Dexamphetamine for Obsessive-Compulsive Disorder

TO THE EDITOR: Obsessive-compulsive disorder (OCD) may emerge with stimulant treatment for attention deficit hyperactivity disorder (ADHD). We report a case of OCD worsening with methylphenidate treatment but not with dexamphetamine. This adds to the sparse evidence for methylphenidate exacerbating obsessions and compulsions (1–3), suggests parallels with the emergence of tics in susceptible individuals when they are treated with stimulants, and may help illuminate genetic and neurochemical relationships between OCD and tic disorders.

Andy, an 11-year-old boy with ADHD diagnosed at age 5, was treated with methylphenidate. His overactivity, impulsivity, and attention improved, but anxiety symptoms emerged as the dose was increased to 40 mg/day. He started washing his hands excessively; this was accompanied by checking rituals, reassurance seeking, and emetophobia. OCD was diagnosed, and behavior therapy was initiated. For 1 year, Andy's hyperactivity and impulsivity were well controlled with methylphenidate, but his obsessions and compulsions continued.

At his assessment in our service, Andy met DSM-IV criteria for OCD, and a cognitive behavior program was continued with some success. After 3 months, Andy still had significant OCD symptoms. Because his ADHD was quiescent, methylphenidate was withdrawn, as it is a potential anxiogenic agent. His response after 1 week was dramatic; Andy had reduced ritualization and anxiety. His hyperactivity and concentration were unaffected, but his parents found him more affectionate. This improvement lasted 3 weeks before Andy experienced a resurgence of hyperactivity, poor concentration, and attacks of rage. Risperidone, 1 mg/day, was added to his treatment and had some effect on his rage but no impact on his anxiety. His OCD symptoms remained in remission, so methylphenidate was gradually reintroduced. His OCD symptoms then returned, especially the reassurance seeking, hand washing, and fear of illness.

Dexamphetamine was substituted for methylphenidate and was gradually increased to 30 mg/day. The anxiety and ritualistic behavior lessened. After 6 weeks, there was still some generalized anxiety and a depressed mood, so citalopram, 10 mg/day, was added. This was associated with significant improvement in affective and anxiety symptoms, socialization, and school performance. These three medications—dexamphetamine, risperidone, and citalopram—have been maintained for Andy, who continues to improve.

Methylphenidate and dexamphetamine are often used interchangeably in ADHD treatment but have differing effects on dopaminergic and serotonergic metabolism. In complex comorbidity, subtle differences in metabolism and receptor sensitivity may require careful pharmacological choice. Dexamphetamine may be more suitable for ADHD with associated OCD (4). Recent case reports (5, 6) have implied that dexamphetamine improves OCD symptoms, further suggesting the need for more research into dopaminergic and serotonergic interactions in OCD (7).

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Hypomania Induced by Adjunctive Lamotrigine

TO THE EDITOR: Adjunctive and monotherapeutic lamotrigine has been effective in the treatment of bipolar (1–4) and unipolar (3, 5) mood disorders. We present a case of potentiation with lamotrigine for major depression that was partially responsive to antidepressants, in which the patient developed hypomania. This is, to our knowledge, the first such reported case.

Ms. A was a 23-year-old woman with a DSM-IV diagnosis of major depression and no personal history of bipolar illness and no family history of mood disorders. She had a partial response to 6 months of combination cognitive therapy and buproprion, 300 mg/day. The buproprion was increased to 400 mg/day for 3 months without further improvement. Lamotrigine was then added. After 1 week of 25 mg at bedtime, Ms. A reported an improved mood. After another week at 50 mg/day, she noted a further improved mood, decreased anxiety, and increased energy. Two weeks later, her lamotrigine dose was increased to 75 mg/day. One week thereafter, she reported decreased sleep (2–4 hours per night), increased energy, distractibility, mood lability, and increased spending. She reported no grandiose or other delusions but scored 9 on the Altman Self-Rating Mania Scale (6) (a score >6 suggests hypomania or mania), and she met DSM-IV criteria for hypomania. Her lamotrigine dose was reduced to 50 mg at bedtime. Two weeks later, the hypomanic symptoms subsided (Altman Self-Rating Mania Scale score=5). Fourteen months later, Ms. A remained euthymic.

All antidepressants can induce hypomania or mania in susceptible unipolar patients when they are given in combination or at a high dose. Our patient's hypomanic state is further evidence that lamotrigine has potentiating antidepressant properties, likely through its ability to decrease glutamate release, thereby reducing binding to the *N*-methyl-D-aspartate receptor complex (4). This case report supports lamotrigine's

role as an adjunctive and potentiation treatment in partially responsive unipolar depression.

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Clozapine and Postmortem Redistribution

TO THE EDITOR: In cases of sudden unexpected death, toxicological studies are performed as part of an autopsy to help establish causality. Toxic postmortem drug concentrations can lead to erroneous conclusions with resulting liability claims, insurance denials, and significant emotional turmoil for all involved. However, postmortem drug concentrations may not accurately reflect antemortem drug levels. Postmortem redistribution of a drug may be the basis for elevated or toxic drug concentrations after death (1). Postmortem drug concentrations vary greatly from drug to drug because of differences in the volume of distribution, the elimination half-life, the site of the postmortem blood sample, protein binding, and the amount of time elapsed between death and obtaining of the postmortem blood sample. To our knowledge, this is the first reported case of postmortem redistribution of clozapine.

