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ARIANNA HUFFINGTON'S OFFICE

Thanks -
Cindy

FACSIMILE TRANSMITTAL SHEET

TO: Arianna Huffington	FROM: Arianna Huffington
COMPANY: Room 578	DATE: 12/31/97
FAX #: 803 842-4695	TOTAL NO. OF PAGES INCLUDING COVER: 5
PHONE NUMBER:	PHONE NUMBER: 310-440-9490
RE:	FAX NUMBER: 310-440-9525

__URGENT __FOR REVIEW __PLEASE COMMENT __PLEASE REPLY __PLEASE RECYCLE

NOTES/COMMENTS:

To Jen/Neera

Please look into this issue re Prozac and kids and advise me what issue is — esp. re possible FDA approval — and what, if any, position I should consider.

Thanks. Ari

ON CULTURE

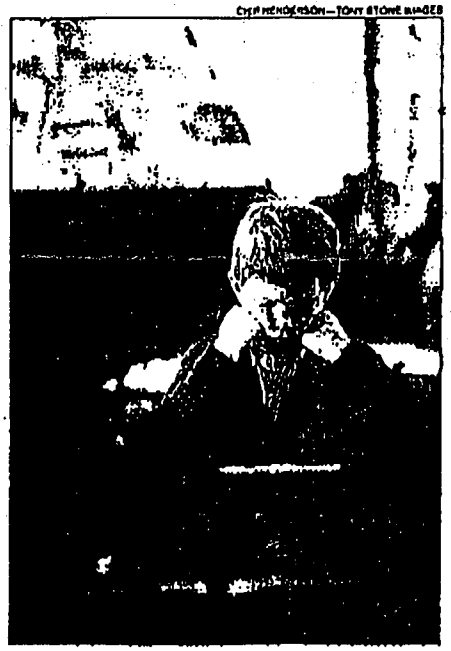
BY ARIANNA HUFFINGTON

Peppermint Prozac

Is your daughter depressed about acne? Soon, you may be able to take her to a dermatologist for peppermint-flavored Prozac. Is your son blue over an ingrown toenail? Take him to a podiatrist for some antidepressants. Is he angry about having to wear braces? His orthodontist may soon be handing out pills along with a dinosaur toothbrush.

Already, at least 580,000 children are being prescribed antidepressants—and those numbers are likely to increase dramatically. For now, doctors can prescribe Prozac to kids but Eli Lilly, which manufactures the drug, can't market it as a children's remedy. According to the *Medical Sciences Bulletin*, however, "the FDA is currently evaluating Prozac for use as an antidepressant in children." If the FDA gives its blessing, Eli Lilly will be free to peddle "children's" Prozac—especially now that the FDA is about to clear the way for TV advertising of prescription drugs. The company already has on the market a peppermint-flavored version of Prozac. And where Prozac leads, other antidepressants, such as Zoloft and Paxil, are sure to follow.

Doctors may prescribe antidepressants to children without any psychiatric evaluation. Yet the symptoms used to identify depression in a recent Prozac ad range from feeling "unusually sad or irritable" to finding it "hard to concentrate." I have two healthy little girls, ages 6 and 8, both of whom have experienced these symptoms. Indeed, I don't know any normal children who haven't.



CYD HENDERSON—TONY STONE IMAGES

Will Prozac be used for childhood blues?

No doubt there are children and teenagers who could genuinely benefit from antidepressants. But it's easy to see how millions might wind up taking antidepressants as a false cure for childhood and adolescence. One father in Southern California wrote to me recently to say that one of his son's friends is on antidepressants "because her parents are 'too strict' and she is depressed at not being able to do what other kids do."

Overprescribing antidepressants to kids is a form of child abuse.

A passing cloud. Signs of depression may be nothing more than a passing cloud—or an indication of unresolved grief and loss. A doctor spending a few minutes with a child cannot possibly know the difference. "It's part of the human condition to feel crummy if something bad is happening in one's life," says Harold Koplewicz, vice chairman of psychiatry at the New York University Medical Center. "But that is very different from having a clinical disorder."

Indeed, substituting the quick fix of a drug for the often frustrating reality of parenting can be a subtle form of child abuse. It is our job as parents to help our kids navigate life's emotional roller coaster. Their mental health depends not only on their life experiences—good and bad—but on how they learn to cope with them.

Children behave notoriously in line with the expectations of the adults around them. If we think they can't cope without a pill, they will grow up believing that. If we teach our children that pills will make them feel better, how can we then tell them not to try a joint or a few drinks to lift their spirits?

It may not be long before stressed parents and teachers, bombarded with ads promising immediate relief for their kids—and themselves—will turn to Prozac with alarming frequency. Forty percent of American children live without a father in the house. How tempting antidepressants will seem to those overwhelmed mothers.

One psychologist, Barbara Ingersoll, recently proclaimed that before long "mood disorders will be treated not as exotic, uncommon conditions in children but more like [cavities] or poor vision . . . There won't be a stigma for kids on Prozac—the stigma will be on not taking Prozac." In the past, the upper classes typically dealt with the stresses of childhood by sending their kids to boarding school. Now, instead of being sent to Hotchkiss, children can be transported to Camp Prozac.

There are so many forces pushing us to accelerate the use of antidepressants for children. But we need to slow down. "Children are so vulnerable," says Michael Faenza, president and CEO of the National Mental Health Association. "We don't have a good body of research yet about how antidepressants will affect them long term." Even in Aldous Huxley's *Brave New World*, Soma—the drug that kept everyone manageably numb—wasn't put in the kids' bottles.

Here is a modest solution. Until much more is known about the effects of antidepressants on children's brains, why can't doctors simply refuse to prescribe the drugs without a full psychiatric evaluation? Since Eli Lilly claims to be concerned primarily with the mental health of its customers—as opposed to opening an enormous new market for Prozac—company executives would no doubt agree to such a restriction. And if they find that pill too hard to swallow, maybe the FDA could give it to them in a nice peppermint-flavored version. ■

Arianna Huffington is a nationally syndicated columnist.

Los Angeles Times

MONDAY, JULY 21, 1997

Exit Joe Camel, but Here Comes Joe Prozac

■ Drugs: Children are the next target as antidepressants are marketed like candy bars.

By ARIANNA HUFFINGTON

Even 1st Amendment fundamentalists acknowledge that there is no absolute protection of free speech in the Constitution. Crying fire in a crowded theater is not covered. Neither is false advertising. The three-page Prozac ad now running in magazines around the country—from Time to Cosmopolitan—is morally indefensible.

Under a storm cloud that on the second page is magically transformed into a bright sun, the ad informs us that "When you're clinically depressed . . . you may have trouble sleeping. Feel unusually sad or irritable? Find it hard to concentrate? Lose your appetite? Lack energy? Or have trouble feeling pleasure? These are some of the symptoms that can point to depression."

These are also some of the symptoms that can point to life. Is there anybody on this planet who has never lacked energy, felt sad or irritable, found it hard to concentrate or had trouble sleeping? Because if there is, I would sure like to meet that perfect specimen.

Prozac has already been prescribed to more than 17 million Americans. And as Eli Lilly, Prozac's manufacturer, admits in the small print of the ad—on strict lawyers' orders no doubt—it has not all come up roses. The adverse side effects listed under "precautions" range from anxiety (I thought Prozac cured anxiety) to suicide (a fail-safe cure for depression, though probably not the one Lilly had in mind).

Despite a page chock-a-block with small-print warnings and small-print advice to consult a doctor, Lilly has launched a multimillion-dollar ad blitz specifically designed to bypass doctors and target consumers directly.

Treating life as an illness is bad enough. But treating childhood as a disease is tragic. And what makes the timing of this campaign so disturbing is that it coincides with the publication of the only large-scale study on the effects of anti-depressants on kids, which is being used by Lilly to get Food and Drug Administration approval for children's Prozac. The University of Texas study found that about half of the 70 8- to 18-year-olds improved. But then, so did one-third of those on a placebo.

On such unshakable evidence, the FDA is widely expected to declare Prozac a drug approved for children. As Wendy Neuberger, a pediatrician who refused to prescribe Prozac, put it: "Prozac is a drug that alters brain chemistry, and we don't know how alteration of brain chemistry in a child might affect their development."

Lilly's worldwide sales in 1996 were $2.36 billion, up by 14% from 1995.

In the search for ever-expanding markets, children were bound to be Lilly's next target. But why does the FDA, so eager to protect children from tobacco, have to cooperate? Already, children's prescriptions of adult antidepressants have soared from 342,900 in 1994 to 579,700 in 1996.

There is obviously a small percentage of children, as there is a small percentage of adults, who suffer from severe depression that needs to be medically treated. But this glossy ad campaign is not for them. The transformation of a gray cloud into a yellow sun is intended to convince the average American pursuing happiness and not quite finding it that there is an instant solution at hand. More troubling is the fact that the childish drawings are clearly aimed at stressed-out parents too busy to deal with children who are acting up, having trouble at school or simply being moody. The solution is simple: Drug them up to your expectations.

"Children on Prozac," Barbara Ingesoll, a child psychologist, cheerily proclaims, "tell us they are not as angry and not as temperamental, behave better and feel better. It is a tremendous development. We can see a future where mood disorders will be treated not as exotic, uncommon conditions in children but more like dental cavities or poor vision." Ingesoll has seen the future, and it works: "There won't be a stigma for kids on Prozac—the stigma will be on not taking Prozac."

Perhaps to avoid the stigma and until the ads reach full penetration, we can put it in the water supply, like fluoride. And since nobody is moodier than a bunch of eighth-graders, why not sell it in vending machines? Exit Joe Camel. Enter Joe Prozac.

At the very moment we are bombarding our children with ads and sermons about saying "no" to drugs, we are blurring for them any distinction between feeling good from Prozac and feeling good from life. "The unexamined life is not worth living," said Socrates, but we are teaching our children that masking symptoms with drugs is the best way to lead busy, productive lives. In the brave new world of designer drugs, we just gulp down another pill and head for another meeting.

And we don't even see the absurdity of a major advertising campaign for a prescription drug for clinical depression, aggressively marketed like a new candy bar. The kiddie Prozac about to debut is in fact peppermint-flavored. Which makes Eli Lilly just a big-time drug pusher.

Arianna Huffington is a syndicated columnist. E-mail: ariannahuf@aol.com

San Diego, CA
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AUG 2 0 1997

Allen's P. C. S. Est. 1888

Children, soft money and McProzac

Arianna Huffington

President Clinton's proposal last week that pharmaceutical companies test all drugs likely to be prescribed for children brought to the forefront once again the unsettling issue of children and antidepressants.

What is particularly chilling is the masterly way Eli Lilly, the manufacturer of Prozac, is continuing to present itself as an innocent bystander in the process to gain Food and Drug Administration approval for pediatric antidepressants.

I was recently on a radio show with Lilly representative Dr. Gary Tollefson, who talked in measured tones about Lilly's "partnership with the academic community," "peer review medical journals" and the need to establish "whether the benefits outweigh the risks." This, at the very moment when Lilly has signed up Leo Burnett of Chicago, the ad agency handling Reebok and McDonald's, to target consumers directly.

