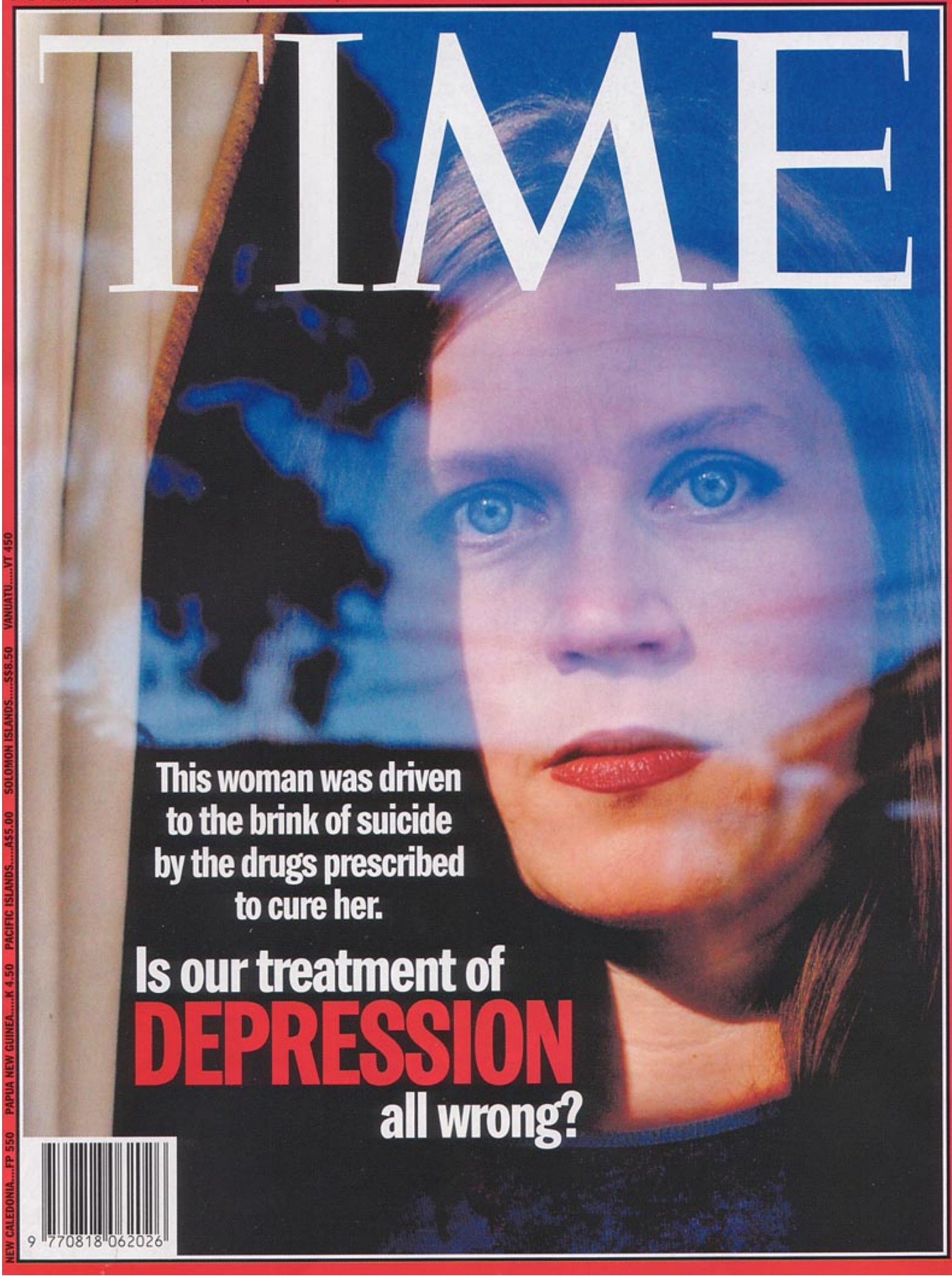

This woman was driven to the brink of suicide by the drugs prescribed to cure her.

Is our treatment of DEPRESSION all wrong?

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DEALING WITH DEPRESSION

Bitter Pills

THEY'RE PRESCRIBED TO MILLIONS, BUT DO THE NEW ANTIDEPRESSANTS WORK? AND ARE THEY WORTH THE RISK?

