CLINICAL AND POLICY IMPLICATIONS FOR PREVENTION

To the Editor:

We read with interest the recent article by O'Conner et al. (2002) on the relationship between maternal anxiety in the antenatal period and subsequent child behavioral/emotional problems after controlling for the association of the latter with postnatal depression. We were surprised to see that we were referenced in the "Clinical Implications" section as having suggested that postpartum depression may be a good target for prevention interventions aimed at improving child mental health. We are hoping that our article was not misunderstood as making such a suggestion. In fact, one of the reasons for writing our article was to question this suggestion. We concluded in that article that there were substantial gaps in the support for such a recommendation (McLennan and Offord, 2002). It is likely that there would be at least as many gaps in a proposed strategy to target antenatal anxiety to improve child mental health outcomes if one were to use the criteria we outlined in our article. However, we reiterate that if a woman is suffering from a postpartum depression, she should be entitled to effective treatment whether or not it benefits her infant. The same could be said about clinical levels of anxiety in the antenatal period.

This apparent misunderstanding brings up a larger issue, that is, encouraging or forcing authors to include clinical or policy implications for their findings when there are no reasonable implications to be made in these domains. This appears to occur particularly at the conclusion of epidemiological studies wherein there is a suggestion to aim interventions toward the variable found to be associated with some outcome. This obscures the many additional factors that need to be considered in choosing an intervention as has been described by others (e.g., Kramer et al., 1997; McLennan and Offord, 2002). To jump to recommending clinical or policy actions based on associations is at best premature and at worst deceptive. To give O'Conner et al. (2002) credit, they did conclude in their article that further testing would be required to pursue the hypothesis that targeting antenatal anxiety would be beneficial for the mother's offspring. However, we have seen other cases in which qualifying statements are not included. These huge leaps from research findings to clinical and policy recommendations may be found at the conclusion of some papers on biological findings.

Although it would seem appropriate that there is increased pressure on the research community to engage in research that has practical implications, many important research activities do not have any immediate clinical or policy implications. Forcing authors of such studies to claim clinical or policy implications will not serve the public interest and may set in place inappropriate decisions, which are then claimed to be informed by, or rooted in, research findings. Some of our policymakers and clinical decision-makers may not appreciate the difference between results finding correlations between risk factors and outcomes and those finding causal risk relationships. Exaggerating the implications of our research findings as they relate to clinical and policy decision-making will not help in fostering the development of sound, evidence-based clinical and prevention services.

We would recommended that authors of important articles for this *Journal,* in those cases in which the findings do not have immediate clinical or policy implications, have the option of concluding their articles with a section titled "Research Implications." This would allow the authors an opportunity to map out the next research steps in response to their findings rather than constructing misleading clinical or policy recommendations.

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Kraemer H, Kazdin A, Offord D, Kessler R, Jensen P, Kupfer D (1997), Coming to terms with the terms of risk. *Arch Gen Psychiatry* 54:337–343

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The Editor responds:

We agree. Even without a "Clinical Implications" section, it is a constant struggle to restrain the tendency of authors to attribute causality when they can demonstrate only association (often not even longitudinally, but only cross-sectionally!). Even if causality is proven, intervention may not be effective. We shall redouble our efforts, and we encourage our reviewers to do the same. For an epidemiological study, the implications may not be for immediate intervention but for the clinician to at least watch for certain phenomena because they are common and/or potentially serious.

The purpose of the "Clinical Implications" section is not to make premature recommendations for prevention or treatment, but rather for the authors to explain why clinicians (who constitute most of our readers) should be interested in the report at all. A great deal of research is not yet applicable to practice, but may still have relevance for the thinking of those who care for patients. For papers with an exclusive methodological focus, we do waive the requirement to consider clinical implications.

A "Research Implications" section with suggestions for how a study may inform the progress of science is not only welcome, but encouraged.

We can only wish that policy recommendations were as easily accomplished from our conclusions as Drs. McClennan and Offord fear!