Lilly's public stance is of a civic-minded company whose sole concern is the well-being of children — especially the millions of children whose quiet suffering could come to an end by imbibing peppermint-flavored Prozac.

Meanwhile, through its extremely active political action committee, Lilly makes sure that elected officials in Washington will not be asking too many questions about Prozac and children. In the last 10 years, the PAC has made several hundred contributions to federal campaigns — among them those of Newt Gingrich, Dick Armey, Tom DeLay, Trent Lott, Chris Dodd and members of the House Commerce subcommittee on health.

Lilly has also become expert at the soft-money game. The company went from zero soft-money contributions in the 1992 election cycle to $746,675 in 1996. When asked to explain this burst of generosity, Lilly spokesman Jeff Newton replied: "We do it because we think we have to participate in the political process. . . . We give to both parties. They are important institutions, basically, and that's why we do it."

Fortunately, Rep. Dennis Kucinich, a member of the Government Reform and Oversight Committee, does not receive Lilly money. When Kucinich asked the FDA for information, the agency responded by citing *F-D-C Reports*, which covers the drug industry: "Prozac is being studied by Eli Lilly and Co. (the sponsor) as an antidepressant for use in patients under 18 years of age and . . . a pre-N.D.A. (New Drug Application) filing' was made."

That directly contradicts the passive stance that Lilly has been assuming for public consumption — including in a letter sent to me and every newspaper that published my column critical of pushing Prozac on kids.

This letter is part of a well-orchestrated, cold-blooded attempt summed up by Lilly executive Christina Hendricks: "We go after those people," she told a drug industry conference in May, referring to anyone who dares be disrespectful of Prozac, even in greeting cards, "with a very serious intent to get them to cease and desist from their activities." Any attack on Prozac is being countered as "belittling those suffering from depression."

Lilly's damage-control strategies include secret settlements with plaintiffs regarding Prozac's adverse effects. The latest occurred in Louisville, Ky., where Lilly quietly reached agreement with the families of the victims of a Prozac user who killed eight and wounded 12 in a printing-plant shooting spree.

Now the pharmaceutical company, whose 1996 profits were $1.52 billion, is cynically planning an expansion into the children's market while pretending it is not and dosing Congress into docility with money soft and hard.

"Lilly's proactive approach to media management may be smoothing the way for antidepressants in children," *F-D-C Reports* observed this year. Indeed. Dr. Tollefson appeared on National Public Radio in May to tell listeners that adult depression "often begins in children and adolescents."

What mom or dad would condemn their young one to a life of depression when, with kiddie Prozac, the Kodachrome perfection of an American childhood could be at hand? Watch out, America. That's how they gild the lily at Lilly. They talk obsessively about the relatively few children with serious depression, while leaving out the millions of kids whose growing brains are being meddled with even though there is no clear medical knowledge of the long-term effects of Prozac.

Next time you hear a Lilly executive talking about improving childhood through chemistry, remember that he stands to make huge profits by getting kids hooked. Last year, Lilly CEO Randall Tobias took home $6.68 million in compensation, a 75 percent increase over the previous year.

And how, precisely, does this incentive plan — growing wealthier by expanding the market of restless and troubled kids medicating themselves against life's emotional roller coaster — differ from that of the Cali cartel?

Prozac and children/adolescents

Key messages

- Lilly does not market Prozac for use in treating children and adolescents. To date, Prozac has been cleared by the FDA only for use in treating patients 18 years of age and older.
- Lilly has not sought an indication from the FDA for the use of Prozac in children and adolescents. The company did recently supply data to the FDA concerning Prozac's use in these populations. However, this was done in response to an FDA request that *all* pharmaceutical companies provide the agency pediatric data related to a variety of medicines.
- Pediatric depression can be a serious illness and can be especially difficult to diagnose. The decision to diagnose and treat pediatric depression should be made only after a thorough evaluation by a child psychiatrist.
- We share the concern that any use of antidepressants in children should proceed with great caution until more research is done.

Peppermint-flavored: targeted to kids?

Media advertising → Media campaign - general audience
↳ Do have a campaign in anti-depressant featured in publications must meet stds - ↳ uses only & promote approved indication ↗ balance ✱ side effects - risk.

U. S. FOOD AND DRUG ADMINISTRATION

OFFICE OF PUBLIC AFFAIRS
PRESS RELATIONS STAFF
5600 FISHERS LANE, ROOM 15A-07
ROCKVILLE, MD 20857

OFFICE #: (301) 827-6242 **FAX #: (301) 443-1388**

TO: Neera Tanden
The White House
(202) 456-[redacted] 5542
FAX NUMBER

FROM: Brad Stone

CONFIRMATION NUMBER

MESSAGE:

Prozac Information by Eli Lilly (the drug's mfger)

Additional study will follow soon

Number of Pages: 3

Date: 1/16/98

Peppermint: form of Prozac - been around ie 7 yrs developed for special needs patients → common thing in pharmaceutical ↳ geriatric

Ads - taxing ads: → stds. no mktg of kids: not other than → approved indication

50% →

new mcs.

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TO: Neera Tanden
White House
202 456 2878
FAX NUMBER

FROM: Brad Stolve

CONFIRMATION NUMBER

MESSAGE:

FDA Background info on Ad Regs. ↓
Examples of Prozac Ads

Number of Pages: 1+2+

Date: 1/3/98

FDA RULES INFO

volved in their own health care.

But, says Nancy Ostrove, a public health analyst in FDA's division of drug marketing, advertising, and communications, "Direct-to-consumer advertising is not inherently bad or good. It can be useful or harmful, depending on how it's done."

Truth in Advertising

FDA has regulated the advertising of prescription drug products since 1962, under the Federal Food, Drug, and Cosmetic Act and related regulations. Most other advertising, including the advertising of over-the-counter drugs, is regulated by the Federal Trade Commission, under a different set of rules.

FDA generally interprets the term "advertisement" to cover information other than labeling that promotes a product. The term includes promotions broadcast on television or radio, conducted by telephone, or printed in magazines or newspapers. (Also see "Drug Promotion in Cyberspace.")

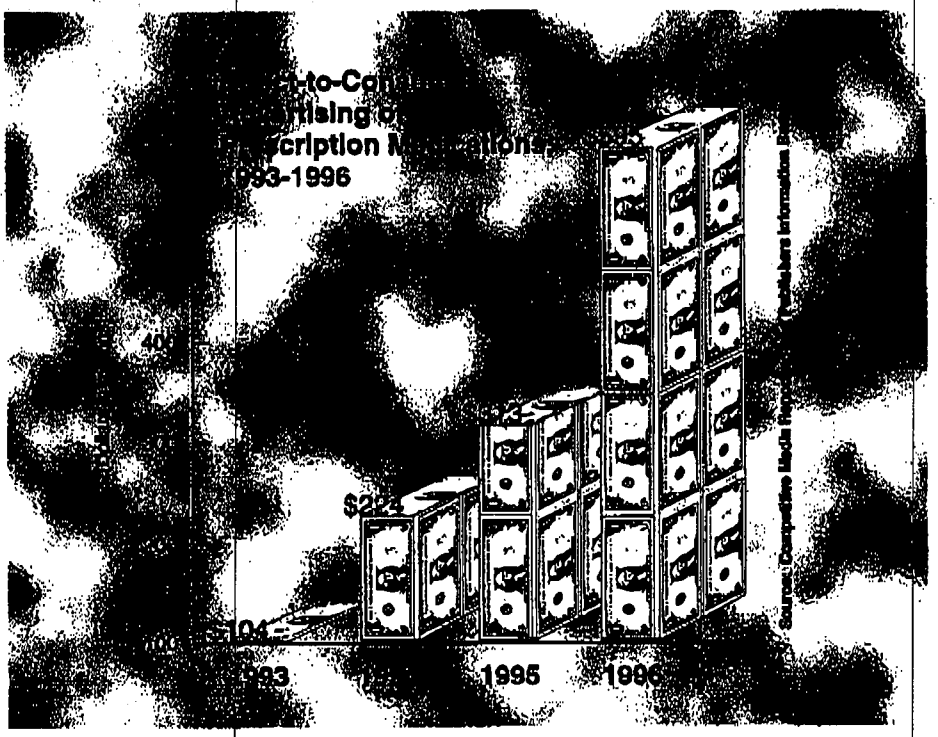
For many years, prescription drug makers promoted their products exclusively to health-care professionals. But about 15 years ago, some manufacturers began to produce ads targeted to consumers.

Since then, direct-to-consumer advertising has become a popular promotional tool. In 1996 alone, prescription drug manufacturers spent almost $600 million on this type of advertising, according to Competitive Media Reporting, which projects 1997 spending to be at least twice that.

And consumer-directed ads seem to be capturing consumers' attention. In a 1996 study by drug industry consultant Scott-Levin, three-quarters of the doctors surveyed said their patients have talked about drug ads they heard or saw.

FDA regulates consumer-directed ads under the same regulations as professional-directed ones. Like promotions directed to health-care providers, consumer ads may only make claims that are supported by scientific evidence and that are not inconsistent with the FDA-approved product labeling. And, like professional-directed advertisements, they may not be false or misleading.

FDA oversight helps ensure that consumers understand both the benefits and



In Trouble with FDA

Generally, FDA does not require pre-clearance of promotional materials. But the agency often reviews drug companies' draft promotional materials at their request.

If FDA finds that an advertisement a company is using is false or misleading, the agency may take enforcement action against the company. The agency regulates all of a drug company's prescription drug promotions, including the promotional tactics of its salespeople.

For the least serious violations of advertising regulations, FDA will send the drug company an "untitled letter" outlining FDA's findings.

For more serious violations, FDA may issue a "warning letter" requesting that the company immediately stop the violative advertising and, in many cases, take other corrective steps.

For example, the company may be asked to send a "Dear Doctor" letter to alert those who prescribe the medication to FDA's finding. The company may also be asked to run corrective advertisements setting forth FDA's concerns and bringing the ad's language into compliance. Finally, a warning letter may request that a company send its future promotional materials to FDA for clearance before they are used.

Beyond sending untitled letters and warning letters, FDA may stop violative promotions by seizing affected products or enjoining the use of promotions that make the same or similar claims. These actions and the most serious remedy, criminal prosecution of the company or the individuals involved, are used rarely—generally when intentional and serious misstatements are involved.

The threat of agency action isn't the only thing that keeps companies honest, says John Kamp of the American Association of Advertising Agencies. "A drug company won't play fast and loose with the rules because its most important asset is its reputation with the American people." ■

—T.N.

limitations of an advertised drug. (See "In Trouble with FDA.") The agency monitors ads to make sure they are tailored for the target audience. For example, a consumer-directed ad may be considered misleading unless it explains the drug's benefits and risks in words that people who aren't medical professionals can understand.

FDA regulations call for "fair balance" in every ad. FDA reviewers look at the entire advertisement to see if it is balanced. The risks as well as the benefits must be clearly identified, with the risks presented prominently and readably so that the benefits are not unfairly emphasized.

