

Letters to the Editor

Manufacturer Support and Outcome

Sir: In reading the *Journal* over the past years, I have found that articles examining specific medications are frequently funded by the manufacturers of those medications, a fact accessible in the small print at the beginning of each article. I have wondered what sort of relationship might be found between support of research and favorable outcome.

To examine this question, I reviewed all regular issues of the *Journal* for the year 1997, not including supplements, which are largely sponsored by pharmaceutical companies. I identified all articles that studied outcome or tolerability for a specific agent and separated them according to their support by the manufacturer or absence of such support, as listed at the front of the article. I then rated outcome in each article as favorable or unfavorable with respect to the manufacturer's drug. I also identified the presence or absence of placebo control, as a rough indication of the quality of the research design. My results are shown in Table 1.

Table 1. Manufacturer-Supported Versus Unsupported Research Articles Published in the *Journal* in 1997

Status	Favorable	Unfavorable	Placebo-Controlled
Supported	16	0	5
Unsupported	10	6	3

The data demonstrate that support by a manufacturer correlates with favorable outcome of the reported study. Conversely, lack of support makes it much more likely that the study will not reflect favorably on the use of the medication. In other words, it is more likely for pharmaceutically sponsored trials to show data that are favorable to the drug studied than studies that are not supported by drug manufacturers. What is not clear is if there is an attempt to publish negative results. Lack of publication of negative results is of course a problem for the field, and perhaps not limited to industry-sponsored studies. It is noteworthy that a substantial percentage of the supported studies were placebo-controlled, suggesting that industry-supported research is at least as likely as nonsupported research to use a sophisticated research design. The frequency of placebo-controlled design in industry-supported research is certainly laudable and may be related to FDA requirements for new indications.

I am by no means impugning the motives or skill of any of my colleagues conducting research under the auspices of the pharmaceutical industry. I also am aware that articles in the *Journal* are reviewed by outside experts. However, I do suggest the following 3 conclusions. First, it is essential that research be funded by sources other than the manufacturer of the drug in question to maximize the chances of negative results being published. Second, when reading a report funded by a drug maker, I would keep the above data firmly in mind. Third, it would be a

service to the reader if the editors of the *Journal* would identify the sources of funding more prominently and include the relevant drugs in the identifying information (e.g., "supported by the X company, makers of Y").

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The Editor Responds

I salute Dr. Mandelkern for his astute observations and systematic analysis. He raises several interesting and timely points.

There is an ongoing debate about the role and justification of placebo controls in clinical research. Beyond controversy, however, is the fact that rigorous clinical investigation tends to be expensive, which means that someone has to fund it. Much research in psychopharmacology is funded by the pharmaceutical industry, whose primary motivation is profit. As I have noted recently, this raises the potential for bias and, in turn, demands ongoing vigilance from academic investigators.¹ Fortunately, the National Institute of Mental Health is increasing its portfolio of large-scale trials on clinically important questions. In addition, a comparatively small but increasing number of projects involving clinical psychopharmacology are being funded by private foundations.

A separate question is whether positive results are more likely to be published than negative results. In psychiatry, as in all of medicine, the answer appears to be yes. Dr. Mandelkern's observations suggest that this is even more likely when a study is funded by a pharmaceutical manufacturer. I must note, however, that a pharmaceutical company goes to great pains to construct studies that are likely to turn out in its favor. There are instances, however, when academic investigators are pressured not to publish negative findings—a phenomenon that has recently been publicized and properly condemned.²⁻¹⁰ *The Journal of Clinical Psychiatry* attempts to subject all submissions to comparably rigorous peer review—whether they are unfunded or funded by public or private monies.

The policy of the *Journal* has been and will continue to be that authors must declare sources of funding, which we then reveal to readers on the first page of the article. This is the format employed by most medical journals. I believe our readers are sophisticated enough to know or to easily find out what relevant product is manufactured by the sponsor.

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—A.J.G.

Early Augmentation of Sertraline With Methylphenidate

Sir: Augmentation of ineffective or partially effective selective serotonin reuptake inhibitors (SSRIs) with methylphenidate appears to be empirically rapid, safe, and efficacious.¹ It had been speculated that stimulants might not only augment SSRIs, but might also shorten the response latency to SSRIs if coadministered early in the course of treatment.² No controlled studies on the efficacy of an early combination of an SSRI and a stimulant have been previously reported.

We attempted to evaluate in a randomized, double-blind, placebo-controlled, parallel design whether adding methylphenidate to sertraline would result in a hastening of the antidepressant effect. We interrupted the study after a preliminary analysis of the initial 9 patients.

