Donepezil for Down's Syndrome

TO THE EDITOR: Down's syndrome is the most common genetic disorder; it is recognizable at birth because of its associated cognitive and adaptive impairments. The neuropathological and neurochemical similarities between Down's syndrome and Alzheimer's disease and the role of cholinergic agents such as donepezil hydrochloride as proven symptomatic therapies for Alzheimer's disease led our group to publish what we believe to be the first report on the use of donepezil therapy in Down's syndrome (1).

A subsequent study was performed by Hemingway-Eltomey and Lerner (2). We commend these authors for drawing attention to the needs of patients with Down's syndrome and agree with their rationale for the use of cholinesterase inhibitor therapy (e.g., donepezil) to treat this syndrome. The authors reported on three patients with comorbid adult Down's syndrome and Alzheimer's disease, aged 57, 59, and 65, respectively, who developed adverse effects when treated with donepezil (2). Two patients were reported to develop urinary incontinence during donepezil therapy (one after 4 months; the other after an unspecified period). The third patient did well taking 5 mg/day, but the patient's behavior worsened when the dose was increased to 10 mg/day. At this point, the investigators discontinued the patient's therapy.

Our experience with the use of donepezil in adult patients with Down's syndrome has been different. In our initial pilot study (1), four patients (mean age=38 years, range=24–64) were treated for an average of 40.5 weeks (one individual was treated for 80 weeks). There were no reports of urinary incontinence or sustained worsening of behavior. Two of the four patients also met DSM-IV criteria for dementia. All of the patients had begun treatment with 5 mg/day of donepezil, which was increased to 10 mg/day after a minimum of 6 weeks. Transient diarrhea in one patient and agitation lasting 2 weeks in another patient at the time of the dose increase were the only side effects we observed (1). We have since treated five additional patients (mean age=42 years and 8 months, range=23–42) for an average duration of 18.2 weeks (range=5–27 weeks) and found tolerability to be good (unpublished data).

These data highlight the difficulties encountered in extrapolating tolerability and causality of adverse events from small case studies. In addition, elderly patients with Alzheimer's disease and Down's syndrome often have multiple comorbidities and are taking concomitant medications that can confound the attribution of causality for adverse events in uncontrolled studies. For example, in patients with Alzheimer's disease, agitation can result from the natural progression of dementia, from environmental or social triggers, from worsening of medical illnesses, and/or as a side effect of their medications. Clinical experience with more than 1 million elderly patients with Alzheimer's disease worldwide has suggested that donepezil is generally well tolerated.

In data from the U.S. phase II and III pivotal Alzheimer's disease clinical trials, which ranged from 3 to 6 months' duration (donepezil-treated group: N=747, placebo-treated group: N=355), 3% of the individuals in the placebo group reported urinary incontinence, compared to 1% of the donepezil group. Agitation was reported in 7% of the patients taking placebo compared to 4% of those taking donepezil. The dose of donepezil in the phase II trial ranged from 1 to 5 mg/day, whereas in the phase III trial, it was either 5 or 10 mg/day after 1 week at a dose of 5 mg/day (data available from Eisai, Inc.). In general, cholinergic side effects can be minimized by increasing the dose from 5 to 10 mg/day more slowly (e.g., after 6 weeks, rather than 1 week) (from donepezil package insert), by instituting temporary drug holidays, and/or by decreasing the dose from 10 to 5 mg/day if side effects occur at the higher dose (3). However, readers must bear in mind that donepezil has not been systematically investigated for use in patients with Down's syndrome. Randomized controlled clinical trials of cholinergic therapy are warranted in adult and pediatric patients with Down's syndrome; both are currently underway at our center.

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Depression in Aging Persons With Schizophrenia

TO THE EDITOR: I read with great interest the article by Sidney Zisook, M.D., and colleagues (1) on their study of depressive symptoms in a clinically stable group of outpatients with schizophrenia who were aged 45–79. They concluded (p. 1741) that their findings confirmed those of Cohen (2). In the introductory section of the article (p. 1736), Dr. Zisook and colleagues cited Cohen's article, saying that it was on a study of "schizophrenic patients aged 55 and older" in whom "high scores on a depression rating scale were associated with positive symptoms, physical limitations interfering with activities, diminished social networks, and lower income."