BY DANIEL WILLIAMS

THERE'S REALLY NOTHING FUNNY ABOUT WHAT HAPPENED to Rebekah Beddoe, except maybe for a little black comedy at the end. In 1999, a psychiatrist diagnosed her with post-natal depression, which she probably didn't have, and for the next three years multiple doctors treated her with drugs that she almost certainly didn't need. As episodes of deliberately cutting herself progressed to bouts of mental torment and suicide attempts, Beddoe's carers, concluding that her illness was worsening, kept upping her dosages and trying new medications. Nothing worked. Eventually, Beddoe acted on a different idea. Without telling anyone, she weaned herself off the drugs and gradually became well again. Her psychiatrist at the time assumed he was responsible for Beddoe's recovery. She remembers watching him one day from the other side of his desk, thinking that this eminent doctor was congratulating himself on having the skill to concoct precisely the right drug regimen. "I could also see his relief," Beddoe says. "It had been a difficult case, but he'd finally cracked it."

These days Beddoe, 33, spends much of her time at home in Melbourne reading up on

Illustration for TIME by Steven Bray

JESSE MARLOW—OCULI FOR TIME

"If you give drugs that target brain chemistry, you should expect

psychiatry while working on a book about her ordeal. She's certain that what made her sick were side effects of the most commonly prescribed class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs). A pharmaceutical phenomenon that began with fluoxetine (Prozac) in the late 1980s, the SSRIs rode a wave of gushing publicity to usurp the older antidepressants, the tricyclics, and reap a fortune for their makers: worldwide sales now exceed $20 billion a year. But the honeymoon is over. Even doctors who swear by SSRIs and newer variants concede that 1-2% of patients have a severe negative reaction to these drugs. That's a small percentage. But it's a small percentage of a very large number. Intractable misery is rife, it seems: in Australia last year, 12 million prescriptions for antidepressants were dispensed through the federal government's Pharmaceutical Benefits Scheme (up from 8.2 million in 1998), a figure equating to more than a million users. Do the math, says Sydney forensic psychiatrist Yolande Lucire: if only 1% of users suffer terrible side effects that aren't recognized for what they are, that's more than 10,000 Australians who've recently been disabled by a drug that was supposed to help them. "That would be enough to fill the beds in every mental hospital in the country."

Lucire's is one voice in a small but growing international chorus of SSRI skeptics. As well as highlighting side effects, these critics question whether the SSRIs do what they're supposed to do in a significant proportion of cases. Based on fresh analyses of clinical-trial results, some researchers have concluded that the drugs are scarcely more effective than a placebo in alleviating depression. "I think they are more or less completely useless," says Dr. Joanna Moncrieff, senior lecturer in social and community psychiatry at University College London. In an article published earlier this year in the *British Medical Journal*, Moncrieff and

SURVIVOR "Of all the other patients I met, there wasn't one whose depression could not be traced to problems in their life," says Beddoe, with daughter Jemima, 6

nies to harden their warnings about the potential side effects of SSRIs. The companies' prescriber information must now feature a black-box warning—the strongest available—stating that in trials "antidepressants increased the risk of suicidal thinking and behavior" in children and adolescents with depression and other psychiatric disorders. The FDA is reviewing the results of several trials to determine whether a similar warning should be introduced for adults. British health authorities have gone further: in September, the National Health Service told doctors to stop prescribing antidepressants to under-18s in the early stages of treatment because of the link with suicidal thinking.

Compared with its American and British counterparts, Australia's Therapeutic Goods Administration has taken a gentler line. Last year it reminded doctors that no antidepressant is approved in Australia for the treatment of depression in under-18s—though it knows many thousands of Australian teenagers with that diagnosis are on the drugs. In August, a TGA bulletin acknowledged a probable link between the SSRIs and suicidal tendencies in children and adults, but overall endorsed the drugs. Still, for perhaps the first time since the SSRIs came on the scene, those who believe the medical profession has lost its way in treating depression feel they have some momentum. "The [non-drug] approach is growing," says Dr. Jon Jureidini, head of the department of psychological medicine at the Women's and Children's Hospital in Adelaide. "I'm probably at one end of the spectrum, but there would now be plenty of psychiatrists who would be very conservative prescribers."

BEFORE DELVING INTO HOW, AND HOW WELL, the SSRIs work, whether they're overprescribed and the sundry other medical, ethical

experiencing is more than just sadness but the effects of a disease that has taken root in their brain. When they prescribe antidepressants, most doctors are working from the idea that depression has somatic underpinnings: that it arises from an imbalance of certain neurotransmitters in the synapses—or spaces—between nerve cells in the brain. While science has implicated dopamine and noradrenaline in depression, and some of the newest antidepressants target these, it's branded a shortage of serotonin as the main culprit. Found in large concentrations not just in the brain but in various parts of the body, including the gut, serotonin plays a role in regulating—among other functions—mood, sleep and appetite.

If depression is a disease, it seems logical that the most effective way to treat it is with biological agents. Secreted into the synapses, serotonin is normally partially reabsorbed by the brain cells that released it. SSRIs block this reabsorption, allowing more serotonin to accumulate in the synapses. The result, hopefully, is that the patient begins to feel better within a few weeks.

