

LETTERS TO THE EDITOR

In the originally published letter to the editor by Hasan et al., the order of authorship was incorrect. It has now been corrected.

Response to the Management of Autism and Its Related Disorders

Sir: I read with interest the supplement to the *Journal* entitled "The Management of Autism and Its Related Disorders" (2005 Supplement 10). Dr. Fombonne notes in his article¹ that most of the upward trend in the prevalence of autism and pervasive developmental disorders can be accounted for by methodological factors such as change in the diagnostic criteria. However, in California where reporting starts at the age of 3, the incidence of autistic disorder has been dropping since 2003, which was the first time a decrease had been seen in 10 years. In 2002, there were 3259 new cases reported. In 2003, there were 3125 new cases reported. In 2004, there were new 3074 cases reported, and in the first half of 2005, there were 1470 new cases reported.²

This drop in incidence cannot be attributed to a change in diagnostic criteria or to a decreased availability of services. However, in 1999 California removed mercury from vaccines, which indicates that we need to look at environmental causes of autism. Furthermore, in Robert Findling's article in the same supplement,³ it is not mentioned that some adult patients with autistic disorders respond to half the antidepressant dose that is usually considered minimally therapeutic and that when placing a patient on what is considered the minimal effective dose, behavioral toxicity can occur resulting in unnecessary polypharmacy. In my practice, I have observed sufficient responses in adults with autism being treated for anxiety symptoms with half of what is considered the minimal therapeutic dose.

Dr. Michael Aman's article,⁴ although informative, did not discuss the Greenspan Floortime approach.⁵ Although applied behavior analysis (ABA)⁶ has been shown in clinical trials to be beneficial, the Greenspan Floortime approach can supplement the ABA by increasing bonding and motivation for the child to learn language and other skills. In *The Child with Special Needs*, by Dr. Stanley Greenspan and Dr. Serena Wieder,⁵ there are many successful cases described using this therapy.

Dr. Staff has no financial affiliations or other relationships relevant to the subject of this letter.

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Dr. Fombonne Replies

Sir: Trends in the numbers of people registered in the Developmental Centers of California with a disability code of "autism" have been widely speculated during the last 5 years as providing a basis for inferences about fluctuations in the incidence of autism and about its possible causes. There are several reasons why these data cannot be used as meaningful epidemiologic indicators of autism occurrence.¹ These numbers are not rates and do not take into account changes in the demographics of the Californian population. Furthermore, the numbers do not account for changes in diagnostic criteria that occurred from 1980 onward, and, more critically, they fail to account for fluctuations in numbers of those subjects with autism who are not accessing the network of public services. Therefore, it is wrong to refer to these data as incidence data, as they merely reflect the proportion of the population prevalence pool that, at any point in time, is eligible and registered as clients of a public system of service delivery.

To illustrate further why these data are inappropriate indicators of disease occurrence, it is sufficient to observe that at the end of December 2005, 20,587 children aged 3 through 17 years were registered in the California database under the autism eligibility category. Population estimates indicate that on January 1, 2005, there were 8.4 million subjects in this age group living in California.² Assuming that the population prevalence of pervasive developmental disorder (PDD) is 0.6%, a figure supported by most recent surveys,³ one would expect to have over 50,000 children with a PDD in this age group living in California, i.e., many more than those actually accounted for in the administrative database. The use of more conservative PDD prevalence estimates for these calculations, such as the 0.34% figure obtained in the Atlanta Centers for Disease Control survey,⁴ would lead to the same conclusion. Thus, as has been known for decades, administrative data sources and referral data identify only a fraction of affected subjects and are a poor reflection of the true population morbidity.

Clearly, the numbers of individuals registered in the Developmental Centers database underestimate the magnitude of autism at the population level. Because these data represent a tip-of-the-iceberg phenomenon, they cannot be used to argue for the presence or disappearance of an epidemic or to evaluate the role of environmental risk factors on disease occurrence.