Ms. A, a 22-year-old obese African American woman, was hospitalized for treatment of schizoaffective disorder, impulse control disorder, mild mental retardation, and borderline personality disorder. Because of previous treatment problems, she was given clozapine. It was titrated to 350 mg/day over the next month; improvement was noted. Ms. A's other medications included haloperidol, gabapentin, ranitidine, benztropine, birth control pills, and docusate sodium. Ms. A displayed no signs of toxicity nor did she complain of side effects. About 6 weeks after starting clozapine, Ms. A was found unresponsive. Resuscitation attempts were unsuccessful. An autopsy performed approximately 8 hours later revealed no clozapine in her stomach (consistent with reports of medication refusal for 24 hours before her death and her history of noncompliance) and a clozapine level obtained from cardiac blood of 4500 ng/ml (a level greater than 1300 ng/ml is considered toxic). The coroner expressed concern over the possibility of suicide. On the basis of our review of the case, suicide seems very unlikely. There were no overt signs of toxicity, and staff reported no change in behavior.

We believe that this is a case of postmortem redistribution of clozapine. Postmortem redistribution of tricyclic antidepressants has been described in the literature (1). Clozapine is similar to tricyclic antidepressants in chemical structure, volume of distribution (6 liter/kg), and protein binding (97% protein bound), leading one to anticipate similar redistribution effects. The time elapsed was sufficient (>2 hours) (2), and central blood samples are associated with higher postmortem concentrations (3).

Clinicians should be aware of the possibility of postmortem redistribution of clozapine because the implications can be significant. More reporting of such cases is needed to establish the phenomenon. Instances in which antemortem plasma levels were obtained and in which there is no possibility of overdose would be most useful.

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Bipolar Disorder With Asperger's Disorder

TO THE EDITOR: The clinical case conference by Jean A. Frazier, M.D., et al. (1) highlighted that diagnosing comorbid bipolar disorder in patients with Asperger's disorder who display prominent affective symptoms is crucial so that these children can receive appropriate treatment. However, this is not a new observation and has already been made by me in a previous report (2). In addition to increasing awareness of the existence of such comorbidity in patients with Asperger's disorder, I emphasized caution in prescribing psychotropic medications—especially antidepressants—to this population. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), have been shown to induce hypomania in some patients with Asperger's disorder (3) and also to worsen aggressive behavior—the latter evident in the case study by Dr. Frazier and colleagues. Thus, when antidepressants are added to treat depression or repetitive stereotyped behavior in such patients, it may be worthwhile to add a mood stabilizer, particularly if there is a positive family history of affective illness.

A growing body of literature now suggests the effective use of mood stabilizers in autistic spectrum disorders with comorbid bipolar disorder. This use may stem from the common neurobiological substrates in these two conditions. Involvement of the amygdala in both of these disorders, as discussed by the authors, leads one to hypothesize as to whether mood stabilizers have a specific role in controlling the emotional dysregulation of Asperger's disorder, which is

often misinterpreted as a part of that disorder. Indeed, there is evidence to suggest that lithium and valproate may change genetic expression in the amygdalal-hippocampal complexes through modulating second-messenger effects (4). Further research in this respect would be encouraging.

Finally, in my observation, some patients with Asperger's disorder with comorbid bipolar disorder require higher doses or a combination of mood stabilizers, which may be partly explained by the fact that bipolar disorder is recognized quite late in these patients, thus conferring some resistance to treatment. Hence, a clinician may have to adequately treat such patients with mood stabilizers at doses higher than those typically used in add-on regimens for control of aggressive or impulsive behavior.

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Biopsychosocial Psychiatry

TO THE EDITOR: In their piece, Glen O. Gabbard, M.D., and Jerald Kay, M.D. (1), correctly pointed out the need for more empirical evidence to guide decisions about when and how to combine psychotherapies with pharmacotherapies. Their assertion, however, that "dividing treatment between a psychiatrist-prescriber and a nonpsychiatrist psychotherapist" can be seen as "a tacit endorsement of Cartesian dualism" (p. 1959) belies a misunderstanding of what dualism is and how it can be combated. It is likely that their misconception is shared by many who see the distinction between psychotherapy and pharmacotherapy as congruent with that between the mind and brain. While they accurately pointed out that "Psychotherapy must work by its impact on the brain" (p. 1959), they did not recognize that that is precisely why divided treatment and dualism, despite superficial resemblances, have no relation to each other. It is the belief that psychotherapies treat the mind while pharmacotherapies treat the brain—not the way such treatments may be delivered in practice—that is dualistic. Moreover, when the psychotherapy involved is behavior therapy, it is largely observable, third-person, non-introspection-based (i.e., nonmental) phenomena that are of interest. And when the pharmacotherapist spends his or her time with a patient inquiring about moods, perceptions, thoughts, and the like, he or she is entering the first-person subjective world that Drs. Gabbard and Kay referred to as "mind." (The absence of constructs such as ego defense, transference, and resistance from such a pharmacotherapist's thinking and work makes that point no less true!)

