What Research Suggests for Depressed Women With Children

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Background: The strong association between maternal and offspring depression has been observed in numerous studies. Understanding this association has implications for early intervention and prevention.

Method: Findings from our communitybased epidemiologic studies and high-risk and longitudinal studies of families with depression are reviewed.

Results and Conclusions: The childbearing years are the high-risk period for major depression in women. The offspring of depressed women are at high risk for depression. The risk begins before puberty in the offspring and is transmitted to the grandchildren. Depression that begins in childhood or adolescence is con² tinuous and is associated with considerable morbidity. Despite the availability of efficacious treatment, the majority of depressed adults and children remain untreated. Without a clear commitment to mental health parity and an effective service system for intervention. little progress will occur in improving the treatment of depression. There are numerous opportunities for research on the etiology, treatment, and prevention of depression in mothers and their children. (J Clin Psychiatry 2002;63:641-647)

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Weissman and Jensen have no significant commercial relationships to disclose relative to the presentation.

his article summarizes over 2 decades of research on depressed mothers and their children. We review findings from our community-based epidemiologic studies as well as high-risk and longitudinal studies based in psychiatric and in primary care settings. This research will show that (1) the childbearing years are a high-risk period for major depression in women; (2) the offspring of women with major depression are at high risk for major depression in childhood and adolescence, and the risk to offspring occurs whether the depressed mothers are identified in psychiatric or medical clinics; (3) the risk of maternal depression is transmitted across the generations to grandchildren; (4) depression that begins in childhood and adolescence is continuous into adulthood and is associated with substantial morbidity and risk of suicide; (5) opportunities for intervention and prevention are numerous and can be found in primary care, pediatric, and obstetric/ gynecologic practices, in child psychiatry clinics, and in school-based clinics; and (6) a large number of depressed patients are never treated, despite the availability of efficacious treatments, and, without a clear commitment to mental health parity and an effective service system for efficacious interventions, little progress will occur in improving the treatment of depression. Numerous research questions are suggested that may improve treatment and prevention as well as add to the understanding of etiology. Some research is ongoing. Many gaps in understanding the treatment of depressed children and in the sequencing of treatment for depressed adults remain.

THE EMERGING EPIDEMIOLOGY

In 1974, we conducted the first community survey using modern psychiatric diagnostic assessment. This survey was a follow-up study of 511 persons in New Haven, Conn.¹ We showed that the rates of major depression were higher in women than men and that the highest rates were present in early adulthood. The latter finding was surprising, as the conventional wisdom at that time was that major depression was a disorder primarily of middle-aged and elderly persons. These findings were confirmed in the 1980 Epidemiologic Catchment Area study, which was based on 18,000 adults in 5 U.S. communities. They were reconfirmed using similar diagnostic methods in 9 community studies from Canada, Puerto Rico, France,

Received Aug. 7, 2001; accepted Sept. 19, 2001. From the College of Physicians and Surgeons, Joseph Mailman School of Public Health (Dr. Weissman) and the Center for the Advancement of Children's Mental Health (Dr. Jensen), Columbia University, and the Division of Clinical and Genetic Epidemiology, New York State Psychiatric Institute (Dr. Weissman), New York, N.Y.

This work is supported by grants MH36197 and MH50666 from the National Institutes of Health, Bethesda, Md. (Dr. Weissman), and the Klingenstein Third Generation Foundation, New York, N.Y. A small portion of this material on treatment research implications appeared in Weissman MM, Olfson M. Science 1995;269:799–801, American Association for the Advancement of Science (permission obtained). This paper was presented at the Summit on Women and Depression, October 5, 2001, Queenstown, Md.

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West Germany, Italy, Lebanon, Korea, Taiwan, and New Zealand that were termed the "Cross-National Study."² The 1990 National Comorbidity Survey, a U.S. probability sample of over 8000 persons aged 15 to 55 years, yielded similar findings concerning the increased rate of major depression in women and the early age at first onset.³ Although the rates of major depression varied by country in the Cross-National Study, the predominance of women with major depression was consistent across countries. The mean age at onset was in the mid- to late 20s. The rates were highest in separated or divorced versus married women. The gender disparity in rates began at puberty and was maintained lifelong. There was a peak of first onset in the childbearing years and a decrease of onset after age 45. The consistent message confirmed across 10 countries and 2 decades was that major depression is a disorder of high prevalence in women of childbearing and child-rearing years. These findings, coupled with the emerging findings on the high morbidity of depression⁴ and the increasing rates of major depression in the young, have implications for the offspring of depressed parents.