However, when I located Cohen's article, I found that it was not a report on a specific study, but a relatively general article on selected aspects (issues in research, psychopathology and social functioning, and treatment outcome) of aging persons with schizophrenia. This must be an error. Since I should not be the only person interested in the earlier study that Dr. Zisook and his colleagues had in mind, I would be much obliged if they could inform all readers of the accurate reference.

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Dr. Zisook Replies

TO THE EDITOR: We appreciate Dr. Tang's careful reading of our manuscript. He is correct that Cohen's cited article was a general report on selected aspects of aging persons with schizophrenia (Cohen, 1995). When commenting on the similarity between our findings and Cohen's, we should have cited reference 49 in our article, which describes a study that showed high levels of depressive symptoms in older outpatients with schizophrenia and indicated that depressive symptoms were strongly associated with the presence of positive symptoms (1). We thank Dr. Tang for pointing this out.

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Paroxetine in Breast Milk

TO THE EDITOR: Zachary N. Stowe, M.D., and colleagues expressed concern in their article (1) that the manner in which we have reported serum levels might be misleading: "The reporting of '0 ng/ml' in infant serum…could be misinterpreted by clinicians as suggesting a complete absence of infant exposure to medication." We welcome the opportunity to clarify the terms used to describe small amounts of drug in breast-fed infants' sera, as we have done previously (2). Assays have a limit of quantifiability. In the report cited (1), it was 2 ng/ml, which means that the limit of the assay for reliable quantification was 2 ng/ml (not truly a limit of detection). Levels below 2 ng/ml frequently are detectable but not are reliably quantified by analytical readouts. Our report of 0 ng/ml means that no amount was detected above the baseline (within instrumental limitations). We use three categories of exposure in our developmental studies of infants (0, not detectable; <2 ng/ml, less than reliably quantifiable but detectable; and ≥2 ng/ml, a reliably quantifiable numeric amount). We have stated that the unknown neurochemical effects of even these small amounts of drug or metabolite remain a concern (3).

More significant than the format of reporting assay results is the pharmacochemical assessment of paroxetine exposure. The principal paroxetine metabolite, a methylated and conjugated catechol, was not found in maternal and baby sera or breast milk measurements (1). Although this metabolite is neurochemically inactive, serum concentrations provide data for assessing *material balance* and treatment adherence. Data for levels of paroxetine and its metabolite have been reported in children (4).

We are concerned that the readership may misinterpret a statement in the article by Dr. Stowe et al. (1). Parents were asked if "the pediatrician had been informed of maternal paroxetine use." The pediatrician must be part of the decision-making team that evaluates the risks and benefits of breast-feeding during pharmacotherapy. Our policy is to discuss the risk-benefit analysis with the baby's pediatrician and document this conversation in the record (3). This procedure allows an opportunity for resolution if the pediatrician disagrees with the plan, as well as a chance to update him or her about new data in this rapidly evolving field.

We applaud the publication of serum level data for infants whose mothers took paroxetine during breast-feeding and appreciate the significance of the contribution of Dr. Stowe et al. (1) to the literature.

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Dr. Stowe and Colleagues Reply

TO THE EDITOR: We are pleased that Drs. Wisner and colleagues consider our report on paroxetine in breast milk to be a significant contribution to the literature. They raise three issues for discussion: 1) the clinical interpretation of 0 ng/ml in previous serum measures in nursing infants (1, 2), 2) the theoretical value of measuring inactive metabolites in nursing infants, and 3) the policy of informing the pediatrician of maternal paroxetine use.