Our main hypothesis was that patients taking methylphenidate (5 mg b.i.d.) and sertraline (50 mg q.d.) would improve more quickly than patients taking sertraline (50 mg q.d.) and placebo, and thus show a greater response on day 7 of combined treatment. The methylphenidate and placebo were taken at 8 a.m. and 2 p.m. All patients were diagnosed with major depressive disorder according to DSM-IV³ and had not been treated with antidepressants for at least 6 weeks. In an attempt to exclude early placebo responders, we excluded patients who reported mood improvement within days rather than within weeks during previous episodes of depression. In addition, the treatment started with sertraline and placebo (single-blind) for 3 days for all patients with the intent to exclude those who would respond as determined by a decrease in score on the Hamilton Rating Scale for Depression (HAM-D)⁴ of 50% at day 3. However, none of the patients enrolled was excluded in this way.

Nine outpatients were enrolled. The protocol was approved by the Institutional Review Board of Beth Israel Medical Center, New York, N.Y. Patients gave signed informed consent. They had an average 21-item HAM-D score of 22.6 ± 5.3. Patients were randomly assigned to the active combination group (2 men and 3 women aged 24–66 years) or the control group (4 women aged 37–55).

The ratings included the 21-item HAM-D⁴ and a global assessment of functioning scale using the Social and Occupational Functioning Assessment Scale (SOFAS).³ We intended to avoid rating depression during the time when, as we have noted in our clinical experience, an acute transitory energizing effect of

methylphenidate may be observed. Due to the real-life constraints inherent to the outpatient setting, the time of the appointment was flexible. The doses of methylphenidate (or placebo) had to precede the rating by at least 6 hours. If there were fewer than 6 hours between the prescribed dose of the stimulant (or placebo) and the time of the appointment, the patients were instructed not to take the stimulant (or placebo) until the rating was completed. The latest rating took place at 5 p.m.

A full response was defined as a 50% reduction in HAM-D score and a maximum HAM-D score of 9. The sertraline dosage was increased on day 10 to 100 mg q.d. in both groups, and methylphenidate to 10 mg b.i.d. in the active group. Methylphenidate was tapered at the end of week 7, and ratings stopped at the end of week 9.

The sample was too small for statistical analysis. We had expected a clinical advantage for patients treated with the active combination. No patient showed any response by day 7 of the combined treatment. Moreover, at no time point did the active combination appear advantageous in regard to either decrease in HAM-D score or improvement in global functioning. By the end of the study (9 weeks), 2 of 4 patients taking sertraline and placebo had fully responded, whereas no patient on combined therapy fulfilled the criteria for full response. Clinical follow-up showed that all patients who did not fully respond achieved full remission at a later date, after using augmenting agents or switching to other antidepressants. The only 2 patients who withdrew from the study because of side effects belonged to the combined-treatment group. One complained (paradoxically) of unbearable somnolence and the other, a writer, of “a very unpleasant reduction in the scope of emotions.”

The results do not match the reported successful early augmentation of tricyclic antidepressants by methylphenidate.⁵ The interpretation of the data is difficult because the overall rates of response were lower than expected. This may be the result of a random selection of a particularly refractory sample, given the small number of subjects. It is unlikely that insufficient dosage contributed to the low overall rates of response, as the dosages of both methylphenidate^{2,5,6} and sertraline^{7–9} were on the higher side. We used a 100-mg q.d. final dose of sertraline, according to clinical guidelines that suggested that a majority of patients will require doses higher than 50 mg to respond.⁹ These clinical guidelines, later criticized,¹⁰ were in line with our clinical impression, but contradicted the fixed-dose placebo-controlled clinical trials, which found the 50-mg sertraline dose as effective as higher doses^{7,8} (note, however, that the probability of a type II error was high¹⁰). It is theoretically possible, although counterintuitive, that, due to some particular sequence and dose-related unfavorable interaction between serotonergic and dopaminergic neurotransmission, specific early combination of sertraline and methylphenidate we used in the study might have an efficacy lower than each medication alone. It is impossible, with a small sample and negative results, to draw definite conclusions from our report. Larger controlled studies are necessary to evaluate the efficacy of early augmentation of SSRIs with stimulant agents.

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Visual Field "Shimmering" Associated With Nefazodone

Sir: Nefazodone,¹ like trazodone,² has been associated with palinopsia (visual perseveration), an otherwise uncommon visual disturbance. I report 2 cases of a different and I believe heretofore undescribed visual disturbance associated with the use of nefazodone.

Case 1. Mr. A, a 51-year-old man treated with 600 mg/day of nefazodone (250 mg in the morning and 350 mg in the evening), described 4 episodes of a perceived prominent "shimmering," a "strobilike undulation" in brightness mainly in his left and right peripheral visual fields, unrelated to visual objects, each lasting approximately an hour. All episodes occurred when he abruptly stepped into a lighted environment after he had been driving in darkness for extended periods; he estimated the frequency of the shimmering to be 5 to 6 Hz. Shimmering had not occurred when he had been on lower doses of nefazodone. The last 2 episodes occurred after bupropion, 150 mg/day, had been added to his regimen, but the frequency, duration, intensity, and character of these latter episodes did not differ significantly from the first 2, when he was taking only nefazodone, arguing against the relevance of bupropion in producing this phenomenon.

