

## Muscle Dysmorphia

**Sir:** Body dysmorphic disorder (BDD), a preoccupation with an imagined or slight defect in appearance, is receiving increasing clinical and research attention.<sup>1</sup> Although most individuals with BDD are preoccupied with a particular body part (e.g., nose, skin, hair), some are preoccupied with their entire body, thinking it is too small and insufficiently muscular.<sup>2</sup> This concern—sometimes colloquially referred to as *bigarexia* by body builders and previously termed *reverse anorexia*<sup>3</sup> in the literature—is perhaps more accurately called *muscle dysmorphia*. We describe a striking example of how this little-recognized form of BDD manifested by compulsive weightlifting may cause serious social, occupational, and even physical impairment.

**Case report.** Mr. A, a 23-year-old single white unemployed car mechanic, presented with a chief complaint of “I’m obsessed with working out.” At age 18, when his brother joined a gym, Mr. A became preoccupied with the idea that his body was too small and inadequately muscular (he was 6 ft 1 in [187.3 cm] tall and weighed 185 lb [83.99 kg]). Previously, from age 15 to 18, he had been preoccupied with his supposedly pale and “ghostly” skin, which he darkened by severely burning it. At times, Mr. A realized that his body build was normal, but at other times was convinced that he looked too small. He stated, “I was consumed with being big. I wanted to be stronger, bigger, less weak, and more masculine. I wanted to be the biggest person on the planet!”

To “bulk up,” Mr. A ate large amounts of food, took vitamins, and drank high-protein drinks. He also frequently checked his appearance in mirrors, compared himself with others, padded his clothes, and wore extra shirts. He tried to steer conversations toward discussions of body size, hoping that people would say he looked big. He repeatedly denied use of steroids to three different psychiatrists.

To increase his body size, Mr. A lifted weights for up to 8 hours a day. He lifted in his basement because he was too self-conscious about his “small” size to exercise in a gym. Eventually, Mr. A weighed more than 230 pounds (albeit with some body fat) and was able to bench press 410 pounds, but he still believed he was not big enough. On several occasions, he did not leave his house for 6 weeks, spending most of his time in his basement lifting weights and feeling suicidal over his appearance. Because of his obsessional focus on his body build and his inability to leave the house without excessively exercising, Mr. A missed most social events, lost most of his friends, dropped out of college, and went on disability. He also developed chronic pain that made him unable to play sports or exercise and required physical therapy; he also sometimes needed a crutch to walk.

On the Structured Clinical Interview for DSM-III-R, Mr. A received a past diagnosis of major depression. He reported a family history of panic disorder and possible motor tics in his brother.

Mr. A received clomipramine, up to 250 mg/day, which led to a moderate decrease in his appearance obsessions. He also exercised significantly less. While his decreased exercising was due in part to his physical injuries, Mr. A stated that the medica-

tion helped him resist the urge to excessively exercise and tolerate not exercising. Nonetheless, he continued to do leg exercises for nearly an hour a day, stating that he was unable to give up exercising altogether.

This case is important because—in contrast to previous reports of muscle dysmorphia among anabolic steroid abusers<sup>4</sup>—it illustrates that this form of BDD can also occur in individuals who do not use steroids. Mr. A’s repeated denial of steroid use, in settings in which he would have derived no particular secondary gain from such denial, supports the likelihood that he did not use steroids. This case also illustrates the extent to which this underrecognized form of BDD can interfere with functioning. In addition, Mr. A’s partial response to clomipramine is consistent with data from uncontrolled studies suggesting that serotonin reuptake inhibitors may be effective for BDD.<sup>2,5</sup> Given the severe impairment that muscle dysmorphia can cause, its clinical features and treatment response deserve further study.

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## Antiepileptic Drug Augmentation for Treatment-Resistant Depression

**Sir:** The recent case report by Ketter, Callahan, and Post<sup>1</sup> illustrating a positive therapeutic drug/drug interaction for treatment-resistant anxious depression is an example of outstanding psychopharmacologic strategizing. The authors explain their successful outcome, achieved when nefazodone was added to alprazolam, with a pharmacokinetic model, hypothesizing that nefazodone extended the duration of action of alprazolam through inhibiting its degradation by the cytochrome P450 3A3/4 system, thereby eliminating “interdose dysphoria.”