There are many reasons why having more than one clinician (psychiatrist and psychotherapist, orthopedic surgeon and physical therapist, etc.) involved in the care of a patient may be desirable or even necessary. As Drs. Gabbard and Kay discussed, there may be countervailing reasons why such arrangements should not be employed in particular instances. We need to learn more about the conditions under which combined treatments are superior to monotherapies and about the circumstances in which the benefits of dividing labor among professionals with different training, talents, and interests may be outweighed by the drawbacks of such practices. Inquiries into those important questions, however, should not be encumbered by the misconception (that Drs. Gabbard and Kay rightly exposed) that "Psychotherapy is a treatment for 'psychologically based' disorders, while 'brain-based' disorders should be treated with medication" (p. 1959) nor by the misconception that dividing the provision of such treatments is a reflection of Cartesian dualism.

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TO THE EDITOR: Drs. Gabbard and Kay presented the first balanced article describing combined treatment that I have read; however, the question of how to bridge these two modalities—or, rather, communities—remains unaddressed. During psychiatry residency, I constantly struggled to learn how to become a biopsychosocial psychiatrist but found little guidance from either the literature or my mentors. Instead, I learned that the excellent practice of psychopharmacology or psychotherapy, by definition, excludes practice of the other. It is well and good to promote research and teaching in combined treatment, but no faculty exists who can teach what has yet to be created.

I have worked with psychiatrists who are well known in the Los Angeles community on both sides of the fence and even a few who attempt combined treatment. I have adapted my style to reflect the knowledge I garnered from a range of practitioners, but I remain very frustrated. My concern and difficulty with learning combined treatment has left the vast majority of my colleagues and mentors unimpressed. Everyone agrees that the current combined approach is adequate. So I tried to wear two hats in two different settings and learned several things. Both approaches demand relentless focus to eradicate illness and constant alteration in strategy to do so; however, the structural framework for decision making in each is incompatible. As a psychopharmacologist, I assessed symptoms to determine if a patient had reached a threshold for illness, then I treated to decrease symptom severity. As a therapist, I identified behavioral, affective, or cognitive templates that disrupted patients' lives and tried to alter them through awareness, analysis, education, and exposure. As a biopsychosocial psychiatrist, I saw no way to integrate a threshold model of illness with a template model. The combined practitioners explained how to switch hats in mid-session, but how can one treat patients expertly when combining

two incompatible clinical methods? Similarly, why cannot one approach suffice when both approaches aim to treat similar conditions? I beg to differ with Drs. Gabbard and Kay, who compared learning these approaches to understanding that light can be both particle and wave because no such proof exists to force us to compromise. Instead, why not see these approaches as classical physics and quantum mechanics before physicists understood that the theories described the same phenomenon?

I think this article is ahead of the current climate in psychiatry. The field needs to develop effective combined psychopharmacology and psychotherapy before focusing on research and teaching initiatives. The reason residencies do not teach this modality is neither neglect nor lack of faculty but because of a lack of theory and practice. In essence, this article asks psychiatry to adopt a nonexistent aspect of the field. The further elucidation of combined treatment can lead us in search of a third form of practice, one that provides a unified approach to the psychiatric patient, not a second-rate blend of two irreconcilable entities.

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TO THE EDITOR: Drs. Gabbard and Kaye wrote an excellent article on the biopsychosocial psychiatrist, but what happened to the social slant? The only remotely social aspect to their article deals with the important question of whether "two treatments [are] better than one" (p. 1957) and then only if one regards the patient and the two therapists as a small society. One hopes—indeed, is sure—that they know about the value of couples and family treatment, not to mention issues of ethnicity, race, community, etc. It is known, for instance, that when there is both marital discord and depression that couples therapy is more effective than treating the depressed person alone (1) and that in work in schizophrenia, collaborating with the family is vital for success (2).

One is left with the question why—and it is a common practice—the social part of the biopsychosocial model is omitted, not only by two such wise psychiatrists, but almost always. It is perhaps that they, like most psychiatrists, are interested in the individual patient and not in social issues. Thus, it is not surprising that in the excellent residency training program in which I teach at Cambridge Hospital, a resident spends 60 hours (less than 1% of his or her time) during all 4 years learning about and working with couples and families, the social, and 99% of his or her time with the "biopsycho," a practice doubtless mandated by the boards.

Fortuitously, in the article that followed the one by Drs. Gabbard and Kay, the importance of the spouse is illustrated in a brief clinical vignette titled "Husband and Wives" (3).

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Drs. Kay and Gabbard Reply

TO THE EDITOR: We welcome the opportunity to respond to the important points raised by Drs. Waterman and Batra, Lissak, and Grunebaum. First, Drs. Waterman and Batra are concerned that we obfuscated the issue of dualism by suggesting that split treatment (in which a psychiatrist might provide pharmacological treatment and a nonmedical mental health professional might provide psychotherapy) is not representative of a Cartesian-based practice model. They argue that the provision of such services is unrelated to a dualistic approach. Although a two-person model of treatment may certainly be implemented in a way that eschews dualism, it is, in fact, this split treatment model that has led clinicians and the general public to reify an artificial separation of mind and brain. As Drs. Waterman and Batra acknowledge, we are fully aware that psychotherapy should not be artificially relegated to "disorders of the mind" or "psychologically based disorders." However, we feel that a split treatment approach forces clinicians to adopt a conceptual model that strengthens the mind-brain split rather than dissolving the mind-brain barrier. We wish to note also that there is emerging evidence that psychotherapy and psychopharmacology may be affecting the same or similar neural pathways (1).