With these general limitations in mind, other more specific arguments must also be considered when evaluating the most recent California data. First, the numbers actually registered every year have continued to increase with the addition of 3575 new clients in 2002, of 3125 in 2003, of 3074 in 2004, and of 2848 in 2005, leading to the highest number of clients with autism ever registered at the end of December 2005 (N = 29,424).⁵ Thus, even though the magnitude of the year-to-year increase has somewhat abated, there has been a continuing increase in the overall numbers of clients accessing the California Developmental Centers under the "autism" eligibility category.

Second, the slowdown in the rate of increase of clients has not been limited to the "autism" eligibility category. In fact, it has been much more pronounced among clients with epilepsy, cerebral palsy, and mental retardation, suggesting that a more widespread problem is occurring in obtaining eligibility for public services.

Third, and in line with the previous point, changes precisely occurred in 2003 in the regulation for assessing eligibility of new clients by the developmental centers. One or 2 areas of ma-

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for functional limitations out of a list of 7 domains of functioning were required previously for a subject to be recognized as having "substantial disability." On August 11, 2003, this requirement was changed to 3 areas of impairment to qualify for eligibility. This change very likely followed the budget cuts that affected the developmental centers as a result of the general downturn of the economic situation in California. Fourth, trends in other U.S. states have not been in the same direction, and this makes it very unlikely that the general removal of thimerosal from vaccines that occurred in 2001 throughout the U.S. would account for a trend confined to California.

Finally, several well-designed controlled-cohort, case-control studies and ecological analyses⁶ have failed to document an association between exposure to thimerosal and the risk of autism in children.^{7,8}

Epidemiologic investigations of autism require proper epidemiologic data. Reliance on referral statistics contained in administrative data sources such as the California Developmental Centers database or the U.S. Department of Education data⁹ is inadequate for properly evaluating trends in autism and PDD rates. In light of the severe limitations of the California data, inferences drawn from looking at trends in numbers of eligible clients are of dubious value.

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In the United Kingdom, Dr Fombonne has provided advice on the epidemiology and clinical aspects of autism to scientists advising parents, to MMR (measles/mumps/rubella) vaccine manufacturers (for a fee), and to several government committees between 1998 and 2001. He has also been consulted by ad hoc U.S. committees from the Institute of Medicine and the American Academy of Pediatrics reviewing the MMR vaccine safety. Since June 2004, Dr Fombonne is an expert witness for vaccine manufacturers in the U.S. thimerosal litigation. None of his research has ever been funded by the pharmaceutical industry. He has received financial or material support for providing expert testimony on behalf of GlaxoSmithKline.

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Dr. Findling Replies

Sir: The clinical observation that adult patients with autistic disorder may respond to low doses of antidepressants is interesting. The goal of the article on pharmacologic treatment of autism and pervasive developmental disorders was to review the extant scientific literature on this subject. The reason this form of intervention was not specifically noted in the paper is that this treatment approach has not yet been systematically studied.

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Dr. Findling receives or has received research support from, acted as a consultant to, and/or served on a speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech-Medeva, Forest, GlaxoSmithKline, Johnson & Johnson, Eli Lilly, New River, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Shire, Solvay, and Wyeth.

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Dr. Aman Replies

Sir: Dr. Ilana Slaff expressed disappointment that I did not discuss Greenspan and Wieder's¹ Floortime approach therapy when discussing "treatment planning" for individuals with autism. Floortime, also known as the "DIR" approach (Developmental, Individual Differences, Relationship-Based therapy), has an enthusiastic following within the autism community. There were 2 main reasons why I did not include the Floortime approach in my discussion. First, there are limited empirical data on the Floortime approach; I am aware of only 1 report of its impact,² which entailed a retrospective review of 200 clinical charts. Second, I was confined to limited space and simply could not address all potential therapies in the pages allowed. For example, my discussion did not include project TEACCH (Treatment and Education of Autistic and related Communication-handicapped Children), which has had an enormous impact in the state of North Carolina, which has a line-item budget for autism spectrum disorders.