Although this is certainly a reasonable and attractive rationale that should have general applicability, I would like to suggest an alternative, based on the following line of reasoning.

1. Not one in the series of antidepressant medications that failed with this patient has antiepileptic properties. Indeed, all antidepressants currently available in the United States are, to some extent, proconvulsant (Feiner NF. Manuscript in preparation).
2. Carbamazepine, which also failed, although an excellent antiepileptic drug that has been widely used for bipolar illness, largely due to the work spearheaded by Post, is only a moderately effective antidepressant at best.<sup>2</sup>
3. I have found, over more than 5 years with several hundred patients, and confirming the earlier observations of others,<sup>3</sup> that—with patients who have subtle symptoms consistent with ongoing partial complex seizures and/or who have paroxysmal EEGs—augmentation of an antidepressant with an antiepileptic drug can lead to relief of depression for which the antidepressant alone had proved ineffective (Feiner NF. Manuscript in preparation).
4. Thus, it can be argued that the key to success in this patient was that with the nefazodone/alprazolam combination, *the epileptogenicity of the antidepressant component was, for the first time, offset by an antiepileptic drug.*

The logical extension of my argument is that certain forms of epilepsy can present as depression. To be sure, no evidence either for or against subclinical epilepsy was given in this case report. Furthermore, Post has not only repeatedly gainsaid the notion that epilepsy screening can predict antiepileptic drug response but has eloquently challenged an ictal basis for affective illness.<sup>3</sup>

Nonetheless, I believe that my conjecture is a reasonable one, ultimately testable, and, moreover, it suggests new strategies for treatment-resistant depression and, as well, the intriguing possibility that there will be identified a single drug that is simultaneously both an antidepressant and an antiepileptic.

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#### Dr. Ketter and Colleagues Reply

**Sir:** We appreciate Dr. Feiner's stimulating comments. We wish to clarify that the patient in our report<sup>1</sup> was taking benzodiazepines (primarily alprazolam, but in some cases clonazepam) to control anxiety during several of the antidepressant trials, and in each case, tapering the benzodiazepine resulted in increased anxiety and depression. Thus, the nefazodone plus alprazolam combination was but one of several trials that combined antidepressants with drugs (benzodiazepines) having anticonvulsant properties. Hence, it seems unlikely that opposing the putative proconvulsant effects of the antidepressants with a drug (benzodiazepine) with anticonvulsant properties was crucial to this patient's improvement. Nevertheless, Dr. Feiner raises several

important issues regarding possible relationships between depression, epilepsy, antidepressants, and antiepileptic drugs.

First, he suggests that all antidepressants available in the United States are to some extent proconvulsant. However, for some antidepressants, there are only extremely weak and limited data supporting proconvulsant effects.<sup>2</sup> This is an extremely complex issue, since drugs may have biphasic effects and be anticonvulsant at low doses and proconvulsant at high doses. For example, in animals, low and high doses of imipramine may have biphasic anticonvulsant/proconvulsant<sup>3</sup> anticonvulsant/proconvulsant<sup>4</sup> properties. Moreover, in humans, imipramine at low doses may have anticonvulsant effects for certain seizure types,<sup>5,6</sup> yet in therapeutic doses and to a greater extent in overdoses can cause seizures.<sup>2</sup>

Second, Dr. Feiner notes that augmentation of antidepressants with antiepileptic drugs can improve mood in some patients, and that the mechanism could be related to obtaining a balance between the putative proconvulsant properties of antidepressants and the anticonvulsant properties of antiepileptic drugs. However, the possible mechanisms of this observed clinical improvement are varied and could include effects other than direct opposition of anticonvulsant and proconvulsant effects. For instance, valproate can increase amitriptyline levels and thus could yield enhanced affective responses based on a pharmacokinetic interaction.<sup>7</sup> On the other hand, valproate also enhances GABAergic neurotransmission, and accumulating evidence suggests that this pharmacodynamic effect could be related to affective improvement.<sup>8</sup> Indeed, a new generation of antiepileptic drugs that enhance GABAergic (inhibitory) and/or diminish glutamatergic (excitatory) effects may offer new agents as candidates for treatment of mood disorders.<sup>9</sup> We have reported synergistic antidepressant effects by combining valproate and carbamazepine,<sup>10</sup> which are better explained by synergistic biochemical effects than opposing anticonvulsant and proconvulsant effects. As the biochemistry of epilepsy and antiepileptic drugs is better understood, specific biochemical models (particularly excitatory vs. inhibitory neurotransmission) may prove more helpful than general proconvulsant versus anticonvulsant models.