Under the Federal Food, Drug, and Cosmetic Act, most ads must include a "brief summary" describing the effectiveness of the drug and its risks. In print ads, drug companies usually meet the requirement by including entire risk-related sections of the approved labeling. Many people have expressed concern to FDA that, because drug labeling is primarily written for doctors, much of it cannot be understood by consumers.

"The brief summary might be fine for someone who went through medical school," says Linda Golodner, president of the National Consumers League. Even then, she says, "you have to get out a magnifying glass to try and sort out the information."

FDA is considering what steps can be taken toward a more consumer-friendly format. In the meantime, says Ostrove, "We encourage manufacturers to write the brief summary information to be more understandable to consumers."

TV Reality

In a short television or radio ad, manufacturers have found it difficult to meet the brief summary requirement. "Scrolling a long, detailed brief summary on a television screen is not practical on commercial television," writes drug law expert Wayne Pines in the Thompson Publishing Group's *Advertising and Promotion Manual.*

So, for television commercials and sometimes print ads, companies have historically opted for two types of ads—"reminder" ads and "help-seeking" ads—that are exempt from the brief summary requirement.

Reminder ads, like the original version of the Claritin commercial, call attention to a drug's name, but don't state the condition it is used to treat.

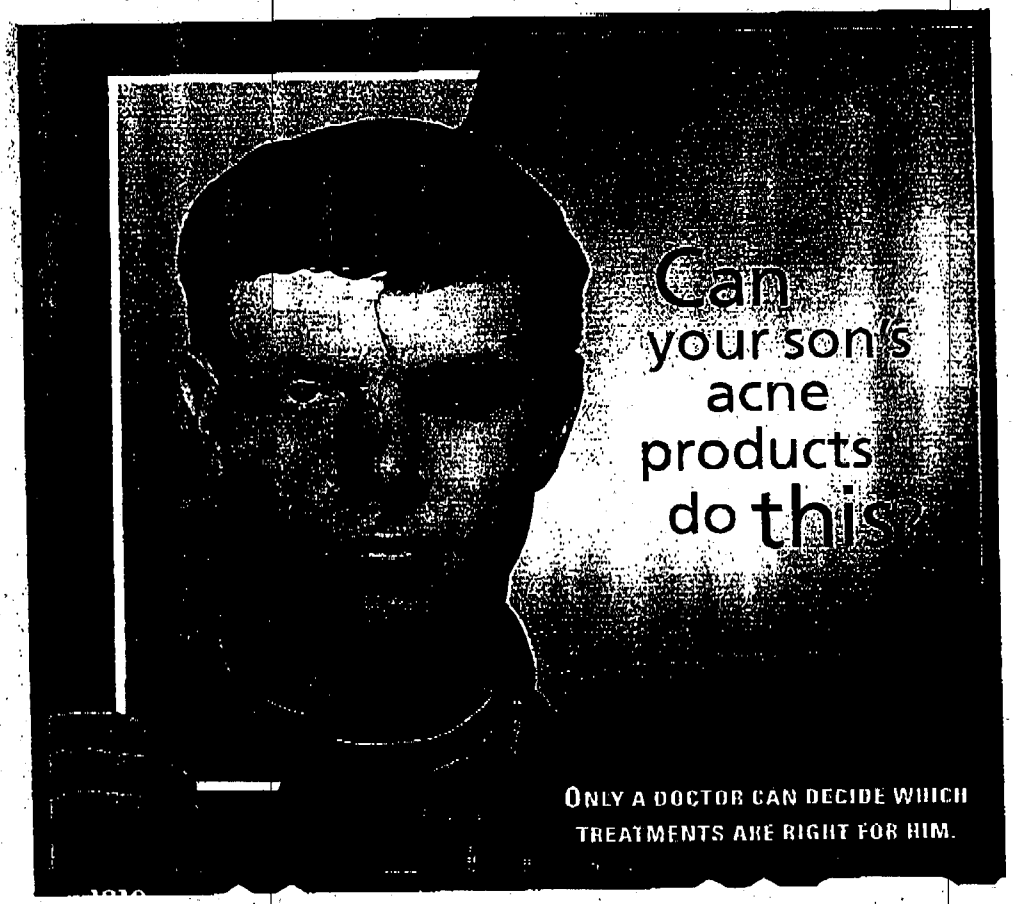
Help-seeking ads tell consumers only that there are treatments available for a particular condition and encourage them to talk to a health-care professional. To be considered a help-seeking advertisement, an ad may not state or imply the name of a particular product, although it can mention the manufacturer's name. One such magazine ad said simply, "Life without ulcers. It is now possible. See your doctor."

The reminder and help-seeking ad "each has only part of the information a consumer wants, which can create a lot of confusion," Ostrove says.

Completing the Puzzle

FDA regulations have always permitted sponsors of television and radio ads to present a brief summary. Or, instead, they could make "adequate provision" for interested people to get the approved labeling.

Before August 1997, FDA had not described "adequate provision" for consumer-directed ads, so drug companies



Help-seeking ads like this one let people know treatments exist for a medical condition, but don't name a specific drug.

(Source: Roche Products Inc.)

Los Angeles Times

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Exit Joe Camel, but Here Comes Joe Prozac

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By ARIANNA HUFFINGTON

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Under a storm cloud that on the second page is magically transformed into a bright sun, the ad informs us that "When you're clinically depressed . . . you may have trouble sleeping. Feel unusually sad or irritable? Find it hard to concentrate? Lose your appetite? Lack energy? Or have trouble feeling pleasure? These are some of the symptoms that can point to depression."

These are also some of the symptoms that can point to life. Is there anybody on this planet who has never lacked energy, felt sad or irritable, found it hard to concentrate or had trouble sleeping? Because if there is, I would sure like to meet that perfect specimen.

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Treating life as an illness is bad enough. But treating childhood as a disease is tragic. And what makes the timing of this campaign so disturbing is that it coincides with the publication of the only large-scale study on the effects of anti-depressants on kids, which is being used by Lilly to get Food and Drug Administration approval for children's Prozac. The University of Texas study found that about half of the 70 8- to 18-year-olds improved. But then, so did one-third of those on a placebo.

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"Children on Prozac," Barbara Ingesoll, a child psychologist, cheerily proclaims, "tell us they are not as angry and not as temperamental, behave better and feel better. It is a tremendous development. We can see a future where mood disorders will be treated not as exotic, uncommon conditions in children but more like dental cavities or poor vision." Ingesoll has seen the future, and it works: "There won't be a stigma for kids on Prozac—the stigma will be on not taking Prozac."

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Arianna Huffington is a syndicated columnist. E-mail: ariannahuf@aol.com

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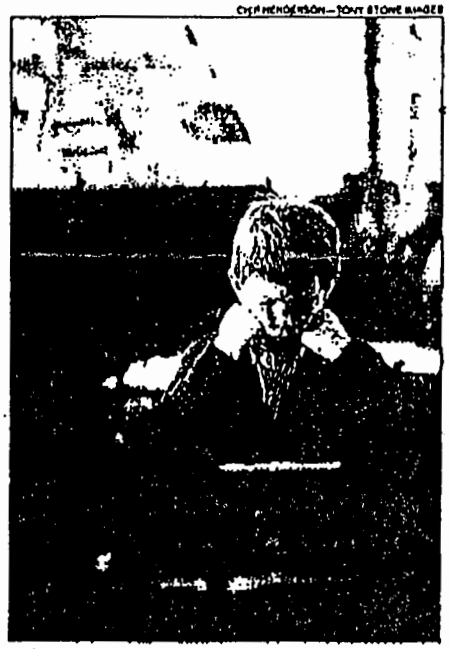

Will Prozac be used for childhood blues?

No doubt there are children and teenagers who could genuinely benefit from antidepressants. But it's easy to see how millions might wind up taking antidepressants as a false cure for childhood and adolescence. One father in Southern California wrote to me recently to say that one of his son's friends is on antidepressants "because her parents are 'too strict' and she is depressed at not being able to do what other kids do."

Overprescribing antidepressants to kids is a form of child abuse.

A passing cloud. Signs of depression may be nothing more than a passing cloud—or an indication of unresolved grief and loss. A doctor spending a few minutes with a child cannot possibly know the difference. "It's part of the human condition to feel crummy if something bad is happening in one's life," says Harold Koplewicz, vice chairman of psychiatry at the New York University Medical Center. "But that is very different from having a clinical disorder."

Indeed, substituting the quick fix of a drug for the often frustrating reality of parenting can be a subtle form of child abuse. It is our job as parents to help our kids navigate life's emotional roller coaster. Their mental health depends not only on their life experiences—good and bad—but on how they learn to cope with them.

Children behave notoriously in line with the expectations of the adults around them. If we think they can't cope without a pill, they will grow up believing that. If we teach our children that pills will make them feel better, how can we then tell them not to try a joint or a few drinks to lift their spirits?

It may not be long before stressed parents and teachers, bombarded with ads promising immediate relief for their kids—and themselves—will turn to Prozac with alarming frequency. Forty percent of American children live without a father in the house. How tempting antidepressants will seem to those overwhelmed mothers.

One psychologist, Barbara Ingersoll, recently proclaimed that before long "mood disorders will be treated not as exotic, uncommon conditions in children but more like [cavities] or poor vision . . . There won't be a stigma for kids on Prozac—the stigma will be on not taking Prozac." In the past, the upper classes typically dealt with the stresses of childhood by sending their kids to boarding school. Now, instead of being sent to Hotchkiss, children can be transported to Camp Prozac.

There are so many forces pushing us to accelerate the use of antidepressants for children. But we need to slow down. "Children are so vulnerable," says Michael Faenza, president and CEO of the National Mental Health Association. "We don't have a good body of research yet about how antidepressants will affect them long term." Even in Aldous Huxley's *Brave New World*, Soma—the drug that kept everyone manageably numb—wasn't put in the kids' bottles.

Here is a modest solution. Until much more is known about the effects of antidepressants on children's brains, why can't doctors simply refuse to prescribe the drugs without a full psychiatric evaluation? Since Eli Lilly claims to be concerned primarily with the mental health of its customers—as opposed to opening an enormous new market for Prozac—company executives would no doubt agree to such a restriction. And if they find that pill too hard to swallow, maybe the FDA could give it to them in a nice peppermint-flavored version. ■

Arianna Huffington is a nationally syndicated columnist.

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Children, soft money and McProzac

Arianna Huffington

President Clinton's proposal last week that pharmaceutical companies test all drugs likely to be prescribed for children brought to the forefront once again the unsettling issue of children and antidepressants.

What is particularly chilling is the masterly way Eli Lilly, the manufacturer of Prozac, is continuing to present itself as an innocent bystander in the process to gain Food and Drug Administration approval for pediatric antidepressants.

I was recently on a radio show with Lilly representative Dr. Gary Tollefson, who talked in measured tones about Lilly's "partnership with the academic community," "peer review medical journals" and the need to establish "whether the benefits outweigh the risks." This, at the very moment when Lilly has signed up Leo Burnett of Chicago, the ad agency handling Reebok and McDonald's, to target consumers directly.