The Floortime approach views interactive play as a key method of building affective interactions between the child with autism and his or her social world. The approach aims to coax the child through 6 hypothesized developmental milestones. Metz and colleagues³ reviewed the Floortime approach and drew the following conclusions: "At its core, the model seems to incorporate an intensive form of incidental teaching, creating and capitalizing on interaction and instructional opportunities and teaching new skills using shaping and reinforcement. These are aspects of intervention important to teaching and generalization of skills that should be an integral part of any intensive intervention program."^{3(p254–255)}

Presumably the Floortime approach will vary from case to case on the basis of therapist training and experience, caregiver style (caregivers—usually the parents—interact with the child in play), and child characteristics. Floortime is a popular therapeutic approach, and it warrants independent empirical assessment. Presumably, because of the numerous therapist, caregiver, and child variables involved, this will be a very challenging task that is likely to pose many of the same hurdles that

are encountered when evaluating the effects of other complex exchanges, such as occur in general psychotherapy.

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Dr. Aman serves as a consultant to Janssen, Forest, and Bristol-Myers Squibb.

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Onset of Unipolar Depression or Bipolar Disorder Prior or Close to Menarche

Sir: In a recent study by Joffe et al.,¹ the authors assessed menstrual cycle irregularities in subjects with unipolar depression, subjects with bipolar disorder, and healthy controls. Women with bipolar disorder reported early-onset menstrual dysfunction more commonly prior to onset of bipolar disorder. Bipolar disorder and unipolar depressive patients having fewer than 5 years between menarche and the first illness episode were excluded from the analyses. A higher proportion of bipolar patients (272/582 = 46.7%) were excluded from the analyses for onset of first episode prior or close to menarche compared with unipolar depressive patients (71/333 = 21.3%). This fact is commented on in the discussion section of the article, but we think that it bears further discussion.

We used data from the Joffe et al. study to determine whether women with bipolar disorder were more likely than women with unipolar depression to report the onset of their first episode prior or proximate to menarche. We reanalyzed data from the article using the programs NCSS and PASS, version 2004 (Number Cruncher Statistical Systems; Kaysville, Utah). After those patients who were missing menstrual cycle data (15 bipolar patients and 17 unipolar depressive patients) were excluded, onset of first illness episode prior or close to menarche was reported to have occurred more commonly in women with bipolar disorder (272/567 = 48.0%) than in women with unipolar depression (71/316 = 22.5%) (Fisher test [2-tailed], $p < .001$). We also calculated the odds ratio and 95% confidence interval (CI) for the association between bipolar disorder (compared with unipolar depression) and onset of first episode prior or close to menarche: OR = 3.2 (95% CI = 2.3 to 4.4, $p < .001$). This means that women with bipolar disorder were 3.2 times more likely to report the onset of the first illness episode prior to or within 5 years after menarche.

We consider this finding very interesting, because it suggests that bipolar disorder patients report a higher prevalence not only of menstrual dysfunction, but also of onset of illness close to menarche. As Joffe and colleagues mentioned in the discussion section, abnormalities in pulsatile release of gonadotropin-releasing hormone have been described in bipolar patients, while the hypothalamic-pituitary-gonadal (HPG) axis appears to be functionally intact in unipolar depressed patients. We wonder if these differences in HPG axis may explain why patients with bipolar disorder report an onset of illness prior or close to menarche more commonly than patients with unipolar depression.

Other studies have reported an onset of bipolar disorder² or unipolar depression³ related to menarche, but to our knowledge no previous studies compared onset close to menarche in a sample with both unipolar depression and bipolar disorder patients. For this reason, we think that the excellent study by Joffe et al. should be underscored, and we hope that our additional analyses and comments may help to widen the knowledge about female reproductive cycle events in relation to bipolar disorder and unipolar depression. We are aware that assessing the onset of the first illness episode in relation to menarche was not an aim of the study, but it is tempting to speculate about such an interesting finding.

The authors report no financial or other relationship relevant to the subject of this letter.

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Methadone Hydrochloride to Prevent Impulsive Behavior in Mental Retardation: A Case Report

Sir: Methadone is a synthetic narcotic that occupies opioid receptors in the brain. Currently, methadone has only 2 indications: the management of severe, chronic pain and detoxification and maintenance treatment of narcotic addiction. We present a case of a 35-year-old woman with severe impulsive behavior and aggression secondary to profound mental retardation and autism who was successfully discharged following initiation of treatment with methadone hydrochloride after 2 years of inpatient hospitalization. The patient returned to her group home and is currently functioning above her baseline.