Third, Dr. Feiner notes that psychosensory symptoms may predict positive affective responses to antiepileptic drugs and that certain forms of epilepsy can present as depression. Psychosensory symptoms clearly occur in mood disorder patients, but not all investigators agree that they predict responses to antiepileptic drugs (Ali SO, Denicoff KD, Ketter TA. Manuscript submitted). Electrical disruption of large groups of neurons (i.e., a "subictal" seizure-like process) in mood disorders is not the only possible explanation for the psychosensory symptom overlap. It is also possible that electrical (seizure) and biochemical (neurotransmitter dysregulation) processes in the same paralimbic structures could yield psychosensory symptoms in seizure and mood disorders, respectively. Put another way, a neuroanatomical rather than a mechanistic overlap could explain the symptomatic overlap. Thus, just as frontal lobe dysfunction (hypofrontality), which occurs in primary depressions, as well as depressions secondary to epilepsy, Parkinson's disease, and Huntington's disease may provide a final common pathway for depressive symptoms,<sup>11</sup> paralimbic dysfunction could explain the occurrence of psychosensory symptoms due to either biochemical or electrical disruptions. Thus, we feel that an attractive explanation for the overlaps of both affective and psychosensory symptoms in epilepsy and mood disorders is that these disorders entail disruption of similar brain regions that mediate affective and sensory experiences. This model is consistent

with the established notion of regional specialization of brain functions and does not entail invoking the unsubstantiated notion that a low-grade epileptiform disturbance underlies primary mood disorders.

Finally, we agree with Dr. Feiner's conclusion that single drugs may be found that are both antidepressant and anticonvulsant. Indeed, preliminary data suggest that lamotrigine could ultimately prove to have such a profile.<sup>12</sup>

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#### Cost-Effectiveness of Divalproex Versus Lithium

**Sir:** We read with interest the recent application by Keck et al. of pharmacoeconomic analysis to the treatment of bipolar disorder.<sup>1</sup> Their study suggested that divalproex was more cost-effective in treating mixed and rapid cycling manic states, that lithium was more cost-effective in treating classic mania, and that divalproex was more cost-effective when mixed, rapid cycling, and classic mania were combined. Like Keck et al., we noted the sensitivity of the model to assumptions about the length of stay (LOS) for divalproex versus lithium. The shorter LOS for divalproex compared with lithium (4.1 days shorter) more than offset the higher cost of divalproex. We agree with the authors that the differences in the model LOSs for divalproex versus lithium probably reflect the more rapid

achievement of therapeutic drug blood levels by the oral loading of divalproex (20 mg/kg/day) compared with standard empiric lithium titration.

The question we raise is whether the evidence is clear that lithium cannot be dosed more quickly than the standard empiric titration technique and, if a more rapid dosing technique is possible, whether this may alter the conclusions about the relative cost advantages for divalproex over lithium. Although rapid lithium dosing is not widely practiced, a number of predictive dosing techniques have been reported that allow more rapid dosing than the standard empiric technique,<sup>2-4</sup> and one technique for actual loading of lithium has been reported.<sup>5</sup> These techniques could benefit from further research, especially studies addressing concerns about tolerability of the rapid lithium-dosing methods.<sup>6</sup> However, with some of the already existing predictive dosing techniques, the investigators have reported more rapid achievement of therapeutic lithium levels in the absence of toxicity<sup>7</sup> or overdosing.<sup>8,9</sup> Indeed, in one study, the predictive dosing technique surprisingly resulted in fewer side effects than empiric dosing of lithium.<sup>10</sup> There appears to be very little published research commenting on shortening LOS with predictive lithium dosing compared with empiric dosing. In the one study of which we are aware, one technique of predictive dosing versus empiric dosing resulted in a 3-day shorter LOS in an acute care ward, although in that study the difference in LOS was not statistically significant.<sup>10</sup>

We suggest that predictive lithium dosing techniques deserve further study. If hospital LOS during initiation of lithium treatment can be decreased with predictive lithium dosing, then the major reason for the cost advantage of divalproex over lithium in the Keck et al. model would be lessened and could be outweighed by the higher cost of divalproex.