Dr. Lissak has had difficulty finding mentors and teachers who are proficient in combining psychotherapy and pharmacotherapy. We noted in our article that integrated treatment is neglected in many training programs, and we hope that situation will improve now that it is mandated as one of the core competencies. But we strongly disagree that the two approaches are incompatible. Many of us combine them every day and teach our residents a systematic approach to integrated treatment.

Dr. Grunebaum appeals to us as clinician educators not to dismiss the social characteristics of our patients. We believe he is right that educators often give short shrift to the social context of our patients. Both of us have written about the centrality of family interventions in the treatment of schizophrenia, bipolar disorder, and some cases of severe depression. We concur with his citations in the literature to that effect. We believe that attention to family, marital, and ethnocultural considerations are vital to the effective treatment of our patients.

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Controlled Trials of Psychotherapy

TO THE EDITOR: J. Stuart Ablon, Ph.D., and Enrico E. Jones, Ph.D. (1), reported that interpersonal therapy and cognitive behavior therapy share similar "processes"; hence, they are misleadingly labeled distinct psychotherapies. The authors

based this on judges' ratings of session transcripts from the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program and on correlations of Q-set items with "ideal-prototype" sessions elicited from experts in interpersonal and cognitive behavior therapy. The authors polemically interpreted these findings to discredit randomized controlled trials of psychotherapy.

Are their methods biased? Perhaps the 100 generic Q-set items ("distant or aloof" [p. 777]), originally designed to measure psychoanalytic psychotherapy, are not comprehensive and cannot discriminate between specific psychotherapies. The Q-set never defined techniques or strategies. The authors' statistical reification blinded them to real differences between therapies.

Which "experts" defined the ideal sessions? I twice failed, as did several interpersonal therapy experts I solicited, to answer the questionnaire, finding it unrelated to the essentials of interpersonal therapy and unlikely to discriminate among treatments. If the authors' study worked from faulty templates (and transcripts rather than sessions tapes), no wonder Drs. Ablon and Jones confounded two overlapping but distinct treatments. At a conference, I once asked the participants about instrumental bias; they simply denied it. The article by Drs. Ablon and Jones did not discuss this limitation.

Adherence (2, 3) and other measures (4) are used to discriminate between interpersonal and cognitive behavior therapy, as can any clinician with casual familiarity. Of course, psychotherapies overlap: "common factors" (5) have long been acknowledged as essential to treatment (even for pharmacotherapy [6], which even the authors might accept is not cognitive behavior therapy) and are responsible for significant outcome variance. A supportive alliance provides common ground, allowing therapists to use different techniques, which may then make a difference. Hence, the sometimes different showings of interpersonal therapy and cognitive behavior therapy in randomized controlled trials, e.g., the advantages of interpersonal therapy for more depressed patients in the NIMH Treatment of Depression Collaborative Research Program and HIV-positive depressed patients (7) and the advantages of cognitive behavior therapy for bulimia nervosa (8). Drs. Ablon and Jones reinvented the common factors, artificially conflating them with therapeutic equivalence and blurring actual distinctions.

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Drs. Ablon and Jones Reply

TO THE EDITOR: Our study did not discredit randomized controlled trials of psychotherapy but rather pointed out their limitations. Brief therapies studied in randomized controlled trials have different brand names and manuals prescribing different therapist interventions. Nevertheless, randomized controlled trials did not reveal what actually occurred in these treatments. Randomized controlled trials can provide evidence of efficacy but not evidence to support a therapy's purported theory of change. Our study demonstrated that treatments may promote change in different ways than their underlying theories of therapy claim.

Dr. Markowitz asks whether our methods are biased and alleges that the Psychotherapy Process Q-set (1) cannot discriminate between interpersonal therapy and cognitive behavior therapy. Dr. Markowitz incorrectly states that the Psychotherapy Process Q-set was designed to study psychoanalytic psychotherapy. The Psychotherapy Process Q-set is pantheoretical, has demonstrated excellent discriminate validity, and can differentiate effectively among any number of therapies (2). In fact, almost one-half of the 100 Q-set items significantly differentiated interpersonal therapy and cognitive behavior therapy in the data set from the NIMH Treatment of Depression Collaborative Research Program (3). The Q items do indeed define strategies and techniques (e.g., "Therapist presents an experience or event in a different perspective" refers to cognitive restructuring). Dr. Markowitz mistakenly seems to think we reported that the Q-set could not differentiate the two treatments. What we found was that interpersonal therapy, as conducted by the therapists in this study, conformed more closely to what experts considered an ideal (or prototype) of cognitive behavior therapy than it did to a distinct prototype of interpersonal therapy.