Lilly's public stance is of a civic-minded company whose sole concern is the well-being of children — especially the millions of children whose quiet suffering could come to an end by imbibing peppermint-flavored Prozac.

Meanwhile, through its extremely active political action committee, Lilly makes sure that elected officials in Washington will not be asking too many questions about Prozac and children. In the last 10 years, the PAC has made several hundred contributions to federal campaigns — among them those of Newt Gingrich, Dick Armey, Tom DeLay, Trent Lott, Chris Dodd and members of the House Commerce subcommittee on health.

Lilly has also become expert at the soft-money game. The company went from zero soft-money contributions in the 1992 election cycle to $746,675 in 1996. When asked to explain this burst of generosity, Lilly spokesman Jeff Newton replied: "We do it because we think we have to participate in the political process. . . . We give to both parties. They are important institutions, basically, and that's why we do it."

Fortunately, Rep. Dennis Kucinich, a member of the Government Reform and Oversight Committee, does not receive Lilly money. When Kucinich asked the FDA for information, the agency responded by citing *F-D-C Reports*, which covers the drug industry: "Prozac is being studied by Eli Lilly and Co. (the sponsor) as an antidepressant for use in patients under 18 years of age and . . . a pre-N.D.A. (New Drug Application) filing' was made."

That directly contradicts the passive stance that Lilly has been assuming for public consumption — including in a letter sent to me and every newspaper that published my column critical of pushing Prozac on kids.

This letter is part of a well-orchestrated, cold-blooded attempt summed up by Lilly executive Christina Hendricks: "We go after those people," she told a drug industry conference in May, referring to anyone who dares be disrespectful of Prozac, even in greeting cards, "with a very serious intent to get them to cease and desist from their activities." Any attack on Prozac is being countered as "belittling those suffering from depression."

Lilly's damage-control strategies include secret settlements with plaintiffs regarding Prozac's adverse effects. The latest occurred in Louisville, Ky., where Lilly quietly reached agreement with the families of the victims of a Prozac user who killed eight and wounded 12 in a printing-plant shooting spree.

Now the pharmaceutical company, whose 1996 profits were $1.52 billion, is cynically planning an expansion into the children's market while pretending it is not and dosing Congress into docility with money soft and hard.

"Lilly's proactive approach to media management may be smoothing the way for antidepressants in children," *F-D-C Reports* observed this year. Indeed. Dr. Tollefson appeared on National Public Radio in May to tell listeners that adult depression "often begins in children and adolescents."

What mom or dad would condemn their young one to a life of depression when, with kiddie Prozac, the Kodachrome perfection of an American childhood could be at hand? Watch out, America. That's how they gild the lily at Lilly. They talk obsessively about the relatively few children with serious depression, while leaving out the millions of kids whose growing brains are being meddled with even though there is no clear medical knowledge of the long-term effects of Prozac.

Next time you hear a Lilly executive talking about improving childhood through chemistry, remember that he stands to make huge profits by getting kids hooked. Last year, Lilly CEO Randall Tobias took home $6.68 million in compensation, a 75 percent increase over the previous year.

And how, precisely, does this incentive plan — growing wealthier by expanding the market of restless and troubled kids medicating themselves against life's emotional roller coaster — differ from that of the Cali cartel?

Eli Lilly and Company
Government Relations
555 Twelfth Street, N.W.
Suite 650
Washington, D.C. 20004

Telephone: 202-393-7950
Facsimile: 202-393-7960

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TO: Brad Stone (301) 827-6251
FDA

Fax Number: **301-443-1388**

FROM: Debbie Hohlt,
Director, Public Affairs

RE: Prozac Ads

COMMENTS:

As promised.

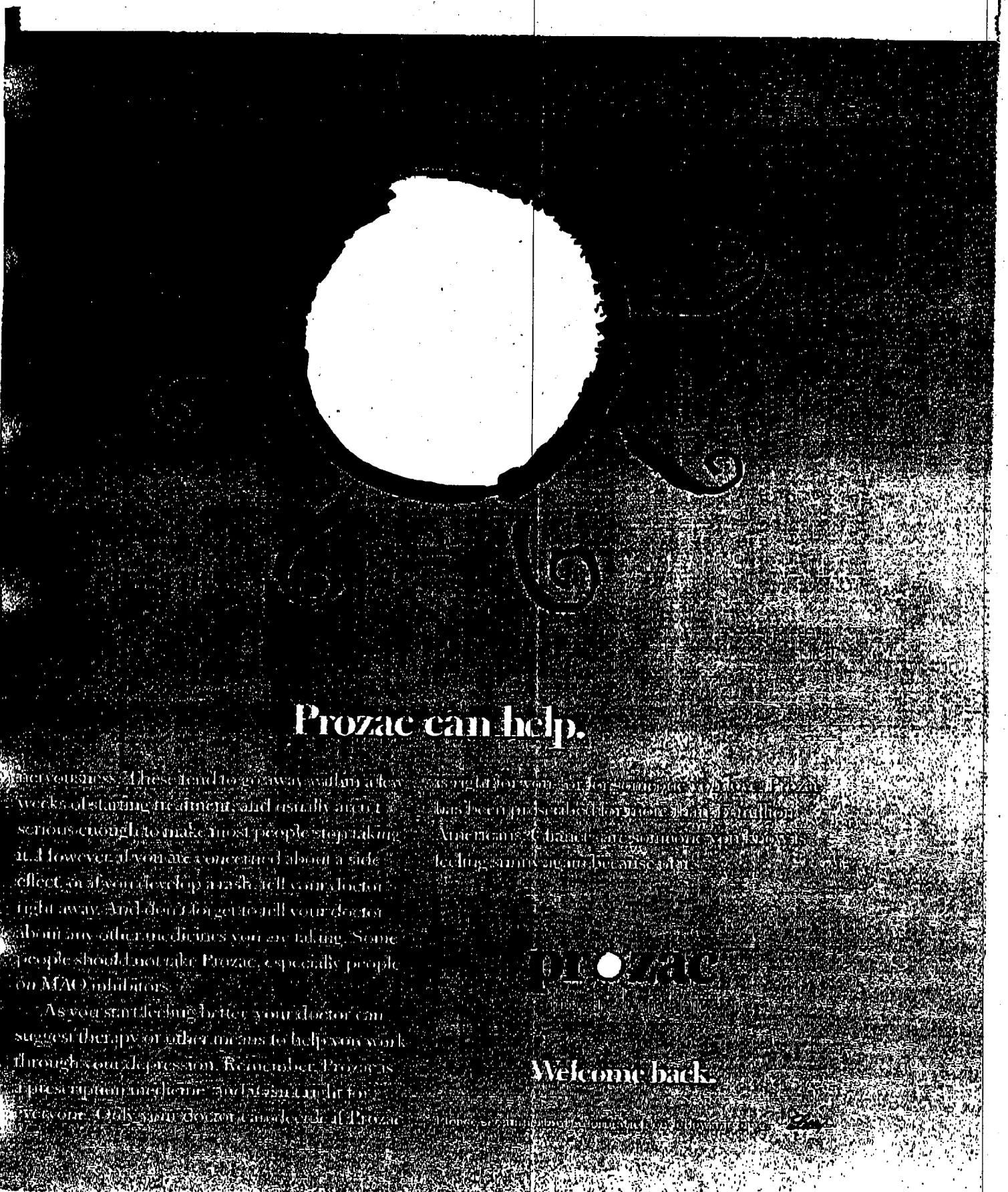
Depression hurts.

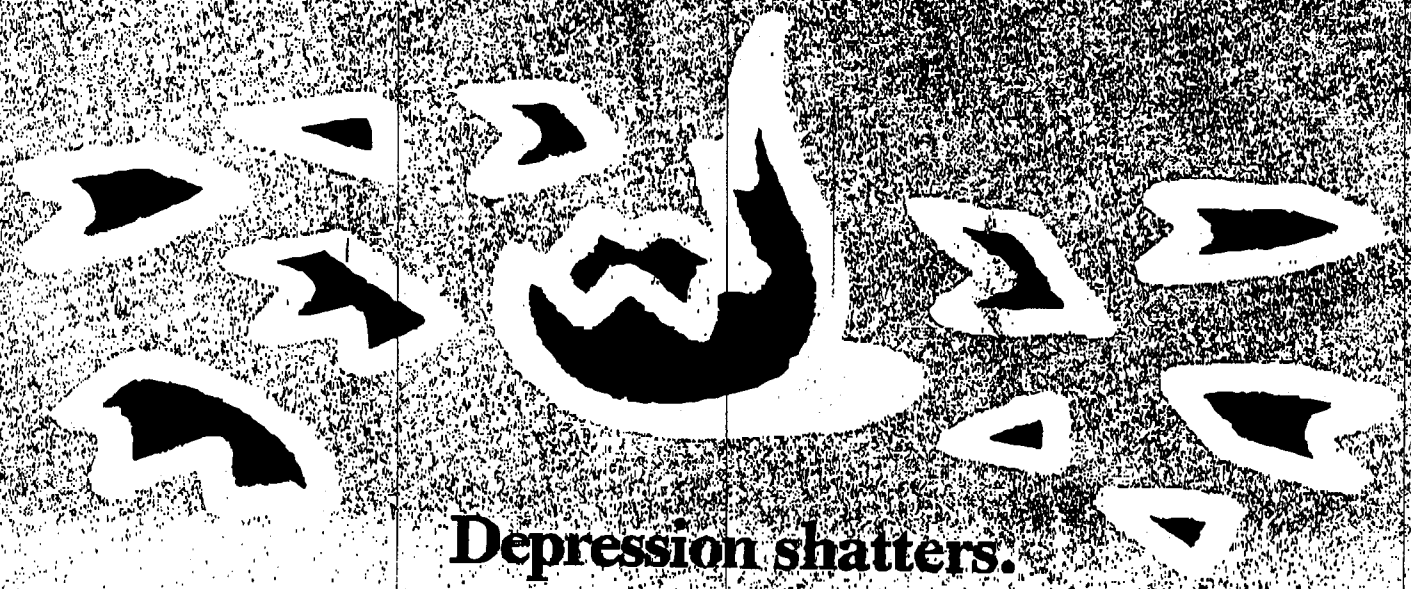
Depression isn't just feeling down. It's a real illness with real causes. Depression can be triggered by stressful life events, like divorce or a death in the family. Or it can appear suddenly, for no apparent reason.

Some people think you can just will yourself out of a depression. That's not true. When you're clinically depressed, one thing that can happen is the level of serotonin (a chemical in your body) may drop. So you may have trouble sleeping. Feel unusually sad or irritable. Find it hard to concentrate. Lose your appetite. Lack energy. Or have trouble feeling pleasure. These are some of the symptoms that can point to depression—especially if they last for more than a couple of weeks and if normal, everyday life feels like too much to handle.