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### Dr. Keck and Colleagues Reply

**Sir:** We appreciate the comments and questions raised by Drs. Baker, Sernyak, and Woods. We agree that it is far from clear as to whether lithium can be administered more quickly than the standard titration techniques common in clinical practice. In addition to the small body of literature regarding rapid dosing of lithium that they reviewed, another report of "rapid lithiumization"<sup>1</sup> has recently come to our attention. In this study, Moscovich et al. reported rapid reduction of manic symptoms in the majority of patients within 1 week and good tolerability overall. In contrast, we found that most (6/8) patients developed intolerable gastrointestinal side effects when administered lithium carbonate at a dose of 30 mg/kg/day (unpublished data).

We agree that the predictive lithium dosing techniques deserve further study. One such study design might examine the comparative efficacy, time course of response, tolerability, and impact on length of stay of lithium standard titration, lithium loading, valproate standard titration, and valproate loading. The results of such a study could provide further data regarding the economic impact of these treatment approaches.

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### Clozapine Use in Two Full-Term Pregnancies

**Sir:** The treatment of pregnant patients who have schizophrenia is a therapeutic dilemma since all antipsychotic medications have at least occasionally been implicated in the development of fetal abnormalities and are classified as Pregnancy Category C.<sup>1-4</sup> We report the cases of two women with treatment-resistant schizophrenia who received clozapine during all three trimesters and delivered at term.

**Case 1:** Ms. A, a 30-year-old white woman (gravida 6, para 3) with a long history of treatment-resistant chronic paranoid schizophrenia, was admitted to an inpatient psychiatric unit with increased delusional behavior during approximately her 23rd week of pregnancy. Ms. A had been started on clozapine treatment 17 months before admission and was currently taking 300 mg/day, but was noncompliant for 2 weeks before admission. During hospitalization, Ms. A received at least one dose of the following medications: lorazepam, haloperidol, acetaminophen, guaifenesin, magaldrate, aluminum/magnesium hydroxide, cephalexin, metronidazole, acetaminophen with codeine, multivitamin with folate, and clozapine titrated to 350 mg/day. Before hospitalization, Ms. A had taken lithium during the first trimester; however, the number of doses she received is unknown.

During the delivery of the female infant at 39 weeks gestational age, Ms. A was uncooperative, and vacuum extraction with gentle traction was used. At birth, the infant weighed 3800 g and had the following vital signs: temperature 36.9°C,

pulse 128 bpm, and 16 respirations per minute. Her Apgar scores were 8 at 1 minute and 9 at 5 minutes, and arterial cord pHs of 7.27 and 7.30, respectively. Abnormal findings at birth included a cephalhematoma, hyperpigmentation folds, and a coccigeal dimple, all of which were resolving at the time of discharge 2 days after delivery.

The infant reportedly experienced a seizure 8 days after delivery that resulted in hospitalization. Results from a postseizure physical examination, serum chemistry, lumbar puncture, and EEG suggested the infant did not have a seizure disorder. The results from a 1-hour intraluminal esophageal pH study (Tuttle test)<sup>5,6</sup> were positive. The Tuttle test is used to detect gastroesophageal reflux and consists of four 15-minute tests that measure esophageal pH while the infant is in four different positions: supine head-elevated, supine flat, prone head-elevated, and prone flat.<sup>5,6</sup> During the hospitalization, the infant developed diarrhea and the treating physicians felt the results of the Tuttle test were unreliable due to the infant's age and the apparent development of gastroenteritis. No treatments were administered, and the infant was discharged after 3 days with a diagnosis of gastroenteritis and possible mild gastroesophageal reflux. At the time of this report, the child is 2 years old and is doing well and has no physical problems.

**Case 2:** Ms. B, a 32-year-old white woman (gravida 2, para 1) with a long history of treatment-resistant chronic undifferentiated schizophrenia, had been treated with clozapine, 600-625 mg/day, for 35 months in combination with lithium prior to learning of her pregnancy. Medication noncompliance was a problem, and she was only partially compliant before becoming pregnant. Hospitalization was not required despite an increase in social isolation, poor insight and judgment, and delusional behavior. Clozapine was continued at 600 mg/day with a subsequent increase to 625 mg/day, while lithium was discontinued at the discovery of her pregnancy during the first trimester.