The method used to create the prototypes, the Q technique, is a statistical approach for studying points of view (4). Dr. Markowitz acknowledges that he failed to respond to our questionnaire. It is a shame that he chose not to register his opinion so that it could be considered in our analyses along with those of the other experts sampled. The large majority of interpersonal therapy and cognitive behavior therapy experts contacted did respond and reported that the method captured the important aspects of their respective treatment ap-

proaches. As stated in the article, the experts were very experienced and had trained therapists in their orientation. Most had published work concerning their approach to therapy, and many were involved in the development of their treatment modality.

Apparent differences among newer manualized therapies may lie mostly in terminology and the ways of conceptualizing psychological constructs and processes that are actually quite similar. As we pointed out, the content of the cognitive behavior therapist's focus (dysfunctional attitudes and irrational beliefs) is often quite different from the content of the interpersonal therapist's focus (e.g., disruptions in personal relationships). However, when we shift our attention from content to process (i.e., the interaction between the therapist and patient), the similarities are compelling. In both treatments, the therapist assumed an active, authoritative role, coached compliant patients to think or conduct themselves differently, and encouraged them to test these new ways of thinking and behaving in everyday life. Most brief therapies probably promote change through similar processes, and specific techniques are likely less important. That is why—Dr. Markowitz's claims notwithstanding—it has been so difficult to demonstrate any large or consistent differences in outcome across types of brief therapies (5).

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Omega-3 Fatty Acid for Schizophrenia

TO THE EDITOR: The failure of ethyl eicosapentaenoic acid (EPA) (omega-3 fatty acid) to produce improvement over placebo in patients with chronic schizophrenia treated with standard drugs in a study by Wayne S. Fenton, M.D., and colleagues (1) has several possible explanations. First, ethyl EPA may have no beneficial effect. This may be a premature conclusion since it is unlikely that any standard drug would show benefit in a trial with this add-on design.

Second, ethyl EPA may have no beneficial effects in patients with a long history of schizophrenia who are presumably taking optimal doses of standard antischizophrenia drugs. The best results in previous studies (2–4), two of which were randomized and placebo controlled, were in patients with a short illness history who were not receiving standard drugs. Neuroleptics may reduce or block response to ethyl EPA. However, Emsley et al. (5) recently reported a robust beneficial effect of ethyl EPA on both schizophrenic symptoms and tardive dyskinesia in a placebo-controlled trial in patients with chronic illness.

A third possibility is that the dose was wrong. Previous studies have used 1–2 g/day rather than the 3 g/day used by Dr. Fenton et al. (1). We conducted a dose-ranging add-on study of schizophrenia patients in which placebo was compared with 1 g/day, 2 g/day, or 4 g/day of ethyl EPA (6). The best results were achieved at the 2-g/day dose, which produced an increase in red cell EPA without any decrease in red cell arachidonic acid. At 4 g/day, there was no beneficial effect, and the increase in red cell EPA was accompanied by a substantial decrease in arachidonic acid, a fatty acid that plays a central role in many neuronal signal transduction systems (7). A similar dose-ranging study in depression (8) also showed a bell-shaped dose-response curve, with a strong beneficial effect at an ethyl EPA dose of 1 g/day and smaller effects at higher doses. The large decrease in the arachidonic acid/EPA ratio reported by Dr. Fenton et al. suggests that the ethyl EPA dose may have been too high because it depleted arachidonic acid.

Fourth, through the informed consent process, patients may have become knowledgeable about the beneficial effects of EPA and changed their diet by consuming EPA-rich foods. In the placebo group, the arachidonic acid/EPA ratio fell by 4.0 points during the study. This is a large decrease, indicative of a substantial change in diet. In our dose-ranging study, we observed a similar decrease in the arachidonic acid/EPA ratio (–4.2) in the group of patients given 1 g/day of ethyl EPA (6). The original data of Dr. Fenton et al. (1) do show that red cell EPA levels rose significantly ($p<0.05$) in the placebo group. The placebo patients may therefore have increased their EPA intake by a suboptimal but still beneficial level, while the actively treated patients may have received too much. This may explain why both groups improved.

The study's failure may have been due to a combination of an insensitive trial design, a blocking effect of standard drugs, too high a dose of ethyl EPA in the active group, and a dietary increase in EPA in the placebo group. Further studies are required, particularly with lower doses of ethyl EPA in otherwise untreated patients, before any firm conclusions can be drawn. Such studies are important because ethyl EPA is so well tolerated. Of 43 patients receiving ethyl EPA, only six (14%) dropped out during the 16-week study—none because of side effects. In the dose-ranging study of depression (8), only 12% of the patients taking any ethyl EPA dropped out, while in the dose-ranging schizophrenia study (6), only 11% dropped out. These dropout rates are much lower than those seen with standard antidepressant or antischizophrenia drugs. Even a modest beneficial effect would be valuable if produced by such a safe drug.

