COMMENTARY

Take a Closer Look at Iron Recommendations

I read with a great deal of interest the recent American Academy of Pediatrics Committee on Nutrition's Clinical Report "Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0-3 Years of Age)" in the November issue of Pediatrics (2010;126:1040-50).

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The authors of this report should be congratulated for calling attention to the underestimated and undertreated problem of iron deficiency (ID) and for recommending iron supplementation for toddlers whose diets are inadequate.

However, after careful analysis, it appears to me that the report not only is confusing, but also places the physician in a difficult and perhaps untenable position, both in terms of screening for and preventing toddler ID. Allow me to explain.

The association of ID and iron deficiency anemia (IDA) in infants and toddlers with long-lasting and perhaps irreversible impaired psychomotor and mental development has been well known and clearly established.

The good news is that the prevalence of ID and IDA during the first year of life has been dramatically reduced. This success has been largely due to increased breastfeeding rates and the use of iron-fortified formulas and iron-fortified infant cereals.

Unfortunately, this success story does not hold during the toddler years, ages 1-3 years.

Large numbers of toddlers, especially those in the low socioeconomic group, continue to suffer from ID and IDA.

This comes as no great surprise to me. Many toddlers are picky and finicky eaters, often consuming large quantities of milk and apple juice and very little iron-rich food. Large-scale studies have demonstrated that the daily dietary iron intake of 1- to 3-year-olds is lower than in any other age group throughout life (Arch. Pediatr. Adolesc. Med. 1997;151:986-8).

The reported prevalence rates of toddler ID vary from 9% to more than 30% (JAMA 1997;277:973-6). Although not proven, I believe that it would be fair to say that the actual prevalence would be even higher if multiple tests for ID were obtained between 1 and 3 years of age.

There is another compelling reason to prevent toddler ID. A number of studies in recent years showed that ID increases lead absorption and that lead-associated cognitive deficits occur at blood lead levels below 10 mcg/dL, a level previously thought to be harmless.

The bottom line is that the large number of toddlers who are ID are doubly at risk for neurodevelopmental damage, from ID and from increased lead absorption.

I take serious issue with both the screening and prevention recommendations for the 1- to 3- year-olds in the report.

► **Screening:** The report recommends screening for ID at 12 months of age for the "high-risk group." This includes low socioeconomic status, prematurity, low birth weight, exclusive breastfeeding beyond 4 months of age without supplemental iron, feeding problems, exposure to lead, and poor growth. These "high-risk" groups represent over one-half of the total.

The problem with this recommendation is the chaos and frustration it will create. The current available laboratory tests for ID all require venipuncture. They also are expensive. Even if ordered, the compliance rate would probably be low. It places the physician in the real predicament of whether or not to order a screening test for ID.

► **Prevention:** As pointed out in the report, toddlers require 7 mg/day of iron-rich foods. The authors state that if the diet is inadequate, iron supplements or iron-fortified vitamins are recommended.

Once again, the physician is put in the difficult situation of determining which toddlers require iron supplementation.

Toddler ID remains a major public health issue. The new screening and prevention recommendations report is important in that it has brought the important subject of ID to the attention of the medical community. However, in my opinion, it has confused rather than helped solve the problem.

For the past 15 years, I have been actively advocating daily iron supplementation for *all* toddlers. Our office routine has been to order a daily iron-fortified vitamin containing 10 mg of iron at the time the baby is switched from breast milk or iron-fortified formula to regular milk. This approach eliminates the need to screen for ID (we do test for anemia with a simple hemoglobin).

This approach to the prevention of ID is easy, effective, and safe. We have never had a problem with iron overdose. If a toddler drank an entire bottle of liquid Poly-Vi-Sol with iron, the iron level would not reach the toxic level.

In 2007, our local AAP Committee on Nutrition, New York Chapter 2 officially recommended the routine use of an iron-fortified vitamin for all children when placed on regular milk. Of interest is that a survey sent out to the membership shortly after the initial mailing showed that 86% of the pediatricians who responded agreed with the recommendation.

It is my sincere hope that groups such as the AAP Committee on Nutrition will revise their recommendations to include routine iron supplementation for at least the high-risk toddlers, and better yet for *all* toddlers when placed on regular milk. ■

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COMMENTARY

New MDD Treatment Guidelines Fall Short

The American Psychiatric Association recently released new treatment guidelines for patients with major depressive disorder.

The guidelines were developed by prominent qualified experts (most of whom had pharmaceutical industry relationships), an independent review panel (without pharmaceutical industry ties), and comments from dozens of experts and organizations (doi:10.1176/appi.books.9780890423387.654001). They are 152 pages in length, and include more than 1,000 references, in addition to a six-page executive summary. Though comprehensive and useful in many ways, the guidelines have four major potential shortcomings.

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First, although the guidelines recommend antidepressant use in mild depression ("An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder"), recent meta-analyses that incorporate all randomized clinical trial data of antidepressants for major depressive disorder (MDD) throw some doubt on the strength of this recommendation (PLoS Med. 2008;5:e45 and N. Engl. J. Med. 2008;358:252-60).