To help bring serotonin levels closer to normal, the medicine doctors now prescribe most often is Prozac.® Prozac isn't a "happy pill." It's not a tranquilizer. It won't take away your personality. Depression can do that, but Prozac can't.

Prozac has been carefully studied for nearly 10 years. Like other antidepressants, it isn't habit-forming. But some people do experience mild side effects, like upset stomach, headaches, difficulty sleeping, drowsiness, anxiety and


Prozac can help.
PROZAC
Welcome back.



Depression shatters.

Depression breaks lives apart. It hurts the person who's depressed. And it's also painful for the people who love them.

You see, depression isn't "all in your head." It's a real illness with real causes. But the good news is that it can be treated.

Some people think you can just will yourself out of a depression. That's not true. When you're clinically depressed, one thing that can happen is the level of serotonin (a chemical in your body) may drop. So you may have trouble sleeping. Feel unusually sad or irritable. Find it hard to concentrate. Lose your appetite. Lack energy. Or have trouble feeling pleasure. These are some of the symptoms that can point to depression—especially if they last for more than a couple of weeks and if normal, everyday life feels like too much to handle.

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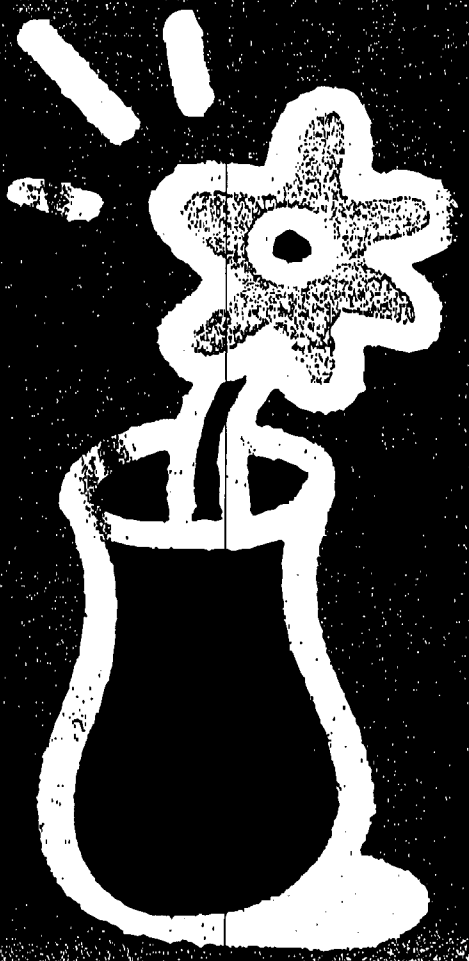

Prozac can help.

prozac

Welcome back.

Prozac®
fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indications: For the treatment of depression, obsessive-compulsive disorder (OCD), and bulimia nervosa.

Contraindications: Known hypersensitivity to Prozac.

Monoamine Oxidase Inhibitors—There have been reports of serious, sometimes fatal, reactions in patients receiving fluoxetine in combination with an MAOI and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

Wait at least 14 days between discontinuing an MAOI and starting therapy with Prozac. Because of the long half-lives of fluoxetine and its active metabolite, wait at least 5 weeks (or longer, if fluoxetine has been prescribed chronically and/or at higher doses) between discontinuing Prozac and starting therapy with an MAOI. Prozac should not be used concomitantly with MAOIs.

Warnings: *Rash and Possibly Allergic Events*—In US fluoxetine clinical trials, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases reported in premarketing clinical trials, almost a third of these discontinued therapy because of rash and/or associated systemic signs or symptoms. Reported in association with rash were fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly upon discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all were reported to recover completely.

Of 2 patients who developed a serious cutaneous systemic illness during premarketing clinical trials, 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Precautions: *General*—The following events occurred in controlled clinical trials. See Tables 1 and 2 also.

- *Anxiety and Insomnia.*
- *Altered Appetite and Weight*—Significant weight loss may be an undesirable result of treatment. Weight change should be monitored during treatment of bulimia.
- *Activation of Mania/Hypomania*—In all US Prozac clinical trials, reported by 0.7% of 10,782 patients.
- *Seizures*—Introduce Prozac with care in patients with a history of seizures. In all US Prozac clinical trials, 0.2% of 10,782 patients reported convulsions.
- *Suicide*—Close supervision of high-risk patients should accompany initial drug therapy.
- *Long Elimination Half-Lives of Fluoxetine and Its Metabolites*—Because of the long elimination half-lives of the parent drug (1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its major active metabolite (4 to 16 days after acute and chronic administration), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.
- *Use in Patients With Concomitant Illness*—Caution is advisable in patients with diseases or conditions that could affect metabolism or hemodynamic responses.
- *Interference With Cognitive and Motor Performance*—Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug does not affect them adversely.
- *Information for Patients*—Physicians should advise their patients to notify them if they:
  - are taking or plan to take any prescription or over-the-counter drugs or alcohol
  - become pregnant or intend to become pregnant during therapy
  - are breast feeding an infant
  - develop a rash or hives
- *Drug Interactions*
  - Drugs Metabolized by P450IID6—Therapy with medications that are predominantly metabolized by the P450IID6 system, especially those that have a relatively narrow therapeutic index (eg, flecainide, vinblastine, and tricyclic antidepressants) should be initiated at the low end of the dosage range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Alternately, the addition of fluoxetine to the treatment regimen of a patient already receiving a drug metabolized by P450IID6 may require a decreased dose of the original medication.
  - Drugs Metabolized by Cytochrome P450IIIA4—Data indicate that fluoxetine's extent of inhibition of cytochrome P450IIIA4 activity is not likely to be of clinical significance.
  - CNS Active Drugs—Caution is advised. Consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status.
    - Anticonvulsants—Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity.
    - Antipsychotics—Some clinical data suggest a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics.
    - Benzodiazepines—The half-life of concurrently administered diazepam may be prolonged in some patients. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.
    - Lithium—There have been reports of both increased and decreased lithium levels and lithium toxicity.
    - Tryptophan—Five patients receiving tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.
    - Monoamine Oxidase Inhibitors—See Contraindications.
    - Other Antidepressants—Previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when concomitantly administered with fluoxetine.
  - Drugs Tightly Bound to Plasma Proteins—A shift in plasma concentrations or displacement of fluoxetine may result in adverse effects.
  - Warfarin—Reports of altered anti-coagulant effects, including increased bleeding. Careful coagulation monitoring is recommended when fluoxetine is initiated or stopped.
  - Electroconvulsive Therapy—Rare reports of prolonged seizures in patients on fluoxetine receiving ECT.
- *Carcinogenesis, Mutagenesis, Impairment of Fertility*—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.
- *Pregnancy*—*Pregnancy Category C*—In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity at doses of up to 1.5 and 3.6 times, respectively, the MRHD (maximum recommended human dose) of 80 mg on a mg/m² basis throughout organogenesis. In the surviving offspring of rats treated at 1.5 times the MRHD, there was no evidence of developmental neurotoxicity. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 1.5 or 0.9 times the MRHD on a mg/m² basis during gestation or gestation and lactation, respectively. Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- *Labor and Delivery*—The effect of Prozac is unknown. Prozac should be used only if the potential benefit justifies the potential risk to the fetus.
- *Nursing Mothers*—Prozac is excreted in human milk. Nursing while on Prozac is not recommended.
- *Pediatric Use*—Safety and effectiveness in pediatric patients have not been established.
- *Usage in the Elderly*—Evaluation of patients over age 60 who received Prozac, 20 mg, daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients with concomitant systemic illnesses or those receiving concomitant drugs.
- *Hyponatremia*—Hyponatremia (some cases with serum Na lower than 110 mmol/L) has been reported which appeared to be reversible on drug discontinuation. Some cases were possibly due to SIADH, and the majority have been in older patients and those taking diuretics or who were otherwise volume depleted.
- *Platelet Function*—Rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

Adverse Reactions: It is important to emphasize that events reported during therapy were not necessarily caused by it.

Incidence in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials)—Table 1 enumerates pooled data on treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo in the treatment of depression, OCD, or bulimia. See full prescribing information for table of treatment-emergent adverse events for each indication.

Table 1.

TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN US DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event	
	Depression, OCD, and bulimia combined	
Body System/ Adverse Event*	Prozac (N=2444)	Placebo (N=1331)
Body as a Whole		
Headache	21	20
Asthenia	12	6
Flu Syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	3	1
Palpitation	2	1
Digestive System		
Nausea	23	10
Diarrhea	12	8
Anorexia	11	5
Dry mouth	10	7
Dyspepsia	8	5
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional disorders		
Weight loss	2	1
Nervous System		
Insomnia	20	11
Anxiety	12	7
Nervousness	13	8
Somnolence	13	6
Dizziness	10	7
Tremor	10	3
Libido decreased	4	—
Respiratory System		
Pharyngitis	5	4
Yawn	3	—
Skin and Appendages		
Sweating	8	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	3	1

*Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (depression, OCD, and bulimia combined): abdominal pain, abnormal dreams, accidental injury, back pain, chest pain, constipation, cough increased, depression (includes suicidal thoughts), dysmenorrhea, gastrointestinal disorder, infection, myalgia, pain, paresthesia, rhinitis, sinusitis, thinking abnormal.

—Incidence less than 1%.

prozac®
fluoxetine hydrochloride

Associated With Discontinuation in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials)—Table 2 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials) in depression, OCD, and bulimia.

Other Events Observed in All US Clinical Trials—Frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Table 2.

MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN US DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

Depression, OCD, and bulimia combined	Depression	OCD	Bulimia
—	—	Anxiety (2%)	—
Insomnia (1%)	Insomnia (1%)	—	Insomnia (2%)
—	Nausea (1%)	—	—
Nervousness (1%)	Nervousness (1%)	—	—
—	—	Rash (3%)	—

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome, photosensitivity reaction.

Cardiovascular System—*Frequent:* hemorrhage, hypertension; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System—*Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:* biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System—*Infrequent:* anemia and ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional—*Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System—*Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System—*Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder,* psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System—*Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses—*Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System—*Frequent:* urinary frequency; *Infrequent:* abortion,† albuminuria, amenorrhea,† anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation,† fibrocystic breast,† hematuria, leukorrhea,† menorrhagia,† metrorrhagia,† nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage;† *Rare:* breast engorgement, glycosuria, hypomenorrhea,† kidney pain, oliguria, priapism,† uterine hemorrhage,† uterine fibroids enlarged.†

*Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

†Adjusted for gender.

Postintroduction Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, priapism, pulmonary embolism, QT prolongation, Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

Overdosage: Prominent symptoms of overdose included nausea and vomiting as well as agitation, restlessness, hypomania, and other signs of CNS excitation.

In managing overdosage, consider the possibility of multiple drug involvement. A specific caution involves patients taking or recently having taken fluoxetine who might have ingested excessive quantities of a TCA. Accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Other Antidepressants under Precautions).

Reports of death attributed to overdosage of fluoxetine alone have been extremely rare.

PV 2171—DPP [040197]

Additional information available to the profession on request.