First, our concern over the potential misinterpretation of 0 ng/ml by clinicians is not negated by the detailed description of how Dr. Wisner and colleagues handled their data set. The interpretation of serum concentrations in nursing infants, in the absence of treatment-emergent side effects, should be both conservative and scientific. To report that an infant's serum concentration was 0 ng/ml on the basis of either visual or computer interpretation of a chromatograph of ultraviolet absorption would be a less conservative interpretation. To date, all antidepressants studied are found in the breast milk of women taking the medication; the infant is exposed, regardless of infant serum concentration. Further, Dr, Wisner and colleagues reported infant serum concentrations as whole numbers (e.g., not as decimals). This implies that 0.1–0.4 ng/ml could be regarded as 0 ng/ml; they acknowledge as much with the statement "within instrumental limitations." We agree that the limits of detection and quantification are not the same, but they are the lowest value that can be reported. In analytic chemistry, "0" does not exist, and the limits of the assay (be it detection or quantification) convey the most scientific representation of the data (3). The description of categorical division on the basis of infant serum concentration is interesting but fails to address our concern that clinicians may misinterpret the data.

Second, the article cited (Findling et al., 1999) was not available at the time we submitted the manuscript of our paroxetine study. To consider the analysis of a nonactive metabolite more significant that accurate assay reporting is overstated. The only mechanism for combining the burgeoning data is to standardize data reporting and, ideally, the methodology used. The potential use of an inactive metabolite concentration (when the parent compound was detectable in the majority of mothers and in all breast milk samples) as a measure of treatment adherence appears to be of limited value. The pharmacokinetic study by Findling and colleagues (Findling et al., 1999) is of great interest but is not easily extrapolated to neonates since the youngest subject in that study was 6 years old.

Finally, Dr, Wisner and colleagues have stated that the pediatrician must be informed of the clinical treatment decision (Wisner et al., 1996). The complexity of this issue extends beyond the use of psychotropic medications in lactation to include the management of other medical conditions during pregnancy and lactation. Collaborative communication with obstetricians, pediatricians, and neonatologists represents the ideal and is strongly encouraged. We agree that communication across subspecialties is preferable, although such clinician-to-clinician contact is not mandatory in our programs as it is secondary to potential infringement on the mother's confidentiality.

We appreciate the opportunity to discuss the issues raised by Dr. Wisner et al. We look forward to seeing how the enhanced scientific rigor being applied to this area ultimately affects clinical practice.

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Hughlings Jackson and Dissociation

TO THE EDITOR: Russell Meares, M.D., is to be lauded for resurrecting the rich model of the mind mapped out by neurologist John Hughlings Jackson a century ago (1). However, his review of recent dissociation research suffers from significant lacunae. In point of fact, by suggesting that Jackson's overlooked contribution can cure what now ails the field, Dr. Meares created a compelling but misleading narrative.

Curiously, Dr. Meares cited studies from the 1960s and 1970s in support of his belief that today's investigators use the term "dissociation" too loosely. He thus neglected to mention new tools and the wealth of recent scientific investigations that have refined our understanding of dissociation (2). For example, clinicians now routinely use both the Dissociative Experiences Scale (3) to screen for symptoms and the Structured Clinical Interview for DSM-IV Dissociative Disorders (4, 5) to evaluate the severity of specific dissociative symptoms and to diagnose dissociative disorders. Furthermore, because of these reliable and valid measures, researchers have been able to document the precise nature of dissociative symptoms in hundreds of publications (6–11).

In the final analysis, although Jackson's work is of historical interest as we continue to reformulate the mind/brain nexus, scientific advances in the past two decades have already rendered dissociation considerably less elusive.

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Dr. Meares Replies

TO THE EDITOR: I thank Dr. Steinberg for her interest in my article. However, in terms of its intended scope, there were no lacunae. The aim of the article, stated in the abstract, was to provide "a preliminary framework for a systematic and dynamic understanding of dissociation through a consideration of the theories of Hughlings Jackson." My purpose was not directed toward description but toward a preliminary understanding of the phenomenon of dissociation. Nevertheless, such an attempt must be based on adequate description. Rather than neglect the Dissociative Experiences Scale (DES), I built my argument around it—or, more particularly—around the DES-T (1), which might be seen as a distillation of the essential features of the Dissociative Experiences Scale.