But how solid is the chemical-imbalance model of depression? That depends on whom you ask. The drug companies present it as fact. On its website, Pfizer, maker of the blockbuster SSRI sertraline (Zoloft), asserts that antidepressants "work by correcting the chemical imbalance in your brain." The Australian mental health lobby group beyondblue is slightly more circumspect in its literature, saying "severe depression appears to be associated with a reduction in the chemicals of the brain." Depression comes in various types and shouldn't be thought of as an "it," says Gordon Parker, a professor in the school of psychiatry at the University of New South Wales. But because the more

psychiatric side effects, often unpredictable ones." —YOLANDE LUCIRE, PSYCHIATRIST

coauthor Irving Kirsch, professor of psychology at the University of Plymouth, argued that it was time for "a thorough reevaluation of current approaches to depression and further development of alternatives to drug treatment." Seldom had a piece about antidepressants so explicitly challenged the reigning orthodoxy in the mainstream medical press, and it was hailed as a breakthrough by those who oppose what they see as disease mongering by the drug industry and other groups.

The drug skeptics have had other recent victories. In the U.S. last year, the Food and Drug Administration told the drug compa-

and ideological questions that swirl around these drugs, it's worth acknowledging that depression in its most severe form is a crippling condition. Over time, sufferers of melancholic depression (formerly known as endogenous depression) lose the ability to feel joy, excitement, empathy—just about anything except a gnawing dread. They eat without appetite and their sleeping patterns are shot to bits. Imagine being alone at 3 a.m., having just awoken from a nightmare. That, depressed people say, is a hint of how they feel in every waking moment.

It's horrible—so horrible that most sufferers need little convincing that what they're

severe form tends to run in families and involves physical symptoms such as sleep and appetite disturbance, and because its onset can't be explained as a reaction to a traumatic event such as a bereavement, it seems "there are some depressions that are quintessentially biological . . . very much chemically underpinned."

Not everyone's convinced. And not everyone will be until there's a biological test for depression instead of the series of questions doctors use now. Don't hold your breath waiting for that, says British academic Moncrieff: "I believe that human emotions will never be located in a simple

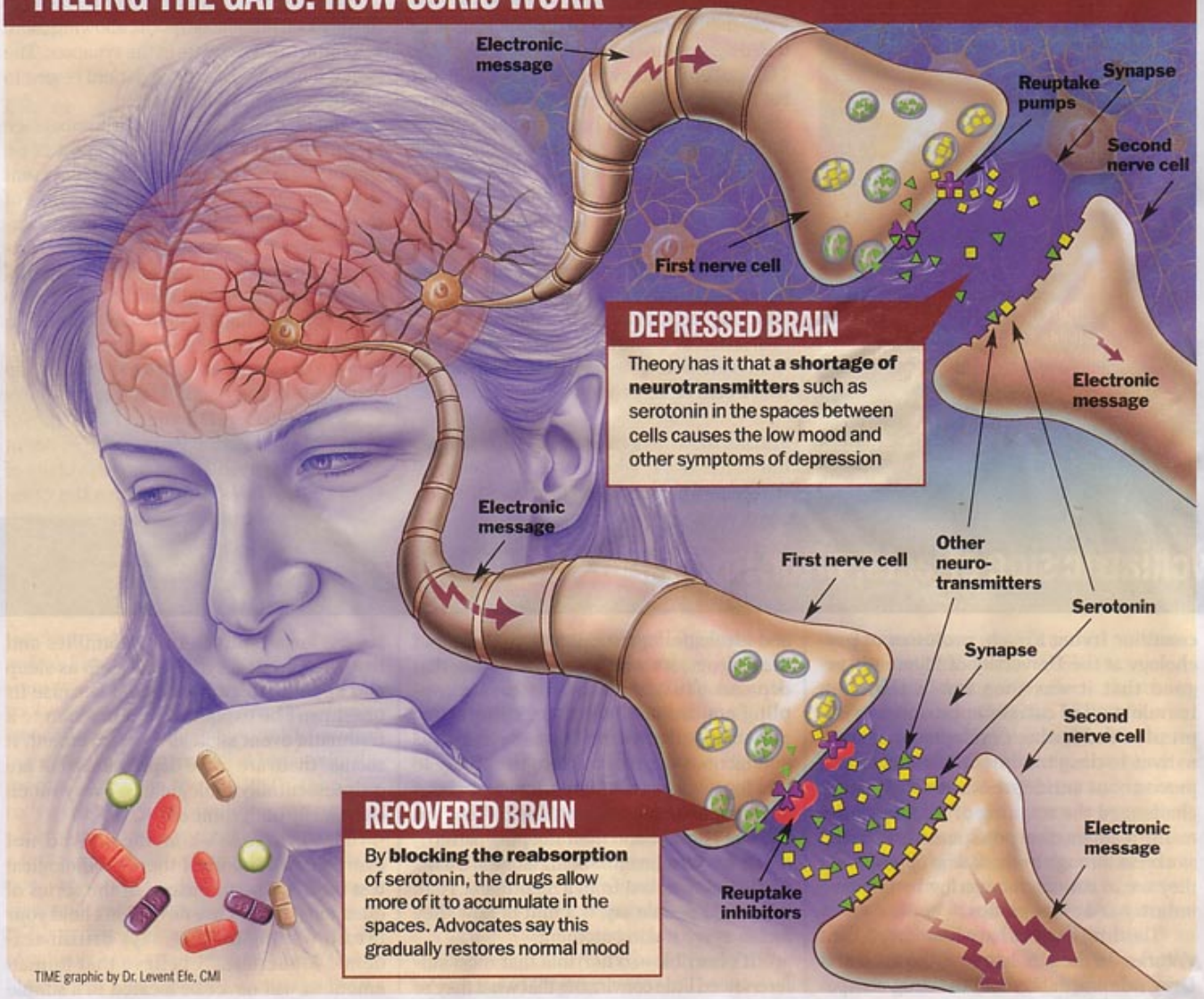
biochemical formula." The chemical-imbalance theory is nonsense, says Adelaide psychiatrist Jureidini. SSRIs alter a patient's serotonin levels within days, he says, but their antidepressant effect—if there is any—doesn't occur for several weeks. "The idea that there's a serotonin deficiency that explains depression is such a gross oversimplification as to be completely misleading," Jureidini says. "A lot of doctors and others are prone to wishful thinking. It'd be nice if this was all scientific and we could give a drug to correct a chemical imbalance and nobody had to think about how complicated it is to become depressed and what the reasons might be for it . . . But it doesn't work like that."