To better understand the impact of major depression on offspring, our next studies focused on children at high risk for depression because of parental major depression,

CHILDREN OF DEPRESSED PARENTS

Onset of Depression and Clinical Course

In the 1980s, we began a study of 220 offspring aged 6 years and over of depressed and never psychiatrically ill parents.^{6,7} We followed up these offspring 2 years later and then again 10 years later when all of the offspring were adults, with all interviews conducted blind to the parents' clinical diagnoses. For purposes of analysis, parents who began with, as well as those who developed, a depression during the 10 years were reassigned to an "ever depressed group," as were non–psychiatrically ill probands married to a depressed spouse.

At the initial interview, we found that the offspring (age range, 6–23 years) of depressed compared with nondepressed parents had a significantly increased risk for major depression, anxiety disorders, and markedly poorer overall functioning.

At the 10-year follow-up, when the offspring were between the ages of 18 and 36 (mean age = 28), we found that, compared with the offspring for whom neither parent was depressed, the offspring of depressed parents had increased rates of major depression, particularly before puberty, and phobias (both at approximately a 3-fold risk); panic disorder and alcohol dependence (at a 5-fold risk); and greater social impairment. The peak age at onset for major depression in both high- and low-risk offspring ranged from 15 to 20 years. The peak age at onset for anxiety disorder was considerably earlier, especially in female offspring in the high-risk group. The onset of alcohol dependence in the offspring of depressed parents, compared with nondepressed parents, was increased and occurred in late adolescence and early adulthood. The offspring of depressed parents had more serious and impairing depressions during the follow-up period but were *less* likely to seek treatment. We concluded that the offspring of depressed parents are a high-risk group for onset of anxiety disorder and major depression in childhood, major depression in adolescence, and alcohol dependence in adolescence and early adulthood. The findings support the potential value of early detection in the offspring of depressed parents.

Use of Health Services and Medical Problems

Our findings also suggested that the full economic cost of maternal depression has not been calculated. Estimates of the cost of depression on work performance have focused on "work for pay," ignoring the fact that a large percentage of the depressed population are women with children whose work at home "does not pay." No economic projections focusing on the cost of depression, to our knowledge, have taken child care or the effects on children into account. Our studies showed that parental depression had costly economic consequences. We found that a history of parental depression increased the risk for general medical problems among depressed offspring. When 2 generations of patients with depression were examined simultaneously, offspring depression was associated with a history of general medical problems and hospital visits among those offspring who also had a depressed parent. This association was demonstrated for an increased risk of a variety of medical problems as well as for psychiatric hospitalizations.⁸ The findings linking offspring depression to medical problems were consistent with numerous studies that have found increased risk of medical problems among depressed patients.9-12

Specificity to Parental Depression

The increased risk of psychopathology in the offspring of depressed parents could be the effect of being raised by a psychiatrically or medically ill parent and not specific to maternal depression. To test this hypothesis, data from 3 independent studies using different sampling methods are relevant.

We conducted a study comparing 114 children, aged 6 to 17, of methadone-maintained opiate addicts with the children of depressed and non–psychiatrically ill parents using the same diagnostic method and blind to parental diagnosis.¹³ We found that school-aged sons of opiate addicts with major depression were at increased risk for conduct disorder and social impairment compared both with sons of opiate addicts with neither major depression nor substance abuse, but not compared with sons of opiate abuse. The sons of opiate

addicts without major depression resembled the sons of controls with neither major depression nor substance use disorders on these outcomes. Conduct disorder in offspring was also more likely if the proband parent was female.

An increase in medical problems was also associated with childhood depression in the offspring of the methadone-maintained opiate addicts.¹⁴ These problems were increased in offspring with a history of major depression and included dermatologic problems, headaches, respiratory problems, neurologic/neuromuscular problems, and an increase in medical hospitalizations.