In no way does it devalue the important work that has gone into building the descriptive catalogues of dissociation carried out by Dr. Steinberg and other researchers to remark that, at present, the term "dissociation" is used too loosely. It has been authoritatively observed that "it is likely that this unfortunately vague term is used to describe a broad range of phenomena" (2, p. 1681), including imaginative activity/absorption, which relates to items in the Dissociative Experiences Scale. In this context, imaginative activity is conceived of as nonpathological dissociation. In my view, this conception is misleading. Imaginative activity is the opposite of dissociation in that it depends on a high level of voluntary, selective attention, whereas the ability to exercise voluntary, selective control of attention is impaired in dissociation. This is evident in Janet's classic descriptions. It is also made explicit in ICD-10: "There is normally a considerable degree of conscious control over the memories and sensations that can be selected for immediate attention, and the movements that are to be carried out. In the dissociative disorders it is presumed that this ability to exercise a conscious and selective control is impaired, to a degree that can vary from day to day or even from hour to hour" (ICD-10, pp. 151–152). In conditions in which dissociation is a feature, selective attention is markedly impaired (e.g., reference 3).

Finally, my article had a second purpose: to renew interest in Jackson's scientific approach to the study of mental illness, which he considered to be "really an experimental investigation of mind," or self. Following Jackson, an understanding of all mental illness, not only dissociation, begins with a neurobiological model of mind, self, or personal being. After decades of neglect and an unfortunate split between psychological and biological approaches, important steps are now being taken down this investigative pathway.

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Juvenile Offenders and Affective Disorder

TO THE EDITOR: The article by Steven R. Pliszka, M.D., et al. (1) raised a number of questions concerning mood disorders—in particular, mania—among juvenile offenders. It is of interest that the rate of major depressive disorder identified in this population was quite similar to those found in two previous studies (2, 3). Although both of these studies characterized the presence of depression, only the former characterized all identifiable affective disorders. With the use of different structured interviews, the authors identified major depressive disorder in 23% of the juvenile delinquents in each study; minor depressive disorder was verified in 15% of the juvenile delinquents in the former study (2). The number of delinquents with affective disorders in these studies was similar to that found by Dr. Pliszka et al.: 38% versus 42%, respectively. The similarity in the frequency of depressive disorder and the correlation of depressive disorder with substance abuse in these studies are quite striking.

However, Dr. Pliszka et al. identified mania in 22% of the delinquents; in our study (2), we identified only 4% with mania. The similarities in the rates of depressive disorder among these studies make the high rate of mania in the study population of Dr. Pliszka et al. not only striking but potentially suspect. In our study, agitation/irritability was not used as the primary mood symptom in the identification of bipolar illness; instead, euphoria of a relatively prolonged nature (over 2 weeks) was used as the defining affect. A total of 36% of the juvenile delinquents with major depressive disorder had agitated subtypes. Could the high rate of mania in the study by Dr. Pliszka et al. be explained by an overuse of agitation as the primary mood symptom to identify mania?

This is an issue that now appears to be vexing child and adolescent psychiatry. There has developed almost a knee-jerk diagnostic reflex in which any anger, agitation, or irritability is immediately labeled "mania" when found among children and adolescents. Is the result an accurate rate of occurrence? The justification offered for this notion appears to be the potential response of these clinical characteristics to treatment with divalproex sodium or lithium. So? Do they really substantiate the diagnostic entity?

Of further significance is the high percentage of juvenile delinquents identified with borderline personality disorder in another of our studies (4). In fact, borderline personality disorder was the most frequent principal psychiatric diagnosis made in this population: 44%. Intense anger, affective lability, and self-injury significantly differentiated the juvenile offenders with borderline personality disorder from those without. I understand that the Diagnostic Interview Schedule for Children does not identify borderline or other types of personality disorders. If so, how many of these youths may have had borderline personality disorder that was not correctly identified? Are all adolescents with borderline personality disorder merely exhibiting bipolar illness?

I wholeheartedly agree that the presence of mood disorders among juvenile offenders is an important finding; however, of greater significance is the correct identification of mood disorders. The implications of high levels of mania in this population are important, especially if this finding is accurate. But before pursuit of this issue is undertaken, it is important that we not attempt to oversimplify complex symptom profiles or use diagnostic instruments that bias either the phenomena identified or the diagnoses derived.