Debate over a physical cause of depression tends to become bogged in uncertainty over cause and effect. Does a spontaneous chemical abnormality trigger the bad feelings we call depression, or might years of unresolved anxiety and festering discontent cause chemical disturbances—disturbances that might fix themselves once sufferers put their lives in order? By slowly unraveling the extraordinary complexity of neurotransmitter interaction, scientists are learning more about how the brain works. But they still wouldn't claim to know the half of it. Pinning depression on a chemical imbalance is problematic when what constitutes normal brain chemistry has yet to be defined. "I think what we have to tell trainee psychiatrists is that this is a far more complex area than we previously thought," says Dr. Louise Newman, director of the New South Wales Institute of Psychiatry. While there's a "suggestion" of a chemical imbalance in some cases of depression, she adds, the next generation of psychiatrists "needs to know the limitations of the evidence."

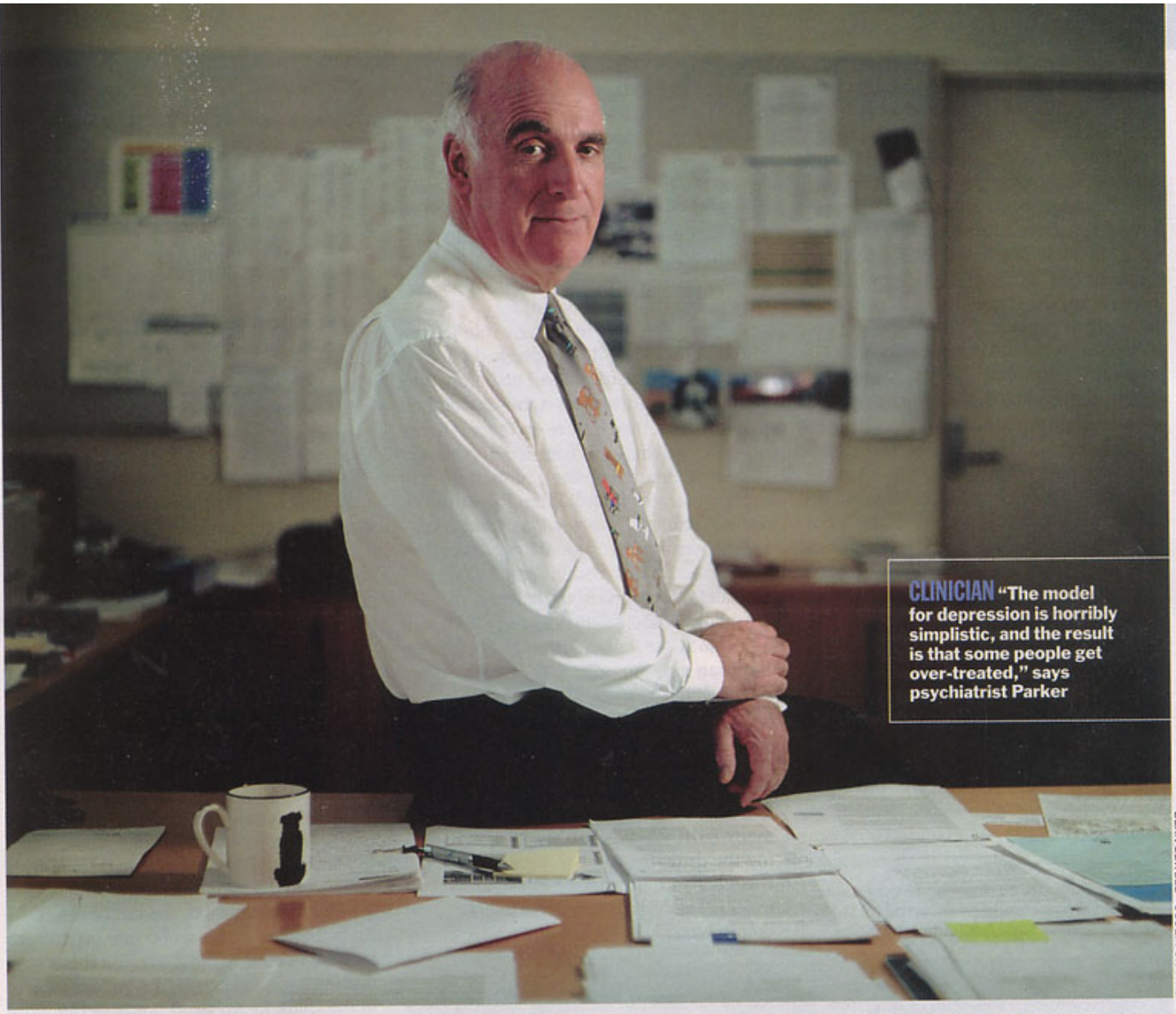
Given the gaps in the science behind the SSRIs and their risk of serious side effects (about half of all users experience side effects ranging from mild to severe), you might think doctors would be very selective in prescribing them—writing scripts only for those people in a deep and prolonged misery that can't be traced to everyday problems. But caution doesn't seem to rule here. In Australia, about 85% of those annual 12 million antidepressant scripts are written not by psychiatrists but by G.P.s, typically at the end of a consultation lasting 20 min. or less.

Prescriber information on the SSRIs in America contains an extraordinary sentence

FILLING THE GAPS: HOW SSRIS WORK



TIME graphic by Dr. Levent Efe, CMI



CLINICIAN "The model for depression is horribly simplistic, and the result is that some people get over-treated," says psychiatrist Parker

DEAN SEWELL—OCULI FOR TIME