The second study was a "bottom-up" design in that we sampled depressed children coming for treatment and examined the rates of illness in their mothers. We surveyed 117 mothers bringing their children to a child psychiatry clinic for the treatment of depression.¹⁵ We found that 14% of the mothers screened positive for current (not a lifetime history of) major depression and 59%, for a subsyndromal depression. Twenty-two percent expressed suicidal ideation or intent. Only 31% of mothers who expressed suicidal ideation or intent were currently receiving treatment. Although this study had no control group of nondepressed children, results clearly showed that the rate of *eurrent* major depression in the mothers was much higher than reported in general population surveys.

In the third study, we surveyed a probability sample of 1007 patients coming to primary care to determine rates of psychiatric illness and treatment needs.¹⁶ Three hundred forty-five of these patients were mothers with children under the age of 18. We found that 25% of the mothers were currently depressed, but less than half had received any mental health treatment in the past month. While this rate of treatment was higher than that reported in the community surveys, all of these patients were actively seeing a physician in primary care, so the opportunities for detection were greater than in a general survey sample. We also found that the depressed mothers as compared with mothers with other psychiatric disorders or controls were likely to report that they had poor relationships with their children and that their children currently had serious emotional problems and were not receiving needed treatment for an emotional problem (M.M.W.; A. Feder, M.D.; D. Pilowsky, M.D., manuscript submitted).

Transmission of Depression to the Third Generation

To determine the transmission of depression across the generations, we followed up 90 grandchildren from the original high-risk study.¹⁷ These grandchildren were still quite young at follow-up (median age = 10 years). We did not expect to see increased rates of major depression in the grandchildren, since the onset of major depression is usually after puberty. We expected to find increased risk of anxiety disorders, as they often present before puberty. We found that grandparent and parent major depression was associated with prepubertal grandchild anxiety. Grandchildren

with a depressed parent and grandparent had the highest risk for anxiety. Forty-nine percent of the grandchildren in families in which both the parent and grandparent were depressed had some form of psychopathology and were the most impaired.

We were surprised to find that grandparent major depression had a stronger effect than parent major depression on the risk for anxiety in grandchildren, since our expectation was that the effect of the grandparent on the psychopathology in the third generation (the grandchildren) would have been attenuated compared with the effect on the second generation (the parents). In fact, the patterns of diagnoses in the grandchildren were very similar to the results from our first interviews with their parents, when the parents were a mean of 17 years of age. Thirty-nine percent of the parents from high-risk families had an anxiety disorder, and 28% had major depression. The grandchildren were approximately 7 years younger than their parents were when first assessed. In the highestrisk families in which both the parent and the grandparent were depressed, 40% of the grandchildren had anxiety, 8% had major depression, and 23% had some form of mood disorder. The parents had higher rates of major depression at their initial assessment at a mean age of 17, partially due to the fact that the majority were at the peak ages of risk for major depression from 15 to 20 years of age. The lowest rates of disorder in the grandchildren were in families in which only the parent (and not the grandparent) was depressed. The implication is that parent psychopathology-unless it is familial-has a minimal effect on grandchild psychopathology. The findings support transmission of major depression across generations. However, due to the young age and relatively small size of the sample, this conclusion was considered tentative. We are currently following up a larger sample of the grandchildren.

The Continuity of Childhood/Adolescent Depression

Questions remained as to the continuity of childhood and adolescent major depression into adulthood and also whether it varied by age at onset of major depression.¹⁸ To answer this question, we followed up (into adulthood) a sample of 73 adolescents (Tanner stage III–V) with clear major depression and 37 control adolescents as well as 83 prepubertally depressed children (Tanner stage < III) and 91 prepubertal controls. The childhood diagnoses were confirmed independently by 2 psychiatrists when the subjects were children. The follow-up interviews were conducted blind to the initial diagnosis.

The clinical outcomes of subjects with adolescentonset major depression in adulthood, compared with those of control subjects without psychiatric illness, include a high rate of suicide (7.7%); a 5-fold increased risk of first suicide attempts; a 2-fold increased risk of major depression, but not other psychiatric disorders; an increased occurrence of psychiatric medical hospitalization; and impaired functioning in work, social, and family life. We concluded that there is substantial continuity, specificity, morbidity, and potential mortality from suicide in adulthood in adolescent-onset major depression patients.

