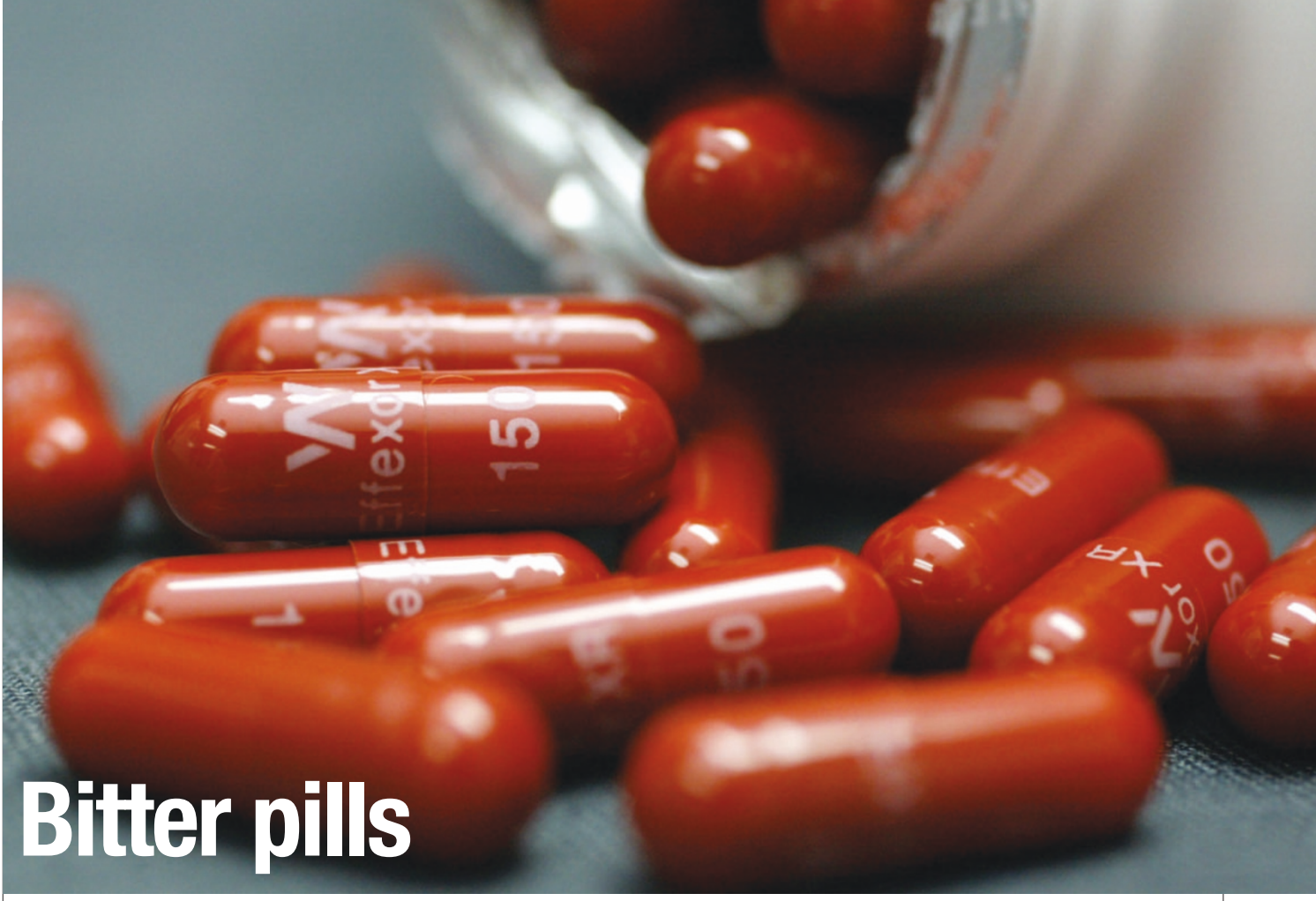

Bitter pills

J. RAEDLE/GETTY IMAGES

They were hailed as wonder drugs to banish depression, but may cause suicidal thoughts in some children. Companies are under attack for failing to publish these data. Erika Check considers the science behind a scandal.