missing from the versions seen by Australian doctors—extraordinary in the context of a debate in which advocates of the drugs assert that depressed people who aren't treated are at heightened risk of contemplating and attempting suicide. "The average risk of such events in patients receiving antidepressants was 4%," the U.S. warning reads, "twice the placebo risk of 2%." In other words, drugs meant to stop depressed people from getting even more depressed or killing themselves may double their chances of doing just that. For the skeptics, that's more evidence they are right.

MELBOURNE'S REBEKAH BEDDOE HAD JUST landed a good job in a computer company when, in late 1998, she found out she was pregnant. While the news threw her, her boss helped out by granting her a stint of maternity leave that she wasn't strictly entitled to. "Things were looking fantastic at that point," she says. She figured she'd spend six months at home, put her baby in daycare, and get back to work. But soon after Jemima's birth, "I realized I'd been living in a dream world." Jemima cried constantly and screamed in cafés when her mother tried to catch up with friends. Confined to a small apartment, worn down by lack of sleep and feeling inadequate and disillusioned, Beddoe visited a G.P., who suspected postnatal depression and handed her a trial pack of Zoloft. "His words to me were, 'They're completely safe, very effective and only work on people with depression.' If he were to take them, he said, they'd do nothing because they just correct chemical imbalance."

Beddoe didn't like the idea of going on drugs and decided not to take them. She checked in to the mother-and-baby unit of a private hospital, where staff helped her to settle Jemima. There, after another brief consultation, a psychiatrist diagnosed Beddoe with postnatal depression and suggested she start on Zoloft right away. This time, she relented. A week later, she was in hospital, waiting in good spirits for a group-therapy session, when something happened. She suddenly couldn't breathe and her heart was pounding. The walls seemed to be closing in. She thought she was having a heart attack, but a nurse took one look at her, disappeared for a few moments, then returned with a paper bag that she placed over Beddoe's mouth. When Beddoe calmed down, the nurse told her she'd had a panic attack but not to worry—they were common in people with depression.