During the delivery of the female infant at 40 weeks gestational age, Ms. B became uncooperative, requiring the use of outlet forceps, moderate traction, and general anesthesia. No other difficulties with delivery were noted. The birth weight of the child was 2510 g, and Apgar scores were 8 at 1 minute and 9 at 5 minutes. The child developed a postpartum low-grade fever that resolved prior to discharge. No other abnormalities were noted.

In both cases reported here, psychotic symptoms developed and intensified during pregnancy. Clinical judgment determined that failure to treat the patients' symptoms of schizophrenia presented a greater risk of harm to "self and fetus" than maintaining treatment with clozapine or other antipsychotics.

Despite the success of the births we report here, several questions were raised concerning the safety of using clozapine during pregnancy, because it crosses the placental barrier.<sup>7</sup> The primary concern was the development of a seizure in Ms. A's child. Given the underdevelopment of hepatic metabolism in the fetus, clozapine could potentially accumulate in fetal serum and increase the potential for clozapine-associated adverse effects such as seizures.<sup>7,8</sup> The possibility also exists that the seizure is related to a withdrawal phenomenon, since the reported seizure occurred 8 days after delivery. The infant reportedly has suffered no long-term sequelae from the seizure and has experienced no further seizure activity.

Clozapine is currently classified as FDA Pregnancy Category B, indicating no animal studies have found a teratogenic effect, but that human studies have not been performed.<sup>1,9</sup> In our two cases, no teratogenic effects were reported. While the potential exists for teratogenic effects, our case findings are encouraging. However, caution should be used in the interpretation of these results because the baseline rate of congenital malformations is

estimated to be 2.0% to 2.5% in the general population, and therefore thousands of similar reports would be required to confirm our findings with significant power.<sup>10</sup>

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#### Nefazodone and Neurotoxicity

**Sir:** I would like to comment on the case report "Nefazodone and Symptoms Suggesting Neurotoxicity: A Case Report,"<sup>1</sup> which raised the possibility of dose-related neurotoxicity with nefazodone and emphasized the need to pay close attention to all possible drug interactions.

While speculation was made on the possible interactions with carbamazepine and cyclobenzaprine, the authors failed to discuss possible interactions with risperidone even though the patient took carbamazepine, cyclobenzaprine, and risperidone in addition to nefazodone.

As was described in their letter, nefazodone is a potent inhibitor of cytochrome P450 3A4 isoenzyme and a weak inhibitor of cytochrome P450 2D6 isoenzyme, and it is highly protein bound. The inhibition of P450 2D6 isoenzyme by nefazodone and the protein-bound mechanism could have raised the risperidone level, and this may have been pertinent if the patient was a poor metabolizer of risperidone. Examination of blood plasma

levels of risperidone and 9-hydroxyrisperidone could have resolved this issue.

The ataxia, lethargy, confusion, and word-finding difficulty that their patient developed could at least partly be explained by interactions with risperidone in combination with carbamazepine and cyclobenzaprine.

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#### Drs. Puzantian and Shaw Reply

**Sir:** Dr. Yong's comments regarding our letter<sup>1</sup> raise the interesting issue of the potential for an interaction between nefazodone and risperidone via inhibition of the cytochrome P450 2D6 isoenzyme, leading to increased levels of risperidone. Interaction studies of nefazodone with the triazolobenzodiazepines triazolam and alprazolam, both metabolized by cytochrome P450 3A4, have revealed substantial and clinically significant increases in plasma triazolobenzodiazepine concentrations.<sup>2,3</sup> Only the benzodiazepines metabolized by the 3A4 isoenzyme have a potential interaction with nefazodone.<sup>2,3</sup> The benzodiazepines metabolized by other isoenzymes or by glucuronidation should not be affected when used concomitantly with nefazodone.<sup>2,3</sup> This distinction is probably due to nefazodone's potent inhibition of 3A4 and extremely weak (and apparently clinically insignificant) inhibition of 2D6.<sup>2,3</sup> Although it is theoretically possible that nefazodone may increase risperidone levels because of 2D6 inhibition, it is unlikely since such inhibition is extremely weak. It is because of this difference in inhibition potency that our discussion centered on the possible 3A4-mediated interactions with carbamazepine and cyclobenzaprine. In addition, we believe that the adverse effects caused by increased serum levels of risperidone would generally include evidence of extrapyramidal symptoms, which were not present in our patient.

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