The clinical outcomes of children with prepubertalonset major depression in adulthood were somewhat different and included a high risk of suicide attempts (nearly 3fold compared with normal controls) and bipolar disorder. Compared with controls, the children with prepubertalonset major depression went on to have an increased risk of substance abuse and conduct disorder, but not other disorders; increased use of long-term psychiatric and medical services; and overall impaired functioning. Children with prepubertal-onset major depression with a recurrence of major depression during follow-up had higher rates of major depression in their first-degree relatives. We concluded that there is high morbidity in clinically referred children with prepubertal-onset major depression, but continuity and specificity of major depression in adulthood are less clear unless there is a family history of major depression.

Opportunities for Interventions and Prevention

These findings support initiatives aimed at early detection and possible treatment intervention in parents of depressed children. Physicians who specialize in pediatrics and adolescent medicine, as well as family physicians and child psychiatrists, are particularly well positioned to inquire about the mental health history of the patient's parents. Unfortunately, the extent to which this happens, and, when attempted, whether it happens effectively, is unclear.

Alternately, psychiatrists who treat adult depressed patients should inquire about the clinical status of the offspring. Successful treatment of parental depression may provide primary prevention by reducing the symptoms of depression. Secondary prevention may be achieved through early detection and treatment of high-risk offspring who exhibit early forms of anxiety, depression, and substance abuse disorder. Finally, the aggressive treatment of established major depression (i.e., tertiary prevention) may reduce the high level of social impairment that characterizes the depressed offspring of depressed parents.

Only a small proportion of young people with mental disorders receive mental health treatment. In our studies, a large number of the offspring who perceived a need for mental health care utilized no treatment whatsoever. The offspring of depressed parents may develop negative attitudes toward mental health treatment because they associate it with their parents' chronic course of illness. Alternately, depressed parents may deny that their offspring have the same disorder. A better understanding of how parental factors influence the seeking of health care for their offspring may help public health planners extend treatment to this vulnerable and underserved population. Moreover, the early detection and treatment of childhood depression may be accomplished by pediatricians and for adolescents in school-based clinics.

One major barrier that currently interferes with the prospects of getting effective treatments to children with depression (and most other disorders) is that adequate (i.e., efficacious) treatments remain largely undefined. A recent comprehensive survey of the evidence base for psychopharmacologic and psychosocial treatments of child and adolescent mental disorders (including youth depression) including about 10 separate controlled studies by different teams of investigators have established the efficacy of various forms of cognitive-behavioral therapy,¹⁹ and 2 studies have provided evidence of the efficacy of interpersonal psychotherapy for the young.^{20,21} There are far fewer studies of pharmacotherapy for youth depression. The studies available support the efficacy of 2 selective serotonin reuptake inhibitors (fluoxetine and paroxetine) over placebo^{22,23} and the lack of efficacy of tricyclic antidepressants in this age group.²⁴ Still, many questions remain about the efficacy of a wide range of treatments (both pharmacotherapy and psychotherapy) used in clinical practices, the length of treatment needed to prevent recurrence, and the value of combination treatment.

PARITY, SERVICES ACCESS, AND RELATED PROBLEMS

Parity refers to the effort to treat mental health financing on the same basis as financing for general health services. In recent years, advocates have repeatedly tried to expand mental health insurance coverage. The fundamental motivation behind parity legislation is the desire to cover mental illness on the same basis as other medical illnesses. A parity mandate would require all insurers to offer the same coverage, equivalent to the coverage for all other disorders. However, use of unnecessary limits may lead to undertreatment or to restricted access to appropriate services. Available information suggests that despite advocacy to expand benefits, unfair limits continue to be applied to mental health services.

Parity legislation in U.S. state and federal governments has attempted to change this situation. Nonetheless, studies indicate that the gap in insurance coverage between mental health and other health services has continued to widen. One study found that although the proportion of employees with mental health coverage increased from 1991 to 1994,^{25,26} more employees had multiple limits on their benefits. Another study found that while health care costs per employee grew from 1989 to 1995, mental health care costs decreased, both per employee and as a proportion of employers' total health care plan costs.²⁷

One study on changes in employers' health plans found that the value of mental health care benefits decreased from 6.1% to 3.1% from 1988 to 1997 as a proportion of the value of the overall health benefit.²⁸ Limits on mental

health benefits can create major financial burdens for patients and their families. One study modeled the outof-pocket costs that families face under the current U.S. mental health coverage system using different mental health expense scenarios²⁹ and found that for families with mental health treatment costs of \$35,000 per year, average out-of-pocket expenses would be \$12,000 and for those with \$60,000 per year in mental health costs, out-of-pocket costs would average \$27,000—in contrast to the out-ofpocket costs of \$1500 and \$1800, respectively, that families would pay for other medical treatments.