Mina K. Dulcan, M.D.
Editor-in-Chief

Note: See related article, this issue, p. 518.
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PAROXETINE IN MAJOR DEPRESSION

To the Editor:

The article by Keller et al. (2001) is one of only two to date to show a positive response to selective serotonin reuptake inhibitors (SSRIs) in child or adolescent depression. We believe that the Keller et al. study shows evidence of distorted and unbalanced reporting that seems to have evaded the scrutiny of your editorial process. The study authors designated two primary outcome measures: change from baseline in the Hamilton Rating Scale for Depression (HAM-D) and response (set as fall in HAM-D below 8 or by 50%). On neither of these measures did paroxetine differ significantly from placebo. Table 2 of the Keller article demonstrates that all three groups had similar changes in HAM-D total score and that the clinical significance of any differences between them would be questionable. Nowhere is this acknowledged. Instead:

1. The definition of response is changed. As defined in the "Method" section, it has a nonsignificant *p* value of .11. In the "Results" section (without any explanation), the criterion for response is changed to reduction of HAM-D to below 8 (with a *p* value of .02). By altering the criterion for the categorical measure of outcome, the authors are able to claim significance on a primary outcome measure.
2. In reporting efficacy results, only "response" is indicated as a primary outcome measure, and it could be misunderstood that response was *the* primary outcome measure. Only in the discussion is it revealed that "Paroxetine did not separate statistically from placebo for…HAM-D total score," without any acknowledgment that total score was one of the two primary outcome measures. The next sentence is a claim to have demonstrated efficacy for paroxetine.

Thus a study that did not show significant improvement on either of two primary outcome measures is reported as demonstrating efficacy. Given that the research was paid for by Glaxo-Smith-Klein, the makers of paroxetine, it is tempting to explain the mode of reporting as an attempt to show the drug in the most favorable light.

Given the frequency with which it is cited in other scientific papers, at conferences and educational functions, and in advertising, this article may have contributed to the increased prescribing of SSRI medication to children and adolescents. We believe it is a matter of importance to public health that you acknowledge the failings of this article, so that its findings can be more realistically appraised in decision-making about the use of SSRIs in children.

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Note: Drs. Jureidini and Tonkin are members of Healthy Skepticism Inc.

Keller MB, Ryan ND, Strober M et al. (2001), Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 40:762–772
DOI: 10.1097/01.CHI.0000046825.95464.DA

Dr. Keller et al. reply:

In response to the letter of Drs. Jureidini and Tonkin commenting on our study of paroxetine in adolescent depression (Keller et al., 2001), we would first like to address the overt issues that they raise and then respond to a covert argument they make.

It seems that they argue that (1) we were insufficiently clear in distinguishing between our primary outcome measures and our secondary outcome measures, and (2) our assessment that this study found paroxetine effective is incorrect. We feel that we were quite clear about which were primary outcome measures and which were secondary: this is explicitly and clearly elucidated in the abstract of the article. Moreover, the manuscript explicitly addressed the various limitations of the study design and discussed in detail these limitations with regard to

the clinical implications of the research results. Within this context, because our two primary outcome measures did not reach a $p < .05$ level of statistical significance, the more complex question that remains is whether or not we fairly interpreted the pattern of significant p values across a range of secondary endpoints as indicating that paroxetine is better than placebo for treating adolescent depression.

This study was designed at a time when there were no randomized controlled trials showing antidepressant (tricyclic antidepressant or SSRI) superiority to placebo, so we had no prior data from which to astutely pick our outcome measures. The field has moved strongly away from using the Hamilton Rating Scale for Depression (HAM-D) in adolescent treatment studies and has gone virtually uniformly to using the Children's Depression Rating Scale-Revised because the latter better and more reliably captures aspects of depression in youth. Surely a national regulatory body charged with approving or not approving a medication for a particular use might well simply say that if a study does not show efficacy on the primary endpoint(s), it is a failed study and secondary outcome measures cannot then be used for approval. However, as scientists and clinicians we must adjudge whether or not the study overall found evidence of efficacy, and we do not have the convenience of falling back on such a simple rule. If we choose wrongly (in whichever direction), we don't treat depressed children as well as the data would permit. Because we found a clear pattern of significant p values across multiple secondary analyses (recovery as assessed by HAM-D < 8, HAM-D depressed mood item, the Schedule for Affective Disorders and Schizophrenia for School-Age Children depression item, and Clinical Global Impression score at endpoint), we thought and still think this provides significant evidence of efficacy of paroxetine compared with placebo in adolescent depression. Without established reliable measures that distinguish medication responders from nonresponders at the time the study was designed, it is not surprising that the primary measures did not reach significance while other measures did. It still provides a strong "signal" for efficacy.