In a packed hotel ballroom on a cold February day, 30 parents stepped one by one to a microphone to testify to the US government. They had come to suburban Maryland from as far away as Texas and Arizona to talk about antidepressant drugs. Some had brought their children. But others could bring only photos.

Mark Miller said that his son, Matt, ended his life after taking seven doses of the antidepressant Zoloft, made by Pfizer. Glenn McIntosh told how his daughter, Caitlin, hanged herself after taking Zoloft and another drug, GlaxoSmithKline's Paxil. A few parents spoke up in favour of the drugs, arguing that they had helped their children. But others echoed McIntosh's anguished plea: "We were told that antidepressants like Paxil and Zoloft were wonder drugs, that they were safe and effective for children. The pharmaceutical companies have known for years that these drugs could cause suicide in some patients. Why didn't we?"

It's a question that has shaken Americans' faith in the companies that provide their medications, and in the regulatory system that is supposed to ensure that drugs work, and are safe. Although most of the drugs have not been licensed for use in children, doctors have widely prescribed them 'off label' to withdrawn and depressed kids. So why, ask campaigners, were regulators and the public not told the results of clinical trials that cast doubts on the wisdom of prescribing the drugs to children?

In this emotionally charged atmosphere, the US Food and Drug Administration (FDA) will meet on 13 and 14 September to consider the scientific evidence about giving drugs called selective serotonin reuptake inhibitors, or SSRIs, to children. After reviewing the available data in February, and hearing the parents' testimony, the agency told manufacturers to label SSRIs with warnings that ask doctors to watch patients closely for suicidal tendencies. It also commissioned a new evaluation of the clinical data, drawing on the assistance of researchers at Columbia University in New York.

Pill power: children are prescribed a range of antidepressants.

J. RAEDLE/GETTY IMAGES

Depressing evidence

The results of this analysis are now in, along with findings from other studies. It seems clear that SSRIs are, in some cases, linked to suicidal behaviours in children. But what this link means — and what regulators should do about it — remains extremely contentious. Does the risk apply to all drugs in the class? Does it exceed the risk of suicide in children whose depression is left untreated? How effective are any of the SSRIs in relieving depression in children? And, more fundamentally, has the controversy exposed worrying gaps in our understanding of childhood psychiatric conditions?

There are no simple answers, but Britain's Medicines and Healthcare Products Regulatory Agency has

R. B. LEVINE/PHOTOGRAPHER SHOWCASE

Up in arms: this year's American Psychiatric Association meeting saw protests at child medication.

already seen fit to advise that SSRIs apart from Prozac, made by Eli Lilly, should not be given to children under 18. Regulators in many other countries are looking to the FDA for leadership. The media are scenting a scandal, and activists are on the warpath (see 'Big pharma's *bête noire*', overleaf). With children's lives and mental well-being at stake, the FDA faces its sternest test in years.

After Prozac was released onto the market in the late 1980s, there was a scare that it caused suicidal impulses in some patients. But in 1991, the FDA ruled that there was no clear evidence, and gave the drug a clean bill of health. The controversy about SSRIs blew up again last year, when the FDA asked GlaxoSmithKline to provide information on its unpublished trials of Paxil in depressed children. When those data revealed disturbingly high incidences of suicidal thoughts and behaviours, the agency demanded the results from 24 drug-company studies on SSRIs in children.

STONE/GETTY IMAGES

Many of the studies, conducted by eight different firms, had never before been published or presented to the public. When FDA epidemiologist Andrew Mosholder combined the data from the trials, he found that children who received SSRIs were 1.89 times as likely than those on a placebo to show suicidal thoughts and behaviours.

But there were doubts about how well these behaviours had been classified. So the FDA asked psychiatrists at Columbia University to reclassify the data. On 20 August, the agency released the results of the reanalysis, which confirmed Mosholder's central finding: children on SSRIs were 1.78 times as likely to exhibit suicidal tendencies.