Beddoe's plunge into madness had begun. When a neighbor revved his motorcycle within earshot of a sleeping Jemima, Beddoe flew into a rage, chasing him and screaming profanities. That night, preparing dinner, she used a knife to make shallow cuts in her left forearm, just to see how it felt. Over time her psychiatrist added tranquilizers, an extra antidepressant, lithium and eventually an antipsychotic to Beddoe's diet of drugs. There was also a course of electro-

convulsive therapy. But her condition worsened. In 2000 she tried to end her life by overdosing on sleeping pills, the first of four such attempts. At her mother's urging she switched psychiatrists, but after stripping back her regimen to a single drug, Prozac, the new doctor gradually built it up again. Beddoe developed akathisia, which she describes "as a horrible energy that fills you with angst and dread and propels you to move about constantly." Akathisia can be a manifestation of SSRI sensitivity, and "it's psychiatry's dirty little secret," says skeptic Lucire. But Beddoe's psychiatrist saw it as just another symptom of his patient's illness.

How rare are cases like Beddoe's? "We see them quite often," says N.S.W. University's Parker, a psychiatrist for 30 years and director of the Black Dog Institute, a not-for-profit research, educational and clinical body specializing in mood disorders. "We see depressed people who've been undertreated and others whose illness is not quintessentially biological," yet their treatment has amounted to "the relentless pursuit of one physical treatment after another." Parker's experience is that, shortly after starting a course of SSRIs, about 7% of patients feel agitation ranging from moderate to profound, while an additional 1% or fewer show psychotic symptoms. "In my view a serotonergic reaction is a true phenomenon," he says, "and we need to be absolutely aware of it. But it doesn't stop me from prescribing." He starts his patients on low doses and warns them about what they might feel when they start taking the drugs (and that they might have symptoms when they go off them). And this is all that many SSRI critics ask of doctors: continue to prescribe the drugs when absolutely necessary, they say, but don't pretend they're as harmless as sweets.

Others struggle to see any role for the SSRIs. As they see it, if depressed people's brain chemistry isn't messed up before they start taking the drugs, it's stone-cold certain that it will be once they're on them. There's no evidence that any drug acts specifically to reverse depression, says Moncrieff. "It's more accurate to understand psychiatric drugs as inducing abnormal states, analogous to how we use recreational drugs to induce euphoria or social disinhibition." The most she can say for the SSRIs is that some of them are mildly sedating, "and this may help someone who is agitated or anxious." Lucire says they can also energize and brighten one's mood—but, she adds, so can cocaine.

The SSRIs do more for men with premature ejaculation than for people with depression, says Dr. David Healy, of Cardiff University in Wales. Healy supports drug treatment for depression, but is a hero to many SSRI skeptics for his work in exposing the drugs' capacity to produce suicidal thoughts and, in what he estimates to be 1 in 500 of all SSRI users, drive people to kill themselves. The serotonin-imbalance theory has been a marketing tool for the drug companies, skeptics say. "It suggests a disorder a bit like a vitamin deficiency that will be put right by vitamins," Healy says, "when in fact the SSRIs produce marked abnormalities in the serotonin system."

Recent reviews of the data from SSRI trials indicate that placebos are on average 80% as effective as the drugs. But this is misleading, argues Parker. The typical subject in the trials, he says, did not have the more serious melancholic depression that doctors invariably treat with drugs but a milder form more likely to resolve spontaneously or from non-drug therapies. A view common among doctors is that if antidepressant trials looked exclusively at people with melancholic depression, the gap in efficacy between the drug and a placebo would widen.

Be careful suggesting to Auckland clinical psychologist Gwendoline Smith that SSRIs don't work much better than a sugar pill. When depression first hit her 10 years ago she was reluctant to use medication, figuring she could get well by exercising more, adjusting her diet and smiling in front of a mirror. But for that approach to work, she says, she'd have needed to practice it for six to 12 stress-free months on a secluded island. Instead, she went on the drugs and felt

Symptoms of Depression

- Loss of appetite
- Insomnia/enervating daytime tiredness
- Inability to feel pleasure
- Feelings of worthlessness, guilt, anxiety/dread
- Withdrawal into self/loss of interest in others
- Recurrent suicidal thoughts

Doctors disagree on how long most of these symptoms need to last before a diagnosis of depression is appropriate. The minimum is two weeks.

Severe SSRI Side Effects

- Worsening of depressive symptoms, including preoccupation with death
- Uncharacteristic rage, aggression, disinhibition
- Extreme agitation/compulsion to move (akathisia)

Symptoms may emerge upon starting drugs, changing dosage, or up to several weeks after going off them. (A host of less severe side effects is also associated with SSRIs.)