Case report. Ms. A, a 35-year-old single white woman with profound mental retardation, entered a psychiatric hospital for

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escalating violent behavior. She had more than 20 previous hospitalizations. In the hospital, she tried to hit her head against a wall repeatedly and attacked others to such an extent that she required physical restraints for much of her 2-year stay. It required 4 staff members to feed, clothe, and bathe her.

She had symptoms of autism such as poor language development and a lack of social interest without emotional responsiveness, as well as very limited interests. She also suffered from epilepsy.

Ms. A's symptoms continued despite behavioral modification efforts and a plethora of medications: lithium, lamotrigine, quetiapine, fluvoxamine, trifluoperazine, chlorpromazine, ziprasidone, olanzapine, aripiprazole, clonazepam, and clozapine. She also received electroconvulsive therapy on 2 occasions. None of these treatments provided persistent benefit.

We eventually treated her with methadone because of reports that it reduced impulsivity¹ and because of the possibility that the patient suffered from pain that she could not express. Methadone treatment was initiated in August 2005.

The patient required methadone 20 mg p.o. at 6 a.m., 1 p.m., and 10 p.m. as an optimal dose. Initial twice-daily dosing allowed breakthrough of aggressive symptoms in the afternoon. She became nonaggressive soon after receiving the optimal dose. Within days, Ms. A required only occasional physical restraint, responded and related to the staff, and exhibited many fewer episodes of self-injurious behavior (SIB). She also gained the ability to eat and dress with minimal assistance and could go on walks on the hospital grounds, which she could not do before.

We observed this dramatic improvement in the patient's behavior for the next 2 months with no relapses. Prior to discharge, we discussed the dosing with the patient's group home, who agreed to continue providing methadone 3 times per day. Eight weeks after starting methadone treatment, we were able to discharge the patient to her group home on treatment with methadone and chlorpromazine, where she continues to function above her baseline with a superior quality of life.

All opioids, whether endogenous or exogenous, have the ability to bind to opiate receptors. When bound, opioids prevent the release of neurotransmitters, such as substance P, that would otherwise elicit a pain response. Methadone, a synthetic opioid, is recognized for its effectiveness in the management of chronic pain and pain associated with cancer states. More commonly, methadone has been used for the treatment of opioid and heroin addiction and has been the primary treatment for addicts for the past 40 years.² To our knowledge, this is the first report of methadone utilization to control impulsive, violent, and self-injurious behavior secondary to profound mental retardation and autism.

Methadone was suggested as a potential treatment option for this patient once all other avenues had been explored. An article published by Gold et al.¹ reported that opiates have antimanic, antipanic, and antidepressant qualities. This patient's aggression and agitation could have been her way of expressing pain and distress, as she has no other means of communication. Because of the possibility of treating unexpressed pain, we did not consider obtaining written consent from the U.S. Food and Drug Administration or Drug Enforcement Administration, since the treatment of pain is an approved indication. Methadone may have helped this woman because of its direct effect on impulsiveness or by reducing discomfort that she indicated by her violent behavior. In addition, SIB may paradoxically elicit pleasure if it causes the release of opioids and results in stimulation of opiate receptors. Thus, further SIB would enable one to reach the same level of pleasure. Blocking these receptors with

methadone could lead to extinction of the reward from SIB.³ This mechanism would explain the possible antiaggressive effect of opioid antagonists, such as naltrexone, as well as the benefits of methadone, an opioid agonist, which would occupy opiate receptors, preventing pleasurable responses due to SIB.

Further studies should indicate whether patients with similar symptoms benefit from methadone treatment.

The authors report no financial or other relationship relevant to the subject of this letter.

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Intimate Partner Violence, Suicidal Intent, and Alcoholism

Sir: According to Heru et al.,¹ over 90% of those with suicidal intent who enter clinical treatment and had been living with an intimate partner also report intimate partner violence in the past year. It can be concluded from this that aggressive-self-aggressive behaviors represent an axis along which patients may continuously change the direction of the aggressive urge between the external world and the self.

