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Letters to the Editor

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Aggression, Mania, and Hypomania Induction Associated With Atomoxetine

To the Editor.—

Atomoxetine is a selective inhibitor of norepinephrine reuptake recently approved for the treatment of attention-deficit/hyperactivity disorder (ADHD). In 4 double-blind, placebo-controlled clinical trials leading to Food and Drug Administration approval, ~70% of child and adolescent subjects responded based on reductions in scores on a variety of measures for ADHD symptomatology.[1,2] Although no major risks were identified in these trials, a small percentage of subjects seem to have experienced mood destabilization. Irritability was reported in 8% of subjects, and mood swings were observed in 2% of subjects. Four subjects discontinued the drug because of irritability or aggression.[3] Our clinical experience has been that mood destabilization is a much more prevalent risk than was observed in the above-mentioned clinical trials. Indeed, the literature contains a case report of the same molecule (under the name tomoxetine) inducing mania in an adult.[4]

Our pooled data include 153 sequential patients (10.5 ± 3.74 years old) treated with atomoxetine in outpatient settings in Denver, Colorado, and North Branch, Minnesota (see Table 1). We have observed extreme irritability, aggression, mania, or hypomania induction in 51 cases (33%). Of those 51 cases, 31 (61%) had a positive family history for mood disorders. Forty-one patients (80%) had a personal history of mood symptoms. Both a personal history and a family history of mood swings were present in 27 cases (53%). Thus, either a personal or family history of mood instability was strongly associated with an increased likelihood of mania/hypomania induction or mood dysregulation. Of great concern, the risk of mood dysregulation with atomoxetine does not seem to be limited to cases with histories of mood symptoms. Six of the 51 cases (11%) had no personal history of mood instability or family history of bipolar disorder. Thus, it will be important to monitor all patients treated with this medication closely.

TABLE 1. Rates of Symptoms After Atomoxetine Treatment

	Total	+ Family History	+ Personal History	No History
N	51	31	41	6
Verbal aggression	88%	90%	90%	83%
Physical aggression	49	52	51	50
Mood swings	96	97	98	83
Irritability	96	97	98	83
Decreased sleep	18	16	22	0
Grandiosity	69	77	73	100
Hypersexuality	6	10	7	0
Increased goal behavior	10	10	12	0
Hyperactivity	14	13	17	10

The following are examples of symptom categories, including quotes from patients and parents. Irritability: hostile, "vicious," "blows up at everything," "huge tantrums," "worse case of PMS ever"; verbal aggression: verbal threats, yelling threats, "I'm going to get a gun and shoot you," "I'll kill you"; physical aggression: physical attacks on another, punching a female peer in the face, strangling a peer, attacking parents, brandishing a weapon; hyperactivity: excessive fidgeting, unable to sit still, "always on the go"; distractibility: unable to maintain attention, distracted by peripheral events, "off in la-la land"; flight of ideas: distracted by many competing thoughts, rapidly changing from one topic to another with or without completing a thought, "too many thoughts in my head"; hypersexuality: increased frequency of talking about sex, inappropriate sexual touching, "touching my breast all of a sudden"; decreased need for sleep: less hours of sleep because of either primary or middle insomnia without feeling tired subsequently; grandiosity: defying adults because patient "knows better" or "is smarter" euphoria: flopping on floor repeatedly, baby talk, unusually silly behavior, uncontrollable laughter; increased goal-directed behavior: beginning multiple projects without completing them, attempting risky behaviors for pleasure.

The diagnosis of mania or hypomania was not based solely on distractibility, motoric hyperactivity, or talkativeness. Irritability, aggression, and grandiose defiance were the most frequently observed symptoms. The majority of cases did not demonstrate hyperactivity concurrent with these mood symptoms. Ten patients developed symptoms severe enough to be considered mania, and 3 of those were hospitalized (see ref 5 for a detailed description of 1 such case), whereas 3 others were incarcerated in juvenile detention centers.

The onset of aggressive and/or mood symptoms occurred at 6.39 ± 5.36 weeks after starting atomoxetine. There was no significant difference between time to onset of symptoms in patients who also were treated with mood stabilizers (5.95 ± 5.68 weeks, $N = 22$) or atypical antipsychotics (5.88 ± 5.22 weeks, $N = 26$). Similarly, resolution of symptoms was independent of the presence or absence of other pharmaceutical agents (1.72 ± 1.20 weeks).

One possible explanation for increased irritability and aggression in these cases is incompletely treated ADHD with its attendant impulsivity. However, a number of patients in this series were either transitioned from stimulants or augmented with stimulants during their course of treatment with atomoxetine, which made it feasible to separate the hyperactivity out from the apparent mood symptoms. Augmentation with a stimulant frequently led to resolution of hyperactivity while the symptoms of irritability, moodiness, and/or aggression would remain. It is unclear why we are seeing a higher rate of mood destabilization compared with the clinical trials.[2,3] Age was not a factor, because the mean age of patients who experienced mood dysregulation was not significantly different from that of the total sample. Furthermore, cotreatment with mood stabilizers or atypical neuroleptics did not prevent mood dysregulation in a substantial portion of the cases. Cross-tapering from a stimulant was also not correlated with this adverse effect, because 32% of the cases in which mania or hypomania occurred were not being treated with stimulants before or during treatment with atomoxetine.