More evidence on the drugs' side effects arrived last month from the Treatment for Adolescents with Depression Study (TADS), led by John March of Duke University Medical School in Durham, North Carolina. His team studied two treatments for childhood depression: Prozac, and cognitive-behavioural therapy, which encourages depressed people to change their thought patterns. A combination of the two seemed to provide the most effective relief of depression. But children given Prozac, in isolation or together with behavioural therapy, were more likely to report harming or thinking about harming themselves or others[1].

Cure and kill?

Critics of SSRIs have leapt on the latest findings. "I think it's pretty clear that the drugs cause a problem," says David Healy of the University of Wales in Bangor, who has persistently attacked drug companies for their promotion of SSRIs.

But why should drugs designed to alleviate depression tip some children over into suicidal behaviour? Some psychiatrists blame a side effect called 'akathisia' — an agitated state that occurs in a minority of patients placed on antidepressants[2]. Others argue that children starting drug therapy might become vulnerable as their depression lifts enough for them to voice or act on impulses that they felt before the treatment began. "In primary care, we've been taught for years that when depressed patients start to feel better, they can get enough energy to commit suicide," says David Price, a psychiatrist based in Denver, Colorado, who writes guidelines on the treatment of depression for the healthcare provider Kaiser Permanente.

Evidence from a large study of depressed adults and children published in July seems to support this theory, showing a peak in suicidal tendencies within nine days of starting treatment with antidepressants[3]. "We don't really know, but the medicine probably makes you less likely to stop yourself," says March.

Nevertheless, none of the children in any of these trials actually killed themselves, and the incidence of behaviours related to suicide was low — in the TADS trial, for instance, only about 10% of the children given Prozac reported harming or thinking of harming themselves or others. So many psychiatrists still argue that the drugs are safer than no treatment at all.

Trials on trial

"Depression is a serious illness that needs treatment," says Graham Emslie, a child psychiatrist at the University of Texas Southwestern Medical Center in Dallas, who has consulted for manufacturers of SSRIs. "And if you want to use the most effective treatment you've got to use the medicine."

The problem with this argument, however, is that Prozac is the only SSRI to have been shown to alleviate childhood depression in rigorous clinical trials, and to be approved by the FDA for that purpose. Nevertheless, doctors routinely prescribe other SSRIs to depressed children, with Zoloft and Paxil topping the list in the United States. Other popular SSRIs include Wyeth's Effexor and Celexa, made by Forest Pharmaceuticals. Because the drugs are considered safe and effective for depressed adults, doctors have simply assumed that the same must be true in children.

Indeed, if Prozac helps depressed children, it's difficult to understand why other SSRIs should not. SSRIs are designed to work by increasing the availability of a neurotransmitter called serotonin, which affects mood and emotions. Seeing no reason to question the underlying pharmacology, many experts have assumed that the clinical trials in depressed children are flawed. Some psychiatrists point out that most SSRIs show some trend towards working in children, even if this is not statistically significant. "It's not the case at all that a failed trial disproves efficacy," says Robert Findling of Case Western Reserve University in Cleveland, Ohio, who has also served as a paid consultant for SSRI manufacturers.

One of the biggest problems with testing antidepressant drugs in children is that

young people are especially likely to show a strong placebo response, which may mask the drugs' biological effects. In one of the successful trials of Prozac, for instance, the children given dummy pills improved 70% as much as those on the drug itself[4]. The attention that depressed children gain simply from being part of a clinical trial may help to explain these results. "Even if a kid gets a placebo, he still has to show up at a clinic, and someone will ask him questions about how he's feeling," says Christopher Varley, a psychiatrist at the University of Washington at Seattle.

Another possible problem is that trials of depressed children may include some individuals with bipolar disorder, formerly known as manic depression, for which SSRIs are not an effective treatment. People with bipolar disorder often don't experience their first manic phase until early adulthood, which could mean that the patients enrolled in adult and paediatric trials of SSRIs may actually have very different clinical profiles. "We could be comparing apples with oranges," says Price.