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Dr. Pliszka and Colleagues Reply

TO THE EDITOR: We thank Dr. Alessi for his thoughtful comments on our study of mood disorders in juvenile offenders. Dr. Alessi is concerned by the high rate of mania found in our subjects, in contrast to the 4% rate found in his own work (Alessi et al., 1984). However, his own work has shown that 36% of the offenders had "agitated subtypes" of depression. He notes that he and his colleagues did not consider agitation/irritability a primary mood symptom in identifying bipolar illness, only "euphoria of a relatively prolonged nature." DSM-IV clearly states, however, that "a manic episode is defined by a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood" (p. 328). Since Dr. Alessi and colleagues used a more narrow definition of mania, it is not surprising that they found a lower rate of bipolar illness in offenders than did we. Of note, we found that only three (6%) out of 50 juveniles met the criteria for pure euphoric mania, which is consistent with the 4% rate of euphoric mania found by Dr. Alessi and colleagues (Alessi et al., 1984).

The offenders who were diagnosed as manic in our study had not only an irritable mood but all the other requirements of a manic episode—e.g., inflated self-esteem, constant talking, flights of ideas. They did not receive the diagnosis of mania on the basis of irritability alone. We agree with Dr. Alessi that the division between bipolar disorder and the cluster B externalizing personality disorders requires more study. He is correct that we did not specifically interview for the diagnosis of borderline personality disorder in our offender group. However, personality disorders and bipolar disorder may overlap rather than be mutually exclusive, as Dr. Alessi suggests. Kutcher et al. (1) examined 20 well-diagnosed bipolar youth and found that 35% met criteria for one personality disorder, whereas three of these concurrently met criteria for borderline personality disorder. A reasonable body of evidence suggests that borderline personality traits may in fact be precursors of bipolar disorder (2). More careful studies are needed to separate youth with severe personality disorders and those with bipolar disorder, but the field should not move to early closure on this issue.

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Levels of Serotonin Receptor 2A Higher in Suicide Victims?

TO THE EDITOR: Gustavo Turecki, M.D., Ph.D., and colleagues (1) recently suggested that an increase in the density of serotonin receptor 2A (5-HTR_{2A}) in the brains of suicide victims (2, 3) may be genetically mediated. They called for a reproduction of their genetic findings in an independent study group of similar composition. We investigated the T102C polymorphism in the 5-HTR_{2A} gene in brain samples (Brodmann's area 9 of the cortex) from 24 depressed suicide victims and 31 matched comparison subjects and, in agreement with Dr. Turecki et al., found no significant differences in allelic or genotypic distribution between suicide victims and comparison subjects (4). In a subset of 10 depressed suicide victims and 15 comparison subjects, the density of 5-HTR_{2A} was significantly higher than in the comparison subjects, but there were no differences in receptor densities among the three genotypes of 5-HTR_{2A}: T/T, T/C, and C/C. We think this might have been because of our small group size—in particular, a low level of binding values in the T/T group.

We re-evaluated the phenotypic-genotypic relationship in a larger group (17 depressed suicide victims and 35 comparison subjects) of the same provenience and found that 5-HTR_{2A} binding in the brains of suicide victims carrying the T allele was higher (mean=153 fmol/mg protein, SD=20) than that of their respective comparison subjects (mean=114 fmol/mg protein, SD=13) (unpublished data). However, C allele carriers who committed suicide also had higher levels of 5-HTR_{2A} binding (mean=159 fmol/mg protein, SD=18) than did the comparison subjects carrying the same allele (mean=119 fmol/mg protein, SD=12). A two-way analysis of variance revealed a significant main effect of suicide on 5-HTR_{2A} binding levels ($F=6.93$, df=1, 100, $p<0.01$) but no significant effect on the two alleles of the 5-HTR_{2A} gene ($F=0.20$, df=1, 100, $p=0.65$).