Our collective experience argues that caution should be used in selecting atomoxetine as a treatment in children with a personal history of mood dysregulation or mood disorder or who have a family history of mood disorders. Moreover, mania/hypomania induction or mood dysregulation can occur in a percentage of patients (4% of our total sample) who have no family or personal risk factors for mood disorder.

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Delay in Referral to Early-Intervention Services

To the Editor.—

In their article regarding early-intervention services provided through Part C of the Individuals With Disabilities Education Act, Bailey et al[1] express concern that the length of time is excessive between the identification of a child with a possible disability and referral for intervention services. However, whether this delay in referral for intervention is harmful totally depends on whether the interventions available are effective.

The Part C program serves a large number of children with a variety of disabilities or risk factors, and the effectiveness of the interventions differs with the disability involved. For example, for children diagnosed early with hearing loss, the effectiveness of early intervention is well-supported by existing data, and a delay in referral for intervention may have a substantial negative impact on the future development of the child with hearing loss.

Depending on how risk is defined, varying numbers of children, perhaps a majority, who might be referred for early-intervention services because they have been deemed at risk, will develop normally even if early-intervention services are not provided. For such children, it can be argued that immediate referral for intervention services is not warranted, especially when the availability of intervention services is limited.

Another group of children is those who have a documented delay but for whom intervention services have not been shown conclusively to be effective. For example, should a 3-month-old child with Down syndrome be referred immediately for physical therapy with the expectation that early intervention will improve muscle tone and result in the child achieving the ability to roll and sit unsupported at an earlier age? Should the same child be referred to speech therapy? Currently, data do not exist demonstrating the effectiveness of such interventions.

Until there are more data available regarding the effectiveness of early-intervention services, no broad generalizations can be made regarding delays in referral to intervention services provided by the Part C program.

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In Reply.—

The efficacy and desirability of early intervention for children with disabilities have been debated in various forums for >40 years. Based on logic, data, and assumptions from a variety of areas (eg, neurobiologic development, concepts of critical and sensitive periods, attachment theory, infant learning paradigms, the incredible amount of change that occurs in human development during the first years of life, research on family stress and coping), a national program of early-intervention services became a reality for infants and toddlers with disabilities with the 1986 passage of Public Law 99–457, now Part C of the Individuals With Disabilities Education Act. Several recent reviews from the fields of medicine, psychology, and education reach a similar conclusion about early-intervention efficacy: early intervention can result in significant and measurable benefits for both children and families.[1–4] Recognizing the potential value of early intervention and the accompanying need for earlier identification, the American Academy of Pediatrics has recommended that pediatricians incorporate systematic screening of all children rather than relying on more passive surveillance of development.[5]

In a recent *Pediatrics* article,[6] we reported data based on the initial experiences of a nationally representative sample of families whose children had recently enrolled in Part C early-intervention programs. Most families were very positive about their entry into early intervention. However, we reported an average delay of 5.2 months between initial diagnosis and a referral for early intervention. We suggested that the average time between diagnosis and referral seemed "unnecessarily long," speculated as to possible reasons for this delay, and suggested future research that could help explain this more fully.

In response to this article, Dr Cunningham argues that the extent to which this delay constitutes a problem cannot currently be determined because of lack of research on the effectiveness of early intervention for children with different types of disability. We agree with the basic premise that more focused research is needed to look at a wide range of outcomes for children who vary widely in terms of the nature and cause of their disabling condition. Particularly critical would be research to determine if advancing identification of disability and referral for services by 6 to 12 months would have marked benefits for children and families, and the field will always be served well by additional research on how to improve the effectiveness of intervention services.

However, it is clear that earlier identification and referral could result in a number of benefits to children, families, and society. We know that earlier identification could 1) provide earlier access to a nationally available program of services that parents almost uniformly endorse as positive and helpful for them and their children; 2) prevent the loss of confidence in parenting competence that occurs when parents are assured that nothing is wrong with their child but they continue to experience difficulty in parenting a child with delayed development or challenging behavior; 3) prevent the financial and emotional costs of the "diagnostic odyssey" that can occur when parents make multiple visits to physicians, psychologists, and other specialists to determine validity of their concerns about their children; 4) support the development of children with conditions with a high probability of resulting in a delay, such as Down syndrome, so that these children's developmental trajectories can stay closer to typical development; 5) provide ongoing assistance and information to the parents of these children as they cope with learning how to parent an infant with a disability. Also, for children with inherited disorders, an earlier diagnosis provides important information for families regarding reproductive risk. We suggest that these benefits are sufficiently compelling to warrant concern about current delays in both identification of children with disabilities and in referral to early-intervention services.

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