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Dr. Fenton and Colleagues Reply

TO THE EDITOR: We share Dr. Horrobin's disappointment that 3 g/day of ethyl EPA added to a current antipsychotic medication regimen was no more effective than placebo in reducing residual symptoms and cognitive deficits in patients with schizophrenia. In agreement with Dr. Horrobin, we indicate that potential explanations for our failure to find a therapeutic effect might include 1) the relative illness duration and severity of our study group, 2) inadequate or excessive doses of ethyl EPA, 3) an inadequate duration of treatment, or 4) ineffectiveness of the putative therapeutic agent. On the other hand, we do not concur that "it is unlikely that any standard drug would show benefit in a trial with this add-on design." Add-on designs such as this have demonstrated the benefit of many augmentation strategies, including lithium augmentation of antidepressants (1), D-cycloserine augmentation of conventional antipsychotic agents for negative symptoms in schizophrenia (2), and pindolol augmentation for patients with treatment-resistant panic disorder (3). Contrary to Dr. Horrobin's contention, if the hypothesis under consideration is that supplemental therapy is beneficial to patients with residual symptoms and deficits despite adequate treatment with standard approaches, a double-blind placebo-controlled add-on study would appear to be the only appropriate experimental design to rigorously assess the hypothesis. Finally, in our view, our failure to find any correlation between changes in the arachidonic acid/EPA ratio and improvement in clinical dependent variables renders unlikely the hypothesis that a diet change in the placebo-treated group explains improvement in both groups. Given that the bulk of the placebo effect for both groups was seen in the first 2 weeks of treatment, however, we recommend that future studies consider using a single-blind placebo lead-in period. Further research will be needed to clarify the potential use of ethyl EPA in schizophrenia and other neuropsychiatric conditions.

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Underuse of Antidepressants

TO THE EDITOR: Tanja Laukkala, M.D., Ph.D., and colleagues (1) reported underuse of antidepressant medications in the Finnish population. Only 13% of the respondents with an episode of major depression in the preceding year, according to the Composite International Diagnostic Interview Short Form, were taking antidepressant medications at the time of the interview.

Unfortunately, Dr. Laukkala et al. did not report the total proportion of subjects using antidepressants. According to a recent Canadian health survey, the National Population Health Survey (2), which also employs a national probability sample, this proportion was 4.0%. Of note, of those with an apparent episode of depression on the Composite International Diagnostic Interview Short Form in the previous 12 months in the Canadian survey, 27.1% (weighted) reported antidepressant use in the preceding month (2), which is reasonably consistent with the results reported by Dr. Laukkala et al. The estimated 30-day point prevalence of major depression in the National Comorbidity Survey was 4.9% (3), so a 4.0% rate of antidepressant use does not suggest drastic underuse. It seems strange that antidepressants should be so frequently used yet paradoxically appear to be underused to such a great extent. In view of this, an interpretive point is worth raising. The 13% rate of antidepressant use reported by Dr. Laukkala et al., like the 27.1% rate reported elsewhere, represents the proportion of individuals with a recent episode of major depression who were currently taking antidepressants. This should not be confused with the proportion who need treatment and are receiving it. Many who have had a successful outcome of antidepressant treatment more than 12 months previously are removed from estimates of this type.

In the National Population Health Survey, of 668 subjects with an episode of major depression (in the preceding year), 194 reported antidepressant use, compared to 482 of 14,108 subjects without a major depressive episode. As expected, the rate of use was much higher in those with a depressive episode, but the fact remains that over 70% of those taking antidepressants had no episodes of major depression in the preceding year. A proportion of these subjects may derive from the 15%–20% of the population with lifetime major depression (3), some of whom have successfully achieved control of their depressive disorders by using antidepressant medications. Such success is not reflected in the 27.1% use rate reported. To illustrate this point, suppose that 10 of 50 persons with active major depression are found to be taking antide-

pressants in a survey with a group size of 1,000. The estimation approach of Dr. Laukkala et al. would put the use rate at 20%. However, if another 50 of the remaining 950 members of the population (who were not depressed in the last year) had recurrent major depression that is successfully controlled by medications, then an alternative way of depicting use would be to estimate it at 60 of 100, or 60%.

Psychiatric epidemiologists will need to develop methods to estimate the adequacy of antidepressant use that can account for the various ways in which antidepressants can improve mood status, including inducing and sustaining remission.

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Drs. Laukkala and Colleagues Reply

TO THE EDITOR: We thank Drs. Patten and Beck for their interest in our article and for an opportunity to discuss our study in more detail. We found that in 1996 in Finland, of the subjects with a major depressive episode during the previous 12 months, only 13% (among the 25% with a current major depressive episode) were taking antidepressant medications. These results are comparable with those from an Australian general population study by Goldney et al. (1), in which 19% of the subjects with a current major depressive episode in 1998 were currently taking antidepressants. In a multinational European telephone survey comprising general population samples from 1993 to 1997 (2), 7% of those with current depressive disorders were currently taking antidepressants.

The unadjusted point prevalence of antidepressant use in Finland in 1996 in our study was 2.6% (158 of 5,993), information that we omitted from our article because of space limitations. This is concordant with the Finnish antidepressant reimbursement statistics for 1996 (3), which suggest a 2.3% point prevalence for antidepressant use. For comparison, the multinational European survey (2) reported point prevalences of about 1% for antidepressant use. The Canadian figures by Drs. Patten and Beck appear high to us but may be explained by a higher level of antidepressant use in Canada during the time period investigated (not specified) or by methods differences. One of these differences is that we reported current use, and Drs. Patten and Beck report use in the preceding month—a longer time period.