PURIST **Patients so depressed they seem to need drugs should be referred by G.P.s to specialists, says Adelaide's Jureidini**

RANDY LARCOMBE FOR TIME

"Psychiatrists are very attached to the idea of an antidepressant, and

MENTOR "Even if there are biochemical changes in depression, that doesn't tell us what causes them," says psychiatry educator Newman

DEAN SEWELL—OCULI FOR TIME

better in two weeks. Author of the recently reprinted handbook *Depression Explained* (ABC Books), Smith espouses the biological theory of depression, of which, in her view, serotonin deficiency is just a component. "The pathway into depression is via anxiety and the overproduction of cortisol," she says. Depression still descends on her intermittently. She can "feel the biology kicking in," she says; when that happens she knows she's left things too late to recover without drugs, which she uses on and off.

Smith says she suffers neither side effects nor withdrawal symptoms but accepts others do. Of those who do pay a price for less depression, many have no regrets. The pills may have switched off their libido and sapped their energy, they say; going off them may have triggered weeks of nausea and nightmares. But the drugs also hauled them out of a blackness from which escape had seemed impossible. "We know they work," says Smith. "Exactly how they're doing it . . . we haven't got that bit yet."

For many critics, though, the key problem with SSRIs is that they are too widely—and casually—prescribed. When the first antidepressant, imipramine (Tofranil), was developed just over 50 years ago, maker Ciba-Geigy balked at taking it to market for fear there weren't enough depressed people in the world to make it profitable. The wisdom of the time was that endogenous depression affected, at the most, about 1 in 1,000 people at some time in their lives. Things have changed. Groups such as beyondblue now promote the idea that about 1 in 5 people will become depressed during their lifetime.

The shift has caused many to ask whether prevalence has really increased 200-fold in half a century, or whether the definition of depression has been deliberately broadened and blurred by drug companies and others—part of a trend to medicalize moods that were once accepted as falling within the normal range of human emotions. Despite record sales of antidepressants in Australia, drug companies and

they become defensive when anyone questions it." —JOANNA MONCRIEFF, LECTURER

mental-health lobby groups maintain there are still hundreds of thousands of Australians with undiagnosed depression.

The national charity SANE Australia is running a campaign—"Mental Illness is Real"—that challenges "misinformed community attitudes that discourage the 1 in 5 Australians affected by mental illness from seeking the treatment they need." Last year, Pfizer Australia urged G.P.s to be alert to depression in the country's three million arthritis sufferers. On the basis of a poll it had commissioned and interpreted, the company found 20% of these people had depression. Months earlier, working from another one of its surveys, Pfizer announced that "alarming numbers" of young Australians were at risk of depression because many around them were "dismissing telltale signs as normal adolescent behaviour."

"The drug companies needed psychiatrists to get

Severe depression does occur in adolescents, and there's a risk of suicide in these cases, says the Institute of Psychiatry's Newman. But she suspects doctors are overprescribing antidepressants across the board. "It's important they distinguish between normal sadness and clinical depression," she says. "We all need to feel sad sometimes. We don't want a society in which people run off to get prescribed rather than feel normal emotions."

While Parker acknowledges that sometimes people who don't need SSRIs receive them, he doesn't think the drugs should be confined to those with severe depression. "Anxious worriers are the new breed of depression," he says. "They're the ones for whom it's nothing like as gray, and the suicide risk is not as great, but they're living lives of quiet desperation, or irritability, or crabbiness, [feelings] that drive their depression." He's concerned about the backlash against the drugs, which he concedes were oversold at first. His worry is that before long authorities, influenced by the "excessive beating" being handed out to the SSRIs, may ban their use by adolescents.

Others have very different concerns. Lucire wants the TGA to write to every G.P.

ADVOCATE The idea of a ban on SSRIs is "horrifying." If it happened, "I would pull out of psychology," says Auckland's Smith

JOCELYN CARLIN FOR TIME

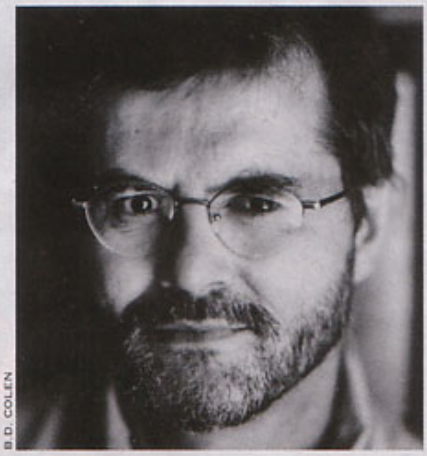
excited about the drugs, and we got overexcited." —GORDON PARKER, PSYCHIATRIST

in the country—in the manner of the drug companies—telling them to recall all their SSRI patients and check them for side effects. Jureidini is worried that doctors with links to the drug industry—as consultants or advisers—may be influencing TGA policy on psychiatric drugs. The obligation to disclose isn't there in this case, and that is "out of step with worldwide practice," he says.