Although federal legislative efforts to achieve parity in mental health insurance coverage failed in the 1994 Health Security Act (the Clinton administration's health care reform proposal), the drive for mental health parity continued in the passage of the Mental Health Parity Act in 1996. This legislation focused only on "catastrophic" benefits, one aspect of inequitable mental health care coverage. While this act is an important first step, parity provisions did not apply to other forms of benefit limits, such as per-episode limits on length of stay or visit limits, federal parity legislation demonstrated an unprecedented commitment to change current inequities in coverage.^{30,31}

State efforts at parity legislation paralleled those at the federal level. During the past decade, a growing number of states have implemented parity.^{32–34} Some states have targeted their parity legislation to include only people with severe mental disorders, while others have used broader definitions of mental illness for parity coverage. Some states have focused on a broad range of insured populations; others focus only on a single population (e.g., state employees).³⁵

Until recently, efforts to achieve parity in insurance coverage for the treatment of mental disorders were hampered by limited information on the effects of such mandates. However, recent analyses of the experience with state and federal parity laws have begun to provide a firmer basis for such estimates. These studies indicate that implementing parity laws is not as expensive as some have suggested.³⁶ Some studies have shown that costs actually declined after parity was introduced.^{31,37}

Available evidence on the effects of parity laws indicates that their costs are minimal. Coupling parity laws with appropriate managed care provisions can limit or even reduce the costs of implementing such laws, often with less than a 1% increase in total health care costs. The urgent need for change in current parity laws is suggested by the recent "Global Burden of Disease" study conducted by the World Bank, the World Health Organization, and private foundations. This major study compared various medical disorders (including mental disorders) to determine their relative contribution to "disease burden," defined in terms of disability-adjusted life-years (DALYs)—healthy life years lost to disease. Results of the study^{4,38} showed that depression ranked as the number-one cause of disability in the world in 1990, and 3 other mental disorders were in the top 10. In terms of DALYs, depression ranks second in established market economies such as the United States and is projected to rank second across the world by 2020. Thus, from a policy perspective, it is clear that to improve general public health, further efforts to achieve parity must be given to making treatment services more available for persons with major depression.

From a policy perspective, the decision to provide services often comes down to the availability of limited resources to provide care for those illnesses that have the greatest impact on public health. Yet it is interesting to note that in general medicine there is no lack of coverage for illnesses that have only temporary and mild disability and no efficacious treatment (e.g., upper respiratory infections of viral origin) and those for which treatments are not particularly effective (e.g., various cancers). In many cases, highly disabling and highly treatable mental disorders such as depression have received far fewer resources.

Research has shown that behavioral and psychotherapeutic interventions are efficacious and cost-effective for depressive disorders. Yet data are still lacking on the expected duration of some of these interventions and whether they can be transferred across different providers and treatment settings. Treatments are affected by the organization, financing, and structure of the service systems in which they are provided. For example, research has shown that organizing and providing outpatient mental health services is more cost-effective than what is traditionally done for persons with these disorders. Data such as these have been compelling enough to encourage public mental health systems to set up such programs, yet without continued attention to the way in which such services are delivered, treatment teams can fall back into old practices. It is not enough to have good treatments if they are never delivered. Thus, developing and disseminating information on actual clinical practice and how to improve it are essential. This need mandates new training requirements for primary care physicians and specialty mental health care providers, not just those in training but also those in practice.

RESEARCH IMPLICATIONS

The data presented have numerous research implications. Many gaps remain in our understanding of depression in women and through what mechanisms secondand third-generation risk is conveyed to offspring (also discussed in Weissman and Olfson³⁹). We lack a coherent explanation of why the rates of major depression are higher in women than in men and why the rates begin to rise in females around puberty. The consistency with which these findings emerge suggests that biological factors, both endocrinologic and genetic, may contribute to the relative excess of depression in women and their offspring (see Leibenluft⁴⁰). However, it is conceivable that there are universal social factors that depress women and account for the cross-cultural predominance of depression in women.