Drs. Jureidini and Tonkin argue that the reviewers failed to understand and appropriately critique the article (and by extension that the editor was not up to the task) and that the authors of the original article swerved from their moral and scientific duty under the influence of the pharmaceutical industry. By extension, of course, they covertly argue that the reader who agrees with them is intellectually and morally superior while a reader who does not agree with their position shares the cognitive and/or moral failing of the rest of us. We say that this article and body of scientific work is a matter for thoughtful and collegial discussion and say, in addition, that their emperor has no clothes.

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AMOXAPINE TREATMENT OF INTERFERING BEHAVIORS IN AUTISTIC DISORDER

To the Editor:

Although there are no specific treatments for children and adolescents with autistic disorder, pharmacotherapy has been used to reduce interfering behaviors such as aggression, hyperactivity, anxiety, and stereotypies. Placebo-controlled studies have demonstrated efficacy for dopamine antagonists such as haloperidol and risperidone as well as for serotonin uptake inhibitors such as fluvoxamine and clomipramine (Posey and McDougle, 2000). Clomipramine is also a norepinephrine uptake inhibitor, and other medications in this class have been shown to be of benefit in the treatment of attention-deficit/hyperactivity disorder. Amoxapine, a dibenzoxazepine antidepressant, is both a norepinephrine uptake inhibitor and dopamine antagonist. Positron emission tomography studies have suggested that its pattern of serotonin and dopamine antagonism

is similar to that seen in atypical antipsychotics (Kapur et al., 1999). This pharmacodynamic profile suggests possible benefit in the treatment of behavioral disturbances associated with autistic disorder. Here we report on the use of amoxapine to treat two children with autistic disorder.

A., a 10-year-old girl with an average Full Scale IQ, had autistic disorder diagnosed according to *DSM-IV* criteria. She had been referred for possible pharmacotherapy to treat her high levels of anxiety, hyperactivity, and impulsivity. She had initially been successfully treated with citalopram, but after a year the beneficial effects of this medicine were lost despite an increase in the dose. Her significant hyperactivity and impulsivity were not affected by the citalopram. After discontinuation of citalopram due to decreased benefit, dextroamphetamine was introduced, without any benefit, to address her impulsivity and hyperactivity as these had become her most interfering symptoms. When the dextroamphetamine was discontinued, it was felt by her teacher and her parents that a trial of another medication was needed to reduce her severe agitation, hyperactivity, and impulsivity. Following a discussion with her parents, therapy with amoxapine was initiated. The amoxapine was started at a dose of 12.5 mg and titrated to 75 mg over a period of several weeks. Within a few weeks after this dose was reached, A.'s teacher and parents noticed a significant reduction in her agitation, hyperactivity, and impulsivity. Her attention was also reported to be improved, and her overall functioning at school and at home was significantly better. In addition, her anxiety was reduced. The dose was increased further to 100 mg to address some ongoing impulsivity and anxiety. A. did not have any evidence of cardiac conduction abnormalities, and there were no signs of anticholinergic adverse effects, extrapyramidal symptoms, or dyskinetic movements.

B., a 9-year-old boy, had autistic disorder diagnosed according to *DSM-IV* criteria and a borderline Full Scale IQ. He had been on methylphenidate at a dose of 45 mg daily for inattention and hyperactivity. Although he derived some benefit from the methylphenidate, he had significant anorexia and insomnia, which limited further increases in the dose. As a result of his ongoing impulsivity, hyperactivity, and aggressive behavior, he had received trials of risperidone and olanzapine without significant benefit. After a discussion with his parents, he was started on amoxapine to address his continuing behavioral problems. The amoxapine was initiated at 12.5 mg daily and increased over a period of a month to 150 mg daily. On this dose, he showed a significant reduction in his hyperactivity, impulsivity, and aggression. His teacher, who was unaware of the introduction of amoxapine, commented on the marked improvement in his behavior. As a result of his overall improvement, B. was able to tolerate a reduction in his dose of methylphenidate to 30 mg daily. Apart from a dry mouth, B. did not have any adverse effects and electrocardiograms did not reveal any significant changes in cardiac conduction parameters.