Gil Anaf, president of Australia's National Association of Practising Psychiatrists, frowns on a system that steers depressed people toward G.P.s, who often lack the time and expertise to make the right call on treatment. Because the cost of SSRIs is subsidized by the government, it's cheaper for patients to be on drugs than to spend a lot of time on the couches of psychoanalysts like Anaf. Anaf isn't anti-drugs. Within that small proportion of depressed patients who are at risk of harming themselves, he says, the antidepressants work well in 70-80% of cases. "The problem is that the new generation of psychiatrists is being exposed less and less to the good results of [psycho] therapy, and more and more to the average results of medication. It's going to be seen eventually to be the norm to prescribe, as if there's never been anything else."

At the Women's and Children's Hospital in Adelaide, Jureidini and others are bucking that trend. The strong showing of placebos in antidepressant trials should tell us something, he says. Subjects in the control group typically receive more than a sugar pill: they have their histories taken and they're monitored and encouraged. In many cases, this personal attention makes them feel better. So why not build on the placebo effect? Jureidini's team is working with 20 GPs in a soon-to-be-expanded pilot program that embraces, he says, a "third way" of treating depression in children and adolescents: instead of drugs or formal talk therapies, they get "rehabilitation" based on exercise, dietary changes, better sleep habits—and talk, to try to find out "what's worrying the kid rather than what's wrong with him." Many doctors would call these chicken-soup remedies. But in all but perhaps the worst cases, says Jureidini, why not try them before reaching for the prescription pad?

Immediately before her encounter with psychiatry, Rebekah Beddoe was a normal girl having a rough trot. By the time of her inspired decision three years later to take herself off her medications, she'd been diagnosed with five separate mental disorders and drugged to within an inch of her life. Heavy doses of an antipsychotic have left her a diabetic and her left arm is a canvas of self-inflicted scars. Somehow, her family remains intact. She married Jemima's father, Nigel, in the midst of her trials and the three of them are going strong. She can find it in her to give the SSRIs their due. People have told her these drugs "pulled them out of the depths of despair," she says, "by what mechanism, I don't know, but it's undeniable they believe this." What she can't stand is the nonchalance with which they're distributed. "People go for help when they're at their most vulnerable," she says. "They're confused and don't trust their own judgment. If they knew the doctor was going to prescribe a drug that has the propensity to induce exactly the feelings they're trying to avoid, they'd run screaming from it." ■



B.D. COLEN

SKEPTIC Drug treatment of depression is "built upon a crumbling scientific foundation," says author Whitaker

J'ACCUSE

Taking on the Drug Defenders

Ever since his coruscating book *Mad in America* was published in 2002, American Robert Whitaker has been a poster boy for the anti-psychiatry movement. In *Mad in America* (Perseus Books), he argued that the assumption of a physical cause for schizophrenia had given rise to many wrongheaded treatments, from ice-water immersion to today's antipsychotic drugs. These days, the Pulitzer Prize finalist makes a similar case against psychiatry over its approach to the treatment of depression.

No one knows for sure whether serotonin has a role in depression, let alone exactly what that role might be. But many doctors pretend they're sure, Whitaker says, because "psychiatry for a long time had a bit of an inferiority complex. It wanted magic bullets like everybody else." Trouble is, the magic bullets, including the SSRIs, don't work very well. By perturbing neurotransmitter activity they can make patients chronically ill, says the Boston-based author.

Is he alleging a conspiracy among psychiatrists? Not exactly. Psychiatrists are taught the biological models of mental illness and come to believe in them, he says. He recalls a recurring exchange he had with doctors while researching *Mad in America*:

Psychiatrist: The [schizophrenia] drugs are like insulin for diabetes.
Whitaker: No, they're not—you have no confirmed biological problem.
Psychiatrist: O.K., that's true.
Whitaker: So why say it?
Psychiatrist: Well, it gets people to take their drugs.

"So what they're doing is a little fudging to pursue what they believe is a good end," says Whitaker. "But at the same time they feel vulnerable because they don't have the science behind it and they don't have the outcomes, either." Those psychiatrists who break ranks and publicly question the biological models and the efficacy of psychiatric drugs, he adds, "get clobbered. They basically have their careers ruined."

The SSRIs, in his view, are a story of a "massively successful capitalistic enterprise"—and the idea that in countries like Australia there's still a multitude of people with undiagnosed depression should be considered in that context. These people are "not clinically depressed, anyway," he says. "The drug companies are setting forth an unrealistic vision of what it is to be human. They're defining normal stresses and worries as pathological, and the only reason they're doing it is that it leads to more business." —**D.W.**