We have thus confirmed the observation by Dr. Turecki et al. of no differences in 5-HTR_{2A} gene allelic or genotypic distribution between suicide victims and comparison subjects, as well as the effect of suicide on 5-HTR_{2A} densities in the frontal cortex. Our data agree with the result of their stepwise logistic regression. It was conducted with suicide as the main outcome and indicated that 5-HTR_{2A} binding, but not 5-HTR_{2A} genetic variation, was significant in predicting suicide. However, we were unable to confirm their finding that allelic variation significantly affects 5-HTR_{2A} densities in suicide victims and comparison subjects; we thus cannot support their suggestion that 5-HTR_{2A} binding is genetically determined by an allelic variation in the T102C polymorphism of the 5-HTR_{2A} gene.

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Dr. Turecki and Colleagues Reply

TO THE EDITOR: Drs. Hrdina and Du report the results they observed in a study (unpublished) in which they attempted to replicate our findings. In observing 17 depressed suicide subjects and 35 comparison subjects, they failed to find a relationship between variation at the T102C 5-HTR_{2A} polymorphism and 5-HTR_{2A} binding. As previously discussed (1), a possible explanation for this inconsistency may be related to the characteristics of the subjects included in our study, who were of French Canadian descent. This is a relatively young and isolated population that has a large background linkage disequilibrium (2). Thus, it is possible that a functional genetic variant located in a different coding or regulatory region of the 5-HTR_{2A} gene, rather than the T102C silent polymorphism, may in fact be responsible for our positive results.

This may not have been the case in the study by Drs. Hrdina and Du because they investigated subjects of Hungarian origin. Although they did not provide details about the specific ethnic composition of their study group, the Hungarian general population is composed of several different ethnic groups with admixture among most of them. The population is not known to have undergone any event leading to the presence of the relatively large linkage disequilibrium that may be observed in subjects chosen at random (3, 4).

An additional point relates to ascertainment differences between the studies. Drs. Hrdina and Du have focused their attention on depressed suicide victims (Du et al., 1999). Our findings are not related to the phenotype, but rather to a relationship between genetic variation and 5-HTR_{2A} binding. However, if there is less variation among binding levels in depressed patients, this group may have lower power to detect a positive association.

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Double Standard on Capacity and Consent?

TO THE EDITOR: In the editorial by William T. Carpenter, Jr., M.D. (1), his juxtaposition of involuntary treatment on one hand and the requirement for consent to participate in research on the other exposes a double standard on decision-making capacity that goes to the heart of the stigmatization of the mentally ill and, by association, of those who care for them.

Dr. Carpenter expresses clearly the need for mentally ill patients to have the capacity to consent to research and describes supporting guidelines adopted by the Maryland Psychiatric Research Center. These aim to enhance capacity (the ability to "understand, appreciate, reason") by providing information in an educational context and to help clarify the consequences of participation by including significant others or advocates in the decision-making process. This approach is excellent.

But why should this not apply equally to a more pressing question for most patients with mental disorders: what justifies treatment against their will? Mental health legislation almost always ignores capacity. This is in sharp contrast to treatment for "physical" disorders, in which capacity and consent are central; a patient who has capacity cannot be treated nonconsensually, no matter how drastic the health consequences. The report by Gardner et al. (2), addressed in the editorial, involved patients involuntarily committed to the hospital according to common criteria—the presence of mental illness and dangerousness to either themselves or others. There was no consideration of the capacity to make treatment decisions and, if capacity is impaired, whether nonconsensual treatment is in the patient's "best interests"—a question in which values loom large.

The standards for nonconsensual treatment for physical disorders should apply equally to those suffering from mental disorders (3, 4). An expert committee to review the Mental Health Act (1983) in England and Wales has supported a capacity and best interests criterion (5), but this is too much for a government preoccupied with dangerousness and public safety (6). Dr. Carpenter sees the recommendations of the National Bioethics Advisory Commission as "another expression of society stigmatizing the mentally ill and those who serve them." This is hardly surprising when we have legislation restricted to a single class of patients (the mentally ill) that, by ignoring questions of capacity and best interests, carries a built-in assumption of incompetence or not-quite-whole personhood. Such legislation fosters stigmatizing stereotypes of mental illness.

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