In our study, 44% of those taking antidepressant medication had a major depressive episode during the preceding 12 months; half (56%) of the antidepressant users took antidepressant medication without a major depressive episode during the preceding year. What proportion of these subjects was receiving antidepressants for continuation and maintenance treatment of depression and what for other possible indications remains unknown. In a survey of primary health care antidepressant use in Helsinki, Finland, in 1995 (4), about 75% of antidepressants were prescribed for depression. In the multinational European survey (2), the proportion of use for depression was even lower (44%). Since not all antidepressants are used for the treatment of depression, we do not find the calculations by Drs. Patten and Beck to be well founded.

Nevertheless, we agree with Drs. Patten and Beck on the need for improved methods in estimating need for antidepressant treatment. As the use of antidepressants is steadily rising, the pharmaco-epidemiology of their use is a moving target. In Finland, we are currently working with the data from the large Health 2000 Survey, which will provide information about antidepressant use for depressive and anxiety disorders in the country for 2000–2001.

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Problems With Odds Ratios

TO THE EDITOR: Gregory B. Bovasso, Ph.D. (1), compared 15 individuals who met DSM-III-R criteria for cannabis abuse with 834 individuals who did not and concluded that for those who met the criteria, the risk of onset of depressive symptoms was 4.49 times greater or, after adjusting for covariates, 4.00 times greater. Neither statement is correct. The 4.49 figure and the 4.00 figure are odds ratios, which have a well-known propensity to exaggerate relative risk (2, 3). In this case, the odds ratios are at least a twofold exaggeration of the relative risk, which I calculate to be 2.16—(10/15)/(257/834).

Odds ratios may be useful in retrospective case-control studies (in which the incident rate of meeting the criteria is unknown) (4); however, this study had a longitudinal cohort design. Odds ratios are also useful in logistic regression, but when estimates from a logistic regression are reported, they should be clearly identified as odds ratios. In this article, the abstract stated only that depressive symptoms were "four times more likely" (p. 2033); there was no mention of odds ratios or logistic regression. Even when logistic regression is used, there is a method for converting the odds-ratio estimates to relative risks (5). For this study, the method yielded a covariate-adjusted relative risk of 2.08, with a 95% confidence interval of 1.15–2.77.

None of this will be apparent to readers who see only the abstract. Additionally, since the abstract mentioned Ns of 1,920 (the entire group), 849 (the subjects with no depressive symptoms at baseline), and 1,837 (the subjects with no cannabis abuse at baseline), readers who see only the abstract will be unaware that the N for the group of interest—the group for which the article was named—is 15. The work described in the article is interesting, and the findings may be important. However, they merit more careful reporting.

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TO THE EDITOR: In the post hoc analysis section of his article, Dr. Bovasso identified the significant baseline covariates for the incidence of suicidal ideation. It is obvious that the risk set Dr. Bovasso used to calculate the incidence rate was the population that was free from a history of any of the nine depressive symptoms in the DSM-III depression module. However, the method for determining the risk set (denominator) of this analysis was not necessarily appropriate. Instead of excluding all of the Epidemiologic Catchment Area (ECA) participants with any baseline depressive symptoms from the post hoc analysis, only participants with a history of suicidal ideation should have been excluded. Under this definition, 1,708 ECA participants—instead of 849—would have been susceptible to the incidence of suicidal ideation. In an analysis by my colleagues and me (1), also of the Baltimore ECA sample, 89 participants reported new onset of suicidal ideation. Among all of the sociodemographic covariates, only age was significantly associated with the incidence of suicidal ideation (odds ratio=0.96, confidence interval [CI]=0.94–0.98; Wald χ^2=16.2, df=1, p<0.001). Gender and race were not associated with suicidal ideation (1). However, our analysis did find that cannabis use at baseline was associated with the incidence of suicidal ideation; cannabis abusers were three times as likely to develop suicidal ideation as were nonabusers (odds ratio=3.00, CI=1.46–6.18; Wald χ^2=8.9, df=1, p<0.01). Even after adjustment for the baseline diagnosis of any depressive episode, cannabis abuse remained a significant risk factor for new onset of suicidal ideation (odds ratio=3.14, CI=1.52–6.50; Wald χ^2=9.6, df=1, p<0.01; data not published).

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Dr. Bovasso Replies

TO THE EDITOR: I agree with Dr. Epstein that relative risk provides a more accurate estimate of the risk of depressive symptoms in cannabis abusers than the odds ratio in the context of the ECA follow-up study. The odds ratio typically provides an unbiased estimate of the relative risk but provides a less biased estimate of risk when the predicted condition is not infrequent (1). The incidence of any depressive symptoms in the study in question was much higher than expected (31%) and explains the difference between the relative risk and odds ratio.

However, I disagree with Dr. Epstein's contention that the use of odds ratios in logistic regression analysis was not clearly stated. Throughout the article, seven odds ratios derived by logistic regression analysis were reported. Dr. Epstein's concern appears to be that the abstract makes "no mention of odds ratios or logistic regression." This concern underscores the importance of readers actually reading articles, rather than just abstracts, which are abbreviated out of editorial necessity.