Proper treatment

While supporters of SSRIs use these arguments to justify their belief that the drugs help children, for others they underline the need for caution. If we don't know enough about childhood depression to accurately diagnose it, and if the attention focused on children in a clinical trial can be enough by itself to improve their condition, then might it be best to avoid drugs?

Jon Jureidini, a child psychiatrist at the University of Adelaide in Australia, believes the real problem is that mental-health services often fail to provide behavioural therapies for children who need them, which leads to an over-reliance on drugs. "The danger is that we're masking this problem by drugging children, which may be quieting them down, but may also be indirectly harming them," he says.

Jureidini also takes little comfort from the relatively low rate of suicidal behaviours reported in the drug companies' clinical trials. Such trials are short, he says, and are not designed to pick up rare events such as suicide attempts. So the fact that a consistent risk of suicidal tendencies appears across all of the paediatric SSRI trials is worrying, Jureidini argues. "We know from our experience with other drugs that harms often become apparent after the trial period is well and truly over," he says.

Most of the psychiatrists who doubt the drugs' efficacy don't want to see them banned for use in children. The main problem, they say, is that they are being prescribed too often by family doctors who have little knowledge of mental health, who don't support drug treatment with behavioural therapy, and who typically don't monitor their patients closely to look for the signs of suicidal impulses. Prescribing SSRIs to adults may now be routine, says Price, but for children it shouldn't be. "I'd advise a primary care doctor to call a psychiatrist when diagnosing depression in a child or adolescent," he says.

The drugs' manufacturers are now changing their labels according to the FDA's instructions, and reject the suggestion that they concealed data. Eli Lilly and GlaxoSmithKline have also announced plans to place data from trials on approved drugs on the web. A spokeswoman for GlaxoSmithKline told *Nature* that the firm is eager to see how the FDA interprets the childhood SSRI trial results. "It is not a black and white issue," she says.

The stakes are high for the FDA. It must make sense of the evidence and take appropriate action — or it might have to answer more questions from devastated parents mourning their lost children. ■

Erika Check is *Nature*'s Washington biomedical correspondent.

Big pharma's *bête noire*

On Sunday 18 July, Congressman James Greenwood's office gave Vera Hassner Sharav some bad news: a hearing on antidepressants in children had been cancelled.

Sharav, an activist for patients' rights who has become a thorn in the drug industry's side, was livid. She was even more upset when she learned that Greenwood had cancelled the hearing because he was stepping down from Congress to take a new job at the Biotechnology Industry Organization, of which many antidepressant manufacturers are members. So Sharav e-mailed her distribution list of journalists, politicians and other opinion formers, accusing Greenwood of "selling out" to the drug industry.

Greenwood, a moderate Republican from Pennsylvania, was so stung that he called Sharav to demand that she distribute his rejection of her accusation, and his assurance that the hearing would be rescheduled — which she did, in a brief statement, on 21 July. But by then, an article quoting Sharav's criticism of Greenwood had already appeared in *The Washington Post*.

The incident demonstrates Sharav's methods, and her growing influence. For those following the controversy surrounding the prescription of antidepressants to children, Sharav's partisan 'infomails' have become a constant narrative. Her exhaustively compiled mailing list includes cabinet members, government officials and scores of journalists.

Sharav began investigating the ethics of clinical research and the drug industry more than a decade ago, after her son died from a reaction to a drug used to treat schizophrenia. After his death, Sharav found out that the prescribing doctor was on retainer for a company conducting research on the drug.

Sharav, a law librarian, began using her research skills to look for cases of what she considered to be ethical abuses in clinical research. Eventually, this became a full-time occupation, and in 2001 she formed the non-profit Alliance for Human Research Protection.

Initially, Sharav was perceived as an outsider. But she has gradually built up her influence by sending her infomails, and by organizing for families to testify at key government hearings. "As events began to catch up with what I was saying, I was proven to be right, and that's what has lent increasing support to the cause," she claims.

Pharmaceutical executives shouldn't expect Sharav to rest on her laurels. "I don't consider this battle in any way over," she says.

www.ahrp.org

E. VUCCI/AP

Public grief: parents of allegedly drug-damaged children at a hearing on the issue in February.

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