When looked at in terms of drug vs. placebo differences in depression rating scales, the amount of benefit (effect size) was much smaller in reality (including all unpublished studies) than in the published scientific literature. In mild depression in particular, antidepressants are almost identical to placebo (the drug placebo differences are nearly zero), whereas clinically notable benefits only occur in severe depression (drug/placebo differences are about 5 points).

These differences could be explained in many different ways. There are statistical possibilities: It is always harder to show a small effect size difference as in mild depression than a large one as in severe depression. It also could be that the extremely broad and heterogenous MDD category does not represent primarily a disease-like antidepressant-responsive biological depression, as with older concepts of melancholia. Response in severe depression might pick out such melancholia.

Second, the discussion of maintenance treatment with antidepressants for recurrent MDD is relatively uncritical ("During the maintenance phase, an antidepressant medication that produced symptom remission during the continuation phase should be continued at a full therapeutic dose").

In the National Institute of Mental Health–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, although acute efficacy was seen in 60%-70% of subjects when all antidepressant classes were used sequentially, about one-half of those persons relapsed in up to 1 year of follow-up, despite staying on the same antidepressants that had helped them acutely (Am. J. Psychiatry 2006;163:1905-17). If those who stopped medications because of side effects are included, only about one-third of patients stayed and remained well for up to 1 year. It might be safe to conclude that antidepressants are more effective acutely than in maintenance treatment. The guidelines do not describe these results.

This possibility of limited maintenance efficacy also is supported by a recent analysis of maintenance randomized controlled trials with antidepressants. These data, presented earlier this year in a poster presentation by Dr. Brian Briscoe and Dr. Rif El-Mallakh at the APA annual meeting in New Orleans, looked at 16 published studies and found that only one could be shown to have benefit beyond 6 months of follow-up. In the absence of a critical review of such studies, the maintenance recommendations have a diaphanous quality.

Third, little acknowledgment exists of the risk of probable increased suicidality with antidepressants. Not only that, but the guidelines suggest that a relationship between antidepressants and suicidality does not exist ("A predictive re-

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lationship to suicide has never been demonstrated"). This statement is made despite an almost twofold increase in suicidal ideation or attempts in the Food and Drug Administration meta-analysis of multiple randomized controlled trials (in young adults and children, but not older groups) (Arch. Gen. Psychiatry 2006;63:332-9).

Such trials are exactly how predictive relationships are established, because of removal of most confounding factors.

Perhaps the work group deliberately used the word "suicide," rather than "suicide attempts," since such trials deliberately exclude subjects with notable suicidality, and thus completed suicide did not occur (Am. J. Psychiatry 2004;161:562-63). But about 13% of those who make suicide attempts eventually commit suicide. Hence, a causative relationship is inferable.

It might not be surprising to find variable benefits with our treatments. The fault may lie not in our drugs, but in us, and the ways in which we diagnose and treat.

This risk is not invalidated by less scientifically valid nonrandomized epidemiological data suggesting otherwise, because of the effect of confounding bias in the latter studies (Int. J. Clin. Prac. 2010;64:1009-14). A predictive relationship to suicide prevention, with randomized controlled trials, also has never been demonstrated with antidepressants.

Yet, in the absence of direct randomized control trial data one way or the other, the work group appears to presume such benefit, while denying such risk. The controversy is deemphasized in the report, and in fact, is not mentioned in the executive summary.

Fourth, the difficult differential diagnosis between bipolar and unipolar depression is hardly mentioned. No reference is made to the repeated evidence that 30%-40% of patients with bipolar disorder are initially misdiagnosed with MDD (BMJ 2010;340:c854) nor to some data indicating that the single most common cause of treatment-refractory depression is misdiagnosed bipolar depression (J. Affect. Disord. 2005;84:251-7).

Recent meta-analyses of antidepressant randomized controlled trials that incorporate previously unpublished data made available through the FDA archives provide a context that appears to be missing from these guidelines. About 95% of the published scientific literature indicates that antidepressants are more effective than placebo in the acute treatment of MDD. An equal number of studies, showing that antidepressants were no better than placebo, have not been published.

When all the actual studies, published and unpublished, are compiled, about 51% of studies are positive and 49% are negative (N. Eng. J. Med. 2008;358:252-60).

In providing this context, I am not suggesting that antidepressants do not work at all. However, it seems reasonable to conclude that the scientific literature has led the profession to believe that antidepressants are far more effective than they really are. This context is not reflected in the new guidelines.

Any treatment guidelines for MDD face a major problem. In debates about DSM revisions, it has become clear that diagnoses such as DSM-IV MDD are invented "pragmatically," based primarily on the opinions of DSM leaders about what is "good" for clinical practice, rather than on scientific research (Association for the Advancement of Philosophy and Psychiatry Bulletin 2010;17, www.alien.dowling.edu/~cperring/aapp/bulletin.htm). Given the way the DSM is created, it might not be surprising to find variable benefits with our treatments. The fault may lie not in our drugs, but in us, and the ways in which we diagnose and treat. ■

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