I disagree with Dr. Kuo, who states that the risk set defined in my article was not appropriate. The risk set that I defined as consisting of individuals without depression is appropriate for the article, whose a priori hypothesis concerned the incidence of depressive symptoms, which includes suicidal ideation and anhedonia, among others. The alternative risk set proposed by Dr. Kuo, which consists of individuals without prior suicidal ideation, is appropriate for a study examining the incidence of suicidal ideation in general, such as what he referenced (Kuo et al., 2001). However, it is not appropriate for a study more strictly focusing on suicidal ideation only as a symptom of depression. The post hoc analysis in question was intended to clarify an analysis based on an a priori hypothesis regarding the degree to which individuals without depression symptoms later manifested any depression symptoms that included, but were not limited to, suicidal ideation. The proposed use of a risk set in the post hoc analysis other than that used in the a priori analysis would not clarify the risk of a particular depression symptom among those without depression symptoms at baseline (N=849). The proposed alternative risk set of individuals without suicidal ideation at baseline (N=1,708) would include individuals with other depression symptoms at baseline and would confuse rather than clarify the estimation of the incidence of depression symptoms in total or individually.

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Consolidated Standard of Reporting Trials Guidelines

TO THE EDITOR: We read with great interest the article by Lorrin M. Koran, M.D., and his colleagues (1) that examined the effects of 28 weeks of double-blind placebo-controlled medication maintenance after 52 weeks of single-blind sertraline treatment.

A randomized controlled trial, more than any other method, can have a powerful impact on patient care and is accepted by medicine as an objective scientific method and, if ideally performed, produces knowledge untainted by bias.

However, it can be flawed in design and is not immune to bias. The relevance of such studies has been criticized on the grounds of selection bias and use of the placebo arm.

Although the selection of patients is known to be a powerful factor affecting the results of clinical trials, little is known about recruitment issues. Many patients who are screened for a clinical trial are ultimately not included in the study. In this study, the authors gave an account of all the patients who dropped out but failed to provide information about how many subjects were initially assessed, how many were excluded, and the reasons for exclusion. We do not have any idea how many subjects responded to the advertisements and what was the participation rate, which has implications for generalizability and future research. In this context, the Consolidated Standard of Reporting Trials (CONSORT) guidelines state that all patients assessed for a trial should be accounted for and that the report should be accompanied by a diagram that explains what happened to all of the patients involved in the trial (2). The authors failed to follow the CONSORT guidelines in this regard.

Placebo-control design raises questions of deception, the withholding of patient information, informed consent, the unblinding of such information, and the withholding of active treatment by randomly allocating trial medication. In this context, the Declaration of Helsinki demands that individual patients in a study be assured of the best proven diagnostic and therapeutic methods, even in the control group (3). This statement discards the use of a placebo group as a control group when a proven treatment exists. In this study, one group of patients received no treatment (placebo) for more than 28 weeks when there were a number of control group options that could have fulfilled ethical and scientific needs.

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Dr. Koran and Colleagues Reply

TO THE EDITOR: We appreciate the comments of Drs. Jainer and Onalaja. We support the CONSORT group's recommendation that the disposition of all patients considered for a trial be reported (and the other CONSORT recommendations [Begg et al., 1996]). These recommendations were published 3 years after we began our trial in 1993—too late to influence our data-gathering procedures.

The proper use of placebo controls remains a contentious issue (1). Most regard their use as ethical if no increase in mortality and no irreversible morbidity are expected (1). Critics argue they should not be used once the efficacy of one treatment is confirmed. The use of placebo controls in our study met both ethical tests. Our study did not entail risks of mortality or irreversible morbidity. Moreover, ours was the first controlled study of medication discontinuation after 12 months of successful treatment of obsessive-compulsive disorder (OCD). Whether to continue effective anti-OCD medication beyond this point in patients doing well was an important unanswered clinical question when our study began. As we noted, uncontrolled studies suggesting substantial relapse rates involved much shorter treatment periods before discontinuation. We found that, compared to continued treatment with sertraline, discontinuation was associated with markedly higher rates of acute symptom exacerbation, insufficient clinical response, and deterioration in the quality of life. This knowledge can improve treatment, since these risks can now be presented to patients when they weigh the cost and risks (e.g., side effect rates) of continuing medication. The study investigators' sensitivity to the best interests of the study patients was evidenced by the fact that few were allowed to meet the a priori relapse criterion—substantial symptom exacerbation observed at three visits over 1 month. Most patients discontinued from the study by investigators were discontinued for insufficient clinical response after one visit or after two visits over 2 weeks. Finally, although the Declaration of Helsinki stipulates that the appropriate test of a new treatment is against the best current treatment, when our study was designed, the best current maintenance treatment for OCD was unknown. Moreover, the National Depressive and Manic Depressive Association, which is the largest patient-directed organization in the mental health field, has issued a consensus statement that delineates considerations for the appropriate use of placebo controls (2). The consensus panel included clinical researchers, biostatisticians, bioethicists, and consumers. Our study design met the ethical tests expressed in that document.

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