Because depression is primarily a disorder of women of childbearing age, more research needs to be conducted on the short- and long-term effects on the developing fetus of in utero exposure to antidepressants. For ethical reasons, these studies need to be conducted on pregnant and nursing mothers who are inadvertently, rather than experimentally, exposed to antidepressants.

Further study is also needed of antidepressant dose requirements during pregnancy, lactation, and the menstrual cycle. Analogous studies need to be conducted on the effectiveness of psychotherapy. At the same time, methods are needed to reliably distinguish depressed pregnant women who can be safely managed with psychotherapy alone from those who require maintenance antidepressants.

Women of childbearing age have historically been excluded from the early stages of drug development of depression primarily out of concern for the effects on fetuses. The U.S. Food and Drug Administration (FDA) has ended its ban on permitting women to enter drug trials and has required drug companies to include more women. in early clinical trials. The FDA requirement that psychotropic drugs being administered to minors be tested on minors has led to a marked increase in clinical trials and efficacy data on the treatment of depression in chil dren.^{26,41,42} In consequence of these policy changes, and also as a result of several new National Institute of Mental Health-funded multisite clinical trials of child and adolescent depression, it is anticipated that the next several years will witness a wealth of new information on the safety and efficacy of medication and psychotherapeutic depressive disorder treatments, alone and in combination.

Little information exists on sex differences in the effectiveness of antidepressants for patients at any age. Some data suggest that postmenopausal women may be less responsive than men to tricyclic antidepressants. One explanation for sex disparities in antidepressant responsiveness involves sex differences in the bioavailability of antidepressants. Important differences between women and men have been described in drug absorption, volume of distribution, hepatic metabolism, body weight, total blood volume, percentage of body fat, renal clearance, and a variety of other physiologic variables that may affect drug bioavailability. Careful studies are needed that compare plasma antidepressant levels in women and men administered comparable test doses.

Although excellent treatments for depression are available for adults, and are becoming increasingly available for children and adolescents, most depressed persons in the United States—children and adults alike—receive no treatment for their symptoms during the course of a year. Issues for health services research include describing gender differences in the act of seeking access to health care and the effectiveness of the various treatments.

Several cultural-economic factors also come into play in gender bias. Women are more likely than men to be covered as dependents, to work part-time, or to work for small businesses that do not provide insurance. They are, therefore, more susceptible to disruption of coverage through divorce, death, and job loss. Studies are needed that evaluate the relation between health care insurance, gender, and outcome of depression.

Pregnancy provides medical opportunities for the detection and management of depression. Although a substantial body of literature describes the management of depression by internists and family practitioners, less attention has been devoted to the role of obstetricians and gynecologists. Research is needed that examines how effective these medical specialists are in managing their patients' depression.

The serious impact of maternal depression on the functioning of offspring has been well described. However, we lack intervention studies to determine whether reducing maternal depressive symptoms with pharmacotherapy or psychotherapy improves offspring outcomes. No data are yet available that follow the course of the treatment of depression in mothers to determine the effects of the remission of maternal symptoms on offspring. Studies of this nature are now underway.

Considerable progress has been made in understanding the epidemiology of depression and in developing effective and well-tolerated treatments. However, much remains to be learned about the basic pathogenesis of depression and the specific treatment needs of depressed women and their offspring, especially during the reproductive years. Much more research on effective treatments for children and adolescents with depression is urgently needed.

The future of new treatments for depression will be founded in basic neuroscience research, especially in the areas of pathophysiology, molecular biology, and genetics.

Policy-relevant information is also needed to improve the treatment and prevention of depressive illness. Given the day-to-day barriers already known to impede the implementation of currently established scientific findings, studies that go beyond those traditionally conducted in clinical treatment trials are needed. Thus, "effectiveness" studiesthose that broaden the studied populations to include persons treated in community settings and that include the outcome measures (e.g., measures of cost and functional status) that matter most to consumers, providers, payers, and policymakers-are needed. Relatedly, "practice research" is also needed, which seeks to understand what happens in clinical practice and seeks means to improve it. With such expanded research efforts, we should move a long way toward reducing the burden of depression on mothers and their children, as well as improving the treatments of other mental illnesses in our society.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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