PL-4300-100088537-697

Eli Lilly and Company
Indianapolis, Indiana 46285

ORIGINAL ARTICLE

A Double-blind, Randomized, Placebo-Controlled Trial of Fluoxetine in Children and Adolescents With Depression

Graham J. Emslie, MD; A. John Rush, MD; Warren A. Weinberg, MD; Robert A. Kowatch, MD; Carroll W. Hughes, PhD; Tom Carmody, PhD; Jeanne Rintelmann

Backgrounds: Depression is a major cause of morbidity and mortality in children and adolescents. To date, randomized, controlled, double-blind trials of antidepressants (largely tricyclic agents) have yet to reveal that any antidepressant is more effective than placebo. This article is of a randomized, double-blind, placebo-controlled trial of fluoxetine in children and adolescents with depression.

Methods: Ninety-six child and adolescent outpatients (aged 7-17 years) with nonpsychotic major depressive disorder were randomized (stratified for age and sex) to 20 mg of fluoxetine or placebo and seen weekly for 8 consecutive weeks. Randomization was preceded by 3 evaluation visits that included structured diagnostic interviews during 2 weeks, followed 1 week later by a 1-week, single-blind placebo run-in. Primary outcome measurements were the global improvement of the Clinical Global Impressions scale and the Children's Depression Rating Scale—Revised, a measure of the severity depressive symptoms.

Results: Of the 96 patients, 48 were randomized to fluoxetine treatment and 48 to placebo. Using the intent to treat sample, 27 (56%) of those receiving fluoxetine and 16 (33%) receiving placebo were rated "much" or "very much" improved on the Clinical Global Impressions scale at study exit (χ^2=5.1, *df*=1, *P*=.02). Significant differences were also noted in weekly ratings of the Children's Depression Rating Scale—Revised after 5 weeks of treatment (using last observation carried forward). Equivalent response rates were found for patients aged 12 years and younger (n=48) and those aged 13 years and older (n=48). However, complete symptom remission (Children's Depression Rating Scale—Revised ≤28) occurred in only 31% of the fluoxetine-treated patients and 23% of the placebo patients.

Conclusions: Fluoxetine was superior to placebo in the acute phase treatment of major depressive disorder in child and adolescent outpatients with severe, persistent depression. Complete remission of symptoms was rare.

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DEPRESSION is a major cause of morbidity and mortality in children and adolescents.[1] School failure and school dropout are common outcomes for children and adolescents with depression,[2,3] and suicide remains one of the leading causes of death in adolescents.[4-6] The age of onset of depression is decreasing in those more recently born,[7] with the result that many individuals will experience their first episodes of depression during their adolescent years. Puberty marks a substantial rise in the overall prevalence of depression and is associated with a shift in the sex ratio, with a preponderance of females.

A meta-analysis of all available placebo-controlled trials (n=12) of tricyclic antidepressants (TCAs) in patients between the ages 6 and 18 years concluded that the difference between active treatment and placebo is too small to be clinically significant.[8] This lack of efficacy, as well as the prevalence of side effects of more noradrenergic antidepressants, has led to an increased interest in selective serotonin reuptake inhibitors.[8] Published articles about selective serotonin reuptake inhibitors in adolescent depression include 2 studies of "treatment-resistant" depression with fluoxetine[9,10]; 2 retrospective medical record reviews with fluoxetine[11] and sertraline treatment[12]; and 1 negative, double-blind, placebo-controlled study of fluoxetine.[13] Despite the lack of evidence of effectiveness in randomized control trials, antidepressant medications continue to be prescribed widely in this age group primarily based on adult data. For adults, the efficacy of antidepressant medications for major depressive disorder (MDD) is well established.[14,15] No one antidepressant is clearly more effective than another, except that monoamine oxidase inhibitors are more effective than TCAs for depression with atypical features.[16,17]

From the Departments of Psychiatry (Drs Emslie, Rush, and Kowatch and Ms Rintelmann), Neurology (Dr Weinberg), and Academic Computing (Dr Carmody), University of Texas Southwestern Medical Center at Dallas, and Terrell State Hospital (Dr Hughes), Terrell, Tex.

PATIENTS AND METHODS

PATIENTS

Child and adolescent outpatients (aged 7-17 years) who were self-referred or referred by other practitioners to our mood disorders program and who met *DSM-III-R* criteria for nonpsychotic MDD, single and recurrent. They were in good general medical health and of normal intelligence. Patients with bipolar I and II disorder, psychotic depression (lifetime), independent sleep-wake disorder, alcohol and other substance abuse (within the last year), anorexia nervosa or bulimia (lifetime), or previous adequate treatment with fluoxetine (20 mg/d for at least 3 weeks) were excluded. Any patient with at least 1 first-degree relative with bipolar I disorder (based on family history by a parent) was also excluded.

Possible patients for study were scheduled for a full evaluation after telephone screening for inclusion and exclusion criteria. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent(s) and assent from the patient. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center at Dallas. In addition to a structured psychiatric interview, the initial evaluation included a medical review of systems, a physical and neurological examination, and laboratory tests (blood chemistry study using an automated multiple analysis system, complete blood cell and differential cell counts, urinalysis, thyroid panel, and electrocardiogram). The evaluation was completed during a 3-week period.

METHODS

At the initial visit, each patient and parent(s) were interviewed separately using the Diagnostic Interview for Children and Adolescents,[25,26] a semistructured *DSM-III-R*–based diagnostic interview to establish that the patient met *DSM-III-R* criteria for MDD and to identify other concurrent and lifetime psychiatric disorders. The final diagnoses were based on information from interviews of the parent(s) and child. Additionally, criterion depressive symptoms and depressive symptom severity were assessed using the depressive items of the Kiddie Schedule for Affective Disorders and Schizophrenia[27] and the Children's Depression Rating Scale–Revised (CDRS-R),[28] respectively. Patients completed 2 self-report scales for depression, either the Children's Depression Inventory[29] (all patients ≤12 years) or the 21-item Beck Depression Inventory[30] (all patients ≥13 years) and the Weinberg Screening Affective Scale.[31] Overall functioning was assessed using the Children's Global Assessment Scale (CGAS).[32]

Following the initial diagnostic interview, the patients were seen for 2 additional follow-up interviews, 1 at visit 2 and 1 at visit 3. During the follow-up interviews, the patient and parent(s) were interviewed separately by 1 of 3 of us experienced in evaluating children and adolescents (G.J.E., W.A.W., and R.A.K.). The Diagnostic Interview for Children and Adolescents was reviewed. The Kiddie Schedule for Affective Disorders and Schizophrenia depressive items were scored for the past week and for the nadir of the present episode and were used primarily as a criteria measure at baseline. The CDRS-R and Brief Psychiatric Rating Scale–Children (BPRS-C),[33] a clinician-rated measure of general psychopathologic characteristics, were also completed. The course of illness, including the number, length, and timing of prior and current episodes, was established and the family history was reviewed.

Final consensus diagnoses were determined following visit 3 in a research conference that has been meeting weekly for the past 10 years. To enroll in the 1-week, single-blind, placebo run-in at visit 4 (3 weeks from initial interview), all patients had to continue to meet criteria for MDD, have a CDRS-R score greater than 40, and meet the previous inclusion–exclusion criteria. At the end of the placebo run-in week, the patients were randomized to either fluoxetine treatment or placebo if they still met all of the enrollment criteria, including a CDRS-R score greater than 40 the preceding week. Randomization was by a table of random numbers stratified for age and sex. Randomization was conducted by the pharmacy and clinicians, who remained blind to assignment until the end of the study. Those patients whose conditions improved (n=7) during the 1-week placebo run-in period continued to receive placebo for an additional week to determine if the symptoms returned. If the patients' conditions still improved, they were withdrawn from the study (n=7).

The possible reasons for the differences between adults and adolescents have been reviewed.[18,19] Ryan[19] noted that medications studied to date have been primarily noradrenergic or were metabolized quickly to noradrenergic metabolites. Based on limited animal studies, it is suggested that the noradrenergic system does not develop fully until early adulthood,[20-22] suggesting that serotonergic agents may be more effective in this age group.[19] Alternatively, high levels of hormones during puberty may decrease the effectiveness of TCAs.[18] Several articles have also commented on design issues,[23,24] small sample sizes, definitions of response, comorbidity, length of treatment, and large placebo response in children and adolescents. A primary concern is whether the populations studied are sufficiently homogeneous to allow a study of the efficacy of medication. The major concerns are that (1) the populations studied are abnormally treatment resistant (incipient bipolar, subjects with atypical depression, and substantial comorbidity), (2) the populations are overly treatment responsive, (3) the samples are too heterogeneous to detect medication effects, or (4) the wrong medications have been evaluated.

Our study was undertaken to evaluate the comparative efficacy, safety, and tolerability of fluoxetine treatment compared with placebo in child and adolescent outpatients with nonpsychotic MDD.

RESULTS

Five hundred eighty-three patients were screened by telephone during the course of the study (April 1, 1991 to January 31, 1995), 256 of whom were interviewed at least once. Of these, 106 patients completed the initial evaluation visits and enrolled in the placebo run-in period. Of the 150 ineligible patients, 34 (23%) refused to participate in the treatment study, 55 (37%) did not meet in-

OUTCOME MEASURES

Outcome was measured weekly. The Clinical Global Impressions (CGI) scale improvement rating and the CDRS-R were selected, a priori, as the major outcome measures. Additionally, the clinician completed the CGAS and the BPRS-C weekly. The patient completed the Beck Depression Inventory or Children's Depression Inventory and the Weinberg Screening Affective Scale at the beginning and the end of treatment. All subjects continued in the study for 8 weeks unless continued nonresponsiveness or adverse events dictated a change in treatment.

Following randomization, each patient was given 1 capsule of placebo or 20 mg of fluoxetine every morning. All patients were seen weekly for 8 consecutive weeks. Serum levels were collected on all patients at weeks 1, 2, 4, 6, and 8, approximately 8 hours after the last dose; however, results of blood chemistry levels were not provided to clinicians. Compliance was monitored by counting returned pills. New bottles were provided weekly, with 2 extra pills in the event of scheduling difficulties for the next visit. The pharmacy provided blinded medication based on the random assignment. Electrocardiograms and routine laboratory work (repeat of baseline studies) were repeated at weeks 4 and 8 (or at last visit) of the study.

STATISTICAL ANALYSIS

The data were computerized and managed using screen- and menu-guided Statistical Analysis System software (SAS, Cary, NC). Throughout our study, quality control procedures were in place to ensure accurate and complete data (eg, dual entry and multiple manual comparisons).

To assess interrater reliability specific for our study, the CGI scale and CDRS-R scores were assessed in the same interviews by 2 experienced clinicians during various stages of the evaluation and treatment phases of the study. Patients receiving dual assessments were selected solely on the availability of clinicians at the time of appointment, though patients were seen by 2 clinicians on completion of the study if at all possible. As the CGI scale improvement score is not completed during evaluation, paired scores are available for 48 patients for the CDRS-R and 41 patients for the CGI scale, 35 of which were performed at visit 8. The intraclass correlation[36] for the CDRS-R was 0.95 and the CGI improvement rating was 0.93. If the CGI scale improvement rating is used as a categorical variable[13] (ie, responder vs nonresponder), then $\kappa = 0.951$.