Both of these patients, who had been only partially responsive to trials of several other medications, showed a significant improvement with amoxapine. The improvement was noted in aggression and agitation, impulsivity and hyperactivity, and anxiety. Amoxapine was well-tolerated and neither patient showed evidence of any cardiac conduction or rhythm abnormalities. The combined actions of amoxapine on norepinephrine and dopamine indicate possible beneficial effects in the treatment of a number of interfering behaviors seen in autistic disorder, and the positive response in the two patients described here suggests that further trials are warranted.

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FRAGILE X SYNDROME IN ADOLESCENT PROSTITUTES IN SOUTHERN TAIWAN

To the Editor:

Several studies have found that mentally ill, drug-using, and homeless people with multiple sex partners who engage in other high-risk sexual behaviors exhibit high levels of psychological distress and severe psychiatric symptoms (Alegria et al., 1994). Important questions remain unanswered regarding the epidemiology and etiology of psychological distress among adolescents who are involved in the sex trade. These adolescents represent a high-risk group that merits professional investigation and requires sensitive clinical approaches.

Factors associated with adolescent prostitution, such as abuse, poverty, neglect, mental illness, drug misuse, and homelessness, are almost endless. These girls run a substantial risk of developing clinical levels of emotional and behavioral problems and psychiatric disorders. Mental retardation and borderline intellectual functioning are also present. Because fragile X syndrome is the second most common single cause of mental retardation, we examined the prevalence of fragile X syndrome in a group of adolescent female prostitutes.

The multicity sample of 127 adolescent female prostitutes (aged 13–18 years) was representative of southern Taiwan. A

stratified random household sample of 248 females were selected as controls from a community of southern Taiwan. For all subjects, the WAIS-R test and DNA screening tests for fragile X syndrome were performed.

A full mutation was present in 6.3% of adolescent female prostitutes, a permutation was found in 5.5% of adolescent female prostitutes, and 88.2% of adolescent female prostitutes had no mutation. According to the WAIS-R test, 5.4% of adolescent female prostitutes exhibited mild mental retardation and 29.7% had a borderline IQ. Adolescent female prostitutes with a full mutation or permutation did not have significantly lower IQ scores than participants in the normal group.

In the stratified random household sample, only 1 of 248 females with a full mutation was identified. It is worth noting that the adolescent female prostitutes had a significantly higher full mutation rate than the stratified random household participants (odds ratio = 16.4:1, Fisher exact test: $p < .001$).

The finding suggests that the prevalence of the fragile X syndrome in adolescent female prostitutes may be even higher than that in mentally retarded males (Crawford et al., 1999; Turner et al., 1997). The IQ scores of participants with a full mutation or permutation were not significantly lower than those found in the normal female. Persons given the diagnosis of intellectual disability during school-age years may disappear into society and function well enough so as no longer to meet criteria for retardation later in life, suggesting that the initial diagnosis may not have adequately considered adaptive function (Forness, 1972) or that adaptive behavior is not as widely or thoroughly assessed in adulthood.

Of the adolescent prostitutes who participated in this study, full mutation was observed in 8 (6.3%) and permutation was found in 7 (5.5%). Once cases are diagnosed, at-risk relatives in the extended family may be offered genetic advice and *FMR1* testing. If resources permit, DNA screening of every adolescent prostitute with unexplained mental retardation is the best way to avoid the negative consequences of a misdiagnosis. Consideration should be given to rescreening selected individuals who were first screened by chromosome analysis alone, in view of potential false-negative and false-positive results using the cytogenetic test (Gringras and Barnicoat, 1998).

It is possible that the characteristics of adolescent prostitutes may be different in the future. As the Internet becomes a more important factor influencing daily life, the Internet sex trade threatens to replace traditional forms. Future studies may need to account for this technological influence.

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See the Instructions for Authors for information about the preparation and submission of Letters to the Editor.