Alcoholics who struggle with suicidal ideation form a distinctive subgroup of the clinical population with suicidal intent. Although the connections between drinking and suicide are known,² there are relatively few empirical data on the correlations between childhood abuse, suicidal behavior, and intimate partner violence in adulthood.³

In recent research,⁴ we investigated the so-called cycle of violence in alcoholics,⁵ that is, how violent behavior is reproduced in the family as a consequence of childhood physical abuse. We were surprised to find that close to half (47%) of 235 alcoholics seeking treatment reported that there had been a significant period in their life when they had serious thoughts of suicide, independently of drug use or drinking (Addiction Severity Index [ASI] psychiatric status). Twenty-eight percent of the interviewees also reported that they had not only had suicidal thoughts in the course of their life but had also attempted suicide. Of these patients, one third attempted suicide once, the remainder more than once. Similar to the research findings of Heru et al.,¹ the suicidal urges of alcoholics were not determined primarily by sociodemographic, objective variables.

We used the Buss and Perry Aggression Questionnaire⁶ to examine the degree of the patients' violent behavior and reached the conclusion that the incidence of suicide attempts shows significant correlation with the level of aggression. We distinguished 3 levels of aggressivity based on scores on the Buss and Perry Aggression Questionnaire: 1 to 40 points: non-violent group, 41 to 60 points: moderately violent group, 61 to 90 points: very violent group. The higher the score a person obtained, the more likely he or she was to make a suicide attempt ($\chi^2 = 9.99$, $p < .01$).

Using multivariate regression models, we examined the correlations in the suicide attempts (dependent variable) between childhood abuse and perpetration-victimization events between the spouses and between sociodemographic variables (age, gender, education, etc.). We reached the conclusion that while there was no significant difference between the male and female subjects with respect to perpetration, there was a significant difference with respect to victimization ($p < .01$). In other words, a much higher proportion of women than men were the victims of intimate partner violence. This result differs in part from the findings of Heru et al.,¹ because in their investigation male and female patients did not differ significantly on any violence perpetration or victimization subscale (all p values $> .05$).

The difference found between the 2 samples in the area of violence victimization could arise less from differences of measure than from the fact that women who are alcoholics are much more at the mercy of their male partners than women who are not struggling with drinking problems. There are 2 possible explanations for this: one is that hazardous drinkers (regardless of gender) are likely to have partners with alcohol and drug problems, and the spouses with alcohol problems are likely to involve them in perpetration-victimization scenarios.⁷ The other is that women with alcohol problems are more likely to be violent in intimate partner relationships, and their partners often retaliate in such a situation.⁸

Comparison between the 2 research samples is, of course, limited by the circumstance that the Heru et al. study and our study used different measures. We used the structured interview method (ASI) and the Buss and Perry Aggression Questionnaire as mentioned above, while Heru et al. used the Beck Scale for Suicide Ideation to assess suicidal ideation and the Revised Conflict Tactics Scale to measure aggressivity.

Both studies draw attention to the large overlap between aggression and self-aggression in 2 clinical groups with alcohol problems, those with violent behavior and those with suicidal intent, and these behaviors are of the same treatment priority in both groups.

The research was carried out in the frame of the Pygmalion Project (NKFP-05/052/2004).

Drs. Gerevich and Bácskai have received grant/research support from the Ministry of Education, Budapest, Hungary.

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Agitated Depression, Panic Anxiety, and Clonazepam

Sir: Maj et al.¹ make the important point that agitated depression is a very common condition and worthy of increased research attention. Their data analysis provides an important syndromal description. When patients with agitated depression are also given a very careful psychiatric interview, they typically have a history of panic disorder. The agitated depression itself begins abruptly, as if it were a panic attack of extremely long duration, sometimes days or more (“status panicus”).² Alternately, some patients have repeated prolonged panic attacks, with only brief panic-free periods in between. Treatment with twice-daily clonazepam (or alprazolam q.i.d.) effects rapid improvement and effects full remission of agitated depression once the appropriate dose is reached.² Commonly, resolution of agitated depression reveals comorbid melancholia or atypical depression. These conditions then respond to addition of a selective serotonin reuptake inhibitor, with little risk of exacerbating agitation.

*This letter was shown to Dr. Maj, who declined to reply. —Editor
Dr. Kahn reports no financial or other relationship relevant to the subject of this letter.*

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