The primary outcome measures for the study were categorical. The proportion of patients who were randomized (intent to treat) who responded in each group (drug and placebo) as defined by a CGI scale improvement rating of 1 or 2 ("very much" or "much" improved, respectively) and dimensional (the group mean weekly) CDRS-R scores. Secondary analyses to explore in more depth the pattern of response to fluoxetine treatment and placebo included a survival analysis of time to remission (defined as the first of 2 consecutive weekly CGI scale ratings of 1 or 2) and repeated-measures of analyses of variance using weekly CDRS-R scores with the last observation carried forward (LOCF).

However, the results of the LOCF method are not always reliable owing to the creation of "carried forward" data for weeks after discontinuation. This could bias the between-group comparison depending on how the pattern of dropouts varies between groups. Therefore, an additional method of analysis was used to obtain results based on all of the data but without the bias inherent in the LOCF method. For this analysis, the rate of change in the CDRS-R score was estimated for each patient (fluoxetine-treated or placebo) individually using all data available for that patient. The rates of change for all patients in each group (fluoxetine-treated or placebo) were averaged together. The averages for these 2 groups were then compared using a t test. The rate of change (or slope) was first estimated using linear regression (which also produces an estimated baseline CDRS-R score). Kraemer and Thieman[36] recommend analysis of linear regression slopes as an efficient method for use with "soft" data. As a check on the validity of this method, the average slope in each group and the variability of the average was estimated using the more sophisticated empirical Bayesian analysis described by Mori et al.[37] The empirical Bayesian analysis was selected because it adjusts for the correlation between the probability of dropout and the true unobservable rate of change (ie, informative right censoring). Such correlation can be tested[37] and was significant in our data ($P = .02$). Secondary outcome measures were compared based on the last available measurement using analysis of covariance with the baseline measurement as the covariate. All tests were 2-sided with $P < .05$ used for significance. Means are presented as ±SD.

clusionary criteria; 24 (16%) met exclusionary criteria; the condition of 22 (15%) improved during the evaluation, thereby, becoming ineligible; and 15 (10%) needed immediate treatment. Of the 106 patients enrolled in the placebo run-in period, 96 were randomized. Of the 10 not randomized, the condition of 7 improved, 2 refused further study, and 1 had significant side effects while receiving placebo. Of the 96 patients randomized, 48 received fluoxetine treatment and 48 received placebo.

As mentioned previously, the sample was stratified by age (≤12 years and and ≥13 years) and by sex. Of the 48 patients randomized to fluoxetine treatment, 24 were aged 12 years and younger and 24 were aged 13 years and older. Of those randomized to placebo, 24 were aged 12 years and younger and 24 were aged 13 years and older. The 2 groups, fluoxetine-treated and placebo, were not different in any demographic or clinical features, except that those assigned to fluoxetine treatment had a greater lifetime incidence of comorbid anxiety disorders ($\chi^2 = 4.2$, $df = 1$, $P = .04$). **Table 1** lists the demographic and clinical characteristics of these 2 groups (fluoxetine treatment and placebo).

Table 2 lists the timing and basis for patients not completing the 8-week trial. The most common reason for discontinuation was continued nonresponse (19 patients who were receiving placebo and 7 who were receiving fluoxetine). Side effects, as a reason for discontinuation, were minimal, affecting only 4 patients who were receiving fluoxetine and 1 who was receiving placebo. The side effects leading to discontinuation of fluoxetine treatment were in 3 patients in whom manic symptoms developed and 1 patient who developed a severe rash.

Based on a CGI scale improvement rating of 1 or 2 (very much or much improved) to define response, 27 (56%) of 48 patients receiving fluoxetine treatment and 16 (33%) of 48 patients on placebo responded to treatment at exit from the study ($\chi^2 = 5.097$, $df = 1$, $P = .02$). On the other hand, of

Table 1. Clinical and Demographic Characteristics

Features	Patient Group* Fluoxetine-Treated	Placebo
Demographics		
Age, y	12.2±2.7	12.6±2.6
(Range)	(7-17)	(8-17)
Female, No. (%)	22 (46)	22 (46)
White, No. (%)	35 (72.9)	41 (85.4)
Socioeconomic status, No. (%)†		
1-2	14 (29.2)	16 (33.3)
3	16 (33.3)	18 (37.5)
4-5	18 (37.5)	14 (29.2)
Clinical characteristics		
CDRS-R score‡	58.5±10.5	57.6±10.4
(Range)	(42-90)	(42-82)
Melancholic, *DSM-III-R* (%)	7 (14.6)	12 (25)
First episode, No. (%)	23 (47.9)	23 (47.9)
No. of episodes	1.7±0.7	1.8±0.8
(Range)	(1-3)	(1-4)
Duration, current episode, wk	14.6±9.7	13.7±7.5
(Range)	(4-56)	(4-32)
Length of illness, mo	18.6±20.9	15.0±19.7
(Range)	(1-84)	(1-72)
Age at onset, y	10.6±2.7	11.0±2.6
(Range)	(6-16)	(5-17)
Positive family history, No. (%)§	29 (62.1)	29 (60.4)
CGAS score‖	47.9±6.3	48.4±7.8
(Range)	(25-65)	(35-60)
Comorbid diagnoses, lifetime, No. (%)		
None	7 (14.6)	11 (22.9)
Dysthymia	20 (41.7)	14 (29.2)
Anxiety disorders	32 (66.7)	22 (45.8)
ADHD	16 (33.3)	13 (27.1)
Oppositional/conduct	13 (27.1)	16 (33.3)

*There were 48 patients enrolled in each group (means±SD).
†Two-factor index (A. B. Hollingshead, unpublished data, 1975).
‡CDRS-R indicates Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale; and ADHD, attention deficit hyperactivity disorder.
§A first-degree relative with affective disorder treated with either hospitalization or medication.
‖Based on average of scores during evaluation.

Table 2. Reasons for Discontinuation Following Randomization

Patient Group	Week 1	2	3	4	5	6	7	8	Total
Fluoxetine-treated									
Lack of efficacy	...	...	...	...	1	3	2	1	7
Side effects	...	...	...	1	2	...	1	...	4
Protocol violation*	...	...	1	...	1	1	...	...	3
Placebo									
Lack of efficacy	...	1	1	1	5	5	5	1	19
Side effects	...	...	...	1	...	...	...	...	1
Protocol violation	1	...	...	1	...	...	...	...	2
Total	1	1	2	4	9	9	8	2	36

*Protocol violations included taking nonstudy medications and missing appointments. Ellipses indicate no patients discontinued.

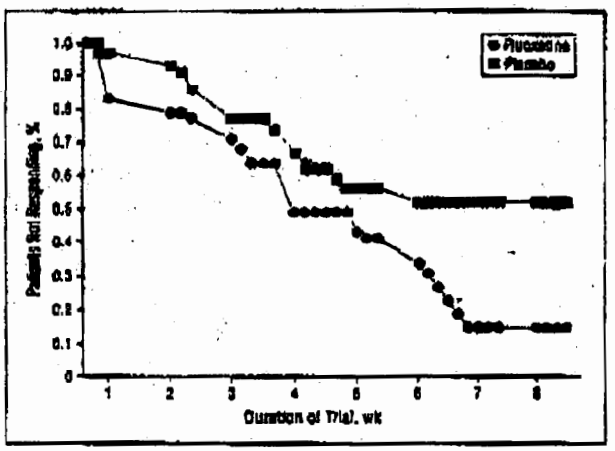

Figure 1. *Survival curve for time to response comparing fluoxetine and placebo. Response is Clinical Global Impressions scale (improvement) rating of 2 or less for 2 consecutive weeks.*

those who completed the entire 8 weeks of treatment 25 (74%) of 34 patients responded to fluoxetine treatment and 15 (58%) of 26 patients responded to placebo (χ^2=1.663, df=1, P=.20). This result is influenced by the differential dropout of nonresponders in the placebo group. While the condition of many patients improved during the study, only 15 (31%) of 48 patients of the fluoxetine-treated group and 11 (23%) of 48 patients of the placebo group had minimal symptoms (ie, a CDRS-R score ≤28) by end of the study.

To examine the pattern of change in the 2 groups, time to response was defined categorically as the first of 2 consecutive weeks when the CGI scale rating was a 1 or a 2 (much or very much improved). Kaplan-Meier survival curves[36] were compared using the log-rank test and were found significantly different (χ^2=5.66, df=1, P=.017) (**Figure 1**).

The other primary outcome measure, the weekly CDRS-R score, was examined as a continuous variable. **Figure 2** shows the traditional method of dealing with patient attrition during the course of the treatment (ie, weekly CDRS-R scores for each group are presented with the LOCF). The last available observation is filled in for the values for patients who discontinued study participation before 8 weeks. A repeated measure (analysis of variance) using all 96 patients showed a significant drug by time interaction (F=3.66; df=8, 752; P=.01). Age group by treatment interaction was also examined but was not significant (P=.76). Comparing the weekly CDRS-R scores for each treatment group using t tests, the first week that the groups were significantly different was week 5. At week 5, the mean CDRS-R score for the fluoxetine-treated group (39.8±13.2) was lower than the placebo group (46.8±16.6) (t=−2.28, df=94, P=.03).

To make the most efficient use of the available data[36] without resorting to a completion analysis or LOCF analysis, the rate of change (slope) and baseline CDRS-R score (intercept) were estimated from linear regressions on each patient and for each group. The estimated baselines were similar (54.2 for the fluoxetine-treated group vs 53.8 for the placebo group). However, the fluoxetine-treated group slope of −2.75±−2.52 was significantly different from the placebo group slope of −1.27±−2.86 (t=2.68, df=94, P<.001).

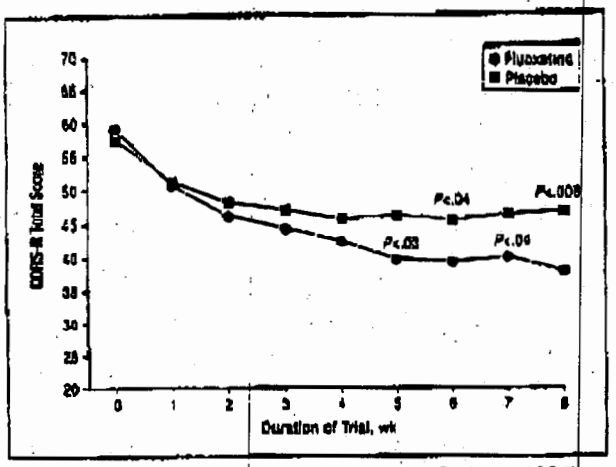

Figure 2. *Weekly Children's Depressive Rating Scale—Revised (CDRS-R) scores (last observation carried forward) for fluoxetine and placebo.*

These results may be interpreted as follows. The fluoxetine-treated group began with an average CDRS-R score of 54.2 and their scores improved by 2.75 U per week to end with an estimated week 8 score of 32.2. While placebo patients began with a similar average CDRS-R score (53.8), their score improved only 1.27 U per week to the end of the study with an estimated exit score of 43.6. Using the empirical Bayesian analysis of estimating slopes (intercept estimates were unavailable) gives an estimated slope of −2.60±2.36 for the fluoxetine-treated group and a significantly smaller slope of −1.32±3.56 for the placebo group (t=2.08, df=94, P=.04).

To further evaluate the effect of age and sex on response, regression lines were calculated for patients aged 12 years and younger and 13 years and older in each group. There were no significant drug by age interactions (F=0.12, df=1, 92, P=.73), though the younger patients independent of the treatment group started with lower CDRS-R scores (F=8.77, df=1, 92, P=.004). Similarly, if the sample is divided by sex, using the same analyses, there was no drug by sex interaction (F=.001; df=1, 92; P=.96).

Finally, for descriptive purposes, **Table 3** lists the initial and last available scores for all 96 patients on the clinician measures and self-report depression scales by groups. Fluoxetine treatment and placebo were associated with significant decreases between baseline and exit scores on these measures. As noted previously, improvement in the CDRS-R scores were greater in the fluoxetine-treated group (final CDRS-R score, 38.4±14.8) than in the placebo group (final CDRS-R score, 47.1±17.0) and the analysis of covariance (F=10.58; df=1, 93; P=.002). However, on measurements of general psychiatric symptoms (BPRS-C) and global functioning (CGAS), there were significant improvements in the condition of the patients in both groups during the course of the study, but the improvement in the fluoxetine-treated group was not significantly superior to the placebo group. Furthermore, self-reported depressive symptom measurements also showed improvement in both groups, but the between-group differences were not significant. However, given the wide variability of initial child self-reports, these findings are difficult to interpret.

Table 3. Baseline to Exit Outcomes

	Patient Group Scores*			
	Fluoxetine-Treated		Placebo	
Scale†	Baseline	Final	Baseline	Final
CDRS-R	55.5±10.5	38.4±14.8	57.6±10.4	47.1±17.0
(Range)	(42-90)	(19-71)	(42-82)	(17-78)
CDI/BDI	15.8±10.6	9.9±12.0	16.3±11.9	11.2±10.8
(Range)	(0-41)	(0-58)	(0-54)	(0-42)
WBAS	20.6±11.8	13.1±12.0	20.8±12.8	15.7±13.6
(Range)	(1-45)	(0-42)	(0-47)	(0-46)
BPRS-C	47.3±7.7	38.9±10.0	46.2±8.9	41.0±10.4
(Range)	(34-65)	(21-68)	(24-68)	(21-67)
CGAS	47.9±8.3	63.9±12.9	48.4±7.8	60.2±14.8
(Range)	(25-65)	(40-89)	(35-60)	(40-85)

*There were 48 patients enrolled in each group (mean±SD).
†CDRS-R indicates Children's Depression Rating Scale–Revised; CDI, Children's Depression Inventory; BDI, Beck Depression Inventory; WBAS, Weinberg Screening Affective Scale; BPRS-C, Brief Psychiatric Rating Scale–Children; and CGAS, Children's Global Assessment Scale.

COMMENT

Fluoxetine treatment was superior to placebo in relieving depressive symptoms. The difference between fluoxetine treatment and placebo was evident in clinician assessment of clinical global improvement (the CGI scale) and in weekly clinician depressive symptom severity ratings (the CDRS-R). Differences between fluoxetine treatment and placebo became statistically significant after 5 weeks.

There was no clear difference in patient responsiveness to either fluoxetine treatment or placebo based on age or sex. The overall rates of response were similar to those reported in adults for fluoxetine treatment and placebo using comparable analyses. For example, the Depression Guideline Panel[11] reports that a meta-analysis of all available double-blind studies of fluoxetine treatment, with intent-to-treat samples, reveals a 46% response rate to fluoxetine treatment and a 22% difference between fluoxetine treatment and placebo.

Despite improvements in depressive symptoms, relatively complete remission of depressive symptoms (a CDRS-R score ≤28) was uncommon, which is not dissimilar to adult data in 6- to 8-week efficacy trials. Differences between the fluoxetine-treated group and the placebo group were less evident in self-report scales (Children's Depression Inventory, Beck Depression Inventory, and Weinberg Screening Affective Scale) and in clinician ratings of general psychiatric symptoms (the BPRS-C) and global functioning (the CGAS).

COMPARISON WITH FINDINGS FROM PREVIOUS STUDIES OF CHILDREN AND ADOLESCENTS

Several factors may explain a positive result in our study compared with previous studies of children and adolescents. While depressed at baseline evaluation, as evidenced by CDRS-R scores, the sample as a whole was neither overly responsive (ie, the placebo response rate of 33%) nor treatment resistant (ie, the fluoxetine-treated group response rate of 56%).

In the study of 38 children by Puig-Antich et al,[39] 56% (9/16) of the children responded to imipramine therapy and 68% (15/22) responded to placebo. Four patients in the imipramine-treated group, but none in the placebo group, failed to complete the 5-week protocol. An open extension of this study suggested that in addition to the high placebo response rate, failure to achieve therapeutic levels of imipramine limited effectiveness.[40]

In part, as a result of this study, Geller et al[41] designed their study of nortriptyline in children to be longer (8 weeks) and controlled for blood chemistry levels. The randomization was preceded by a 2-week placebo washout phase. The patients had severe depression, had a chronic course, and had a high rate of comorbidity including family histories of bipolar disorder. Of the 30 children randomized, 30.8% responded to active treatment and 16.7% responded to placebo based on an earlier version of the CDRS. The mean unrevised CDRS scores at the end of the study for active and placebo were 32.9±11.4 and 32.0±9.8, respectively.

In adolescents, using the same design as for children, Geller et al[42] enrolled 52 patients, 35 of whom were randomized. Response was defined as a CDRS score of less than 25 and a Kiddie Schedule for Affective Disorders and Schizophrenia depressive items score of 2 or less, except concentration. One active treatment patient and 4 placebo patients responded despite mean nortriptyline levels for the active treatment group of 350±70 nmol/L. Kutcher et al[18] reported on a randomized, double-blind, placebo-controlled study of 750 nmol/L of desipramine per day in adolescent outpatients, which was an extension of an earlier report. Of 60 adolescents randomized, 18 dropped out before 6 weeks, 13 of whom were receiving desipramine. With response defined as a 50% or greater decrease in the Hamilton Depression Rating Scale, 48% responded to desipramine treatment compared with 35% to placebo, a difference that failed to reach significance.

Simeon et al[13] described 40 adolescent outpatients with MDD in a double-blind, placebo-controlled study of fluoxetine. All of the patients completed a 1-week, single-blind placebo run-in prior to randomization, though the length of time prior to enrolling in the single-blind placebo run-in was not described. Patients' dosages were titrated to 60 mg of fluoxetine by week 2 and studied for 6 weeks. Fifteen patients in each group completed the study. Simeon et al reported that 2 of every 3 patients showed mild to moderate improvement with either fluoxetine treatment or placebo. All clinical measures showed a greater improvement with fluoxetine treatment than placebo except sleep although none were statistically significant, perhaps owing to the relatively few patients tested. Similar to the study by Puig-Antich et al,[39] the placebo response rate was high.

The design of our study benefited from the experience of previous studies. Factors possibly contributing to a positive result included sample characteristics such as a relatively large sample, the exclusion of patients with psychotic depression, bipolar symptoms or a family history of bipolar disorder, and the recruitment of patients from a range of socioeconomic backgrounds, including those who were able to pay for treatment. All patients were self-identified patients. None were recruited by media methods. Methodologic issues included an extensive evaluation period (3 weeks) and a single-blind placebo period (1 week) prior to randomization.

The choice of the drug studied resulted in the ability to attain adequate levels of medication with few side effects. Also, previous studies, apart from Simeon et al,[13] have used medications that are more noradrenergic or metabolized to noradrenergic metabolites.

To our knowledge, there have been no studies in this age group comparing selective serotonin reuptake inhibitors and TCAs directly. However, in an open trial of 15 adolescents and young adults (aged 16-24 years) who had failed to respond to a TCA, Boulos et al[9] found a 64% response rate to fluoxetine treatment during a 6- to 7-week trial. Also, it has been proposed theoretically that differences in the rate of development of neurotransmitter systems could contribute to differences in response to antidepressants. Data from studies of nonprimates[20] and rhesus monkeys[21] suggest that the development of monoaminergic storage capacity and synthesis continues through childhood and is generally more rapid for serotonin than for catecholamines.

STUDY LIMITATIONS

The patients recruited evidenced relatively severe and persistent symptoms of depression and would not be representative of all children and adolescents with MDD. Of 150 patients who did not enroll in the treatment phase of the study following the initial interview, only 55 (37%) had not met MDD criteria initially. The rest improved, met exclusionary criteria, or refused enrollment in the study. Twenty-nine patients responded to the evaluation or single-blind placebo.

Following randomization, attrition during the study resulted in greater attrition from the placebo group because of failure to respond. Most patients had been seen weekly for at least 8 visits and discontinuation from the study came at the patient's or parent's request and it would have been unethical to continue studying these patients. Every effort was made to have the patients continue with the study as long as possible. It is impossible to know whether nonresponders at week 4 or later would have become responders if they had continued longer in the study in either group, which would effect the result of the χ^2 test of the CGI scale at exit. However, data in adults suggest that placebo responders are more likely to occur early in treatment and the placebo response rate in this study parallels adult findings and is not excessively low. Additionally, the analysis of the CDRS-R using slopes from individual regressions should not be effected much by attrition. Several simulation studies have shown that an unweighted average of individual slopes is subject to little bias owing to dropouts.[37,38] Also, an additional slopes analysis was performed using the procedure of Mori et al[37] that was designed specifically to adjust for nonrandom dropouts. Both of these analyses showed significant treatment effect.

Finally, the study may have been too short to demonstrate significant differences between the groups in global functioning (the CGAS) and, as comorbid disorders were frequent, measurements assessing other symptoms, not only depression (the BPRS-C), might change differentially as a function of treatment, although both

groups improved on both measurements. Self-report measurements for children and adolescents, as mentioned previously, did not significantly differentiate the 2 groups, presumably in part because of relatively poor reliability. For example, some patients rated themselves on self-report as having minimal or no symptoms, whereas on clinical interview, they met criteria for MDD.

CONCLUSION

These data indicate that fluoxetine at 20 mg/d is safe and effective in children and adolescents with MDD. Replication is needed to evaluate the certainty of this finding. In addition, whether long-term treatment would result in the amelioration of school, general functioning, or concurrent comorbidities is unknown. How long to continue fluoxetine treatment, assuming it is effective, deserves study. Subsequent analyses to evaluate predictors of response are planned.

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Reprints: Graham J. Emslie, MD, Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75235-9070.

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