Case 2. Mr. B, a 52-year-old man, reported a 5-minute episode of shimmering in his visual field, most pronounced as "jiggly lines" in the left and right visual periphery, after walking from darkness into his kitchen and turning on the light. This episode occurred after his dose of nefazodone had been increased to 550 mg/day; he was also simultaneously taking bupropion, 150 mg/day. This was an isolated incident for Mr. B; upon questioning, he believed he had inadvertently taken an extra 300-mg dose of nefazodone that evening before the episode.

Both individuals denied any history consistent with migraine headaches (which can manifest with unformed visual hallucinations), seizure disorder, cerebrovascular or retinal disease, or pathology; neither had had any brain imaging studies. The

events were presumptively binocular (they reported the effect in left and right peripheral fields), but neither individual closed each eye during an episode to absolutely establish this. These experiences were unlike palinopsia, in which specific visual imagery persists or recurs after the stimulus is gone ("visual trailing"). Neither individual experienced dizziness, headache, or significant anxiety related to this experience, although both found it surprising and somewhat disconcerting. I have not been able to uncover any other previously reported similar phenomena associated with either nefazodone or trazodone.

Although they modestly inhibit bioamine reuptake, nefazodone and trazodone are believed to be distinguished among antidepressants in achieving efficacy principally by blocking 5-HT₂ serotonin receptors.³ Both also share an active metabolite, *m*-CPP (*m*-chlorophenylpiperazine), which has multiple serotonergic actions, including significant agonist properties at 5-HT_{2C} receptors. *m*-CPP has been reported to be associated with abnormal visual perceptions and with migraine headaches.^{4,5} Of possible pertinence, LSD and similar agents are associated with a variety of visual disturbances, including palinopsia and pulsating peripheral field disturbances (usually provoked, however, by going from light into the dark, the reverse of the trigger reported for these 2 cases).⁶ Interestingly, it has been suggested that hallucinogens may cause visual disturbances via stimulation of 5-HT₂ receptors.^{7,8}

The cause of these newly described cases of nefazodone-associated visual disturbance is unclear, but the above considerations suggest that 5-HT₂ receptor-blocking and/or other serotonergic actions may be of relevance.

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Pharmacists Lack Knowledge of Antidepressant Discontinuation Symptoms

Sir: We read with interest the article by Young and Currie¹ demonstrating that a significant proportion of physicians lacked detailed knowledge of antidepressant discontinuation phenomena. We recently used a questionnaire, similar to that used by Young and Currie, to assess knowledge among pharmacists working in the United Kingdom. We felt this was important for several reasons. First, pharmacists have a key role in providing

general information about medication to patients, e.g., the importance of compliance. Second, patients often take specific queries to their pharmacist, e.g., can a drug be stopped safely? Could a symptom be a side effect of medication? Finally, pharmacists are an expert source of drug information for doctors, including psychiatrists. These roles mean that pharmacists are ideally placed to help prevent, recognize, and treat discontinuation symptoms.

Like Young and Currie, we found that a substantial proportion of respondents (55/147, 37%) denied being confidently aware of antidepressant discontinuation symptoms. Furthermore, subsequent answers indicated that some of those who claimed to be "confident" had overrated their knowledge. Young and Currie found that psychiatrists were more knowledgeable about discontinuation symptoms than were general practitioners. Similarly, we found that specialist psychiatric pharmacists were more knowledgeable about these symptoms than community pharmacists were. These findings are important as most cases of depressive illness are managed within primary care, i.e., most patients are treated by general practitioners and receive their antidepressant prescriptions from community pharmacists.

Young and Currie concluded that clinicians need to be educated about discontinuation phenomena. We suggest that educational programs need to be extended to pharmacists as well as other key health professionals, for example, community psychiatric nurses.

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Dr. Young Replies

Sir: We read the letter of Donoghue and Haddad with great interest. We agree entirely that their data support the need for education about discontinuation phenomena and indeed other aspects of psychotropic drugs to be extended to pharmacists and other key health professionals. In addition, we feel that it would be useful to consider increasing the amount of information made available to patients directly. A noteworthy point is that discontinuation phenomena may exist with other classes of psychotropic drugs and that such educational initiatives should not be confined only to antidepressants.

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Hyperprolactinemia and Male Sexual Dysfunction

Sir: Neuroleptics cause sexual problems including diminished desire, orgasmic dysfunction, and performance difficulties. The underlying pathomechanisms of neuroleptic-induced sexual dysfunction are difficult to evaluate since (1) traditional antipsychotics affect multiple neural pathways while simultaneously elevating prolactin levels¹ and (2) male schizophrenia

patients may have gonadotropin abnormalities unrelated to antipsychotic treatment.²

Serendipitous variance in the effect of the newly marketed antipsychotic agents on serum prolactin levels will help clarify whether drug-induced sexual dysfunction is secondary to hyperprolactinemia or other mechanisms. Risperidone, like traditional neuroleptics, elevates prolactin levels; in contrast, olanzapine has modest effects on prolactin as compared with haloperidol.³ We report a case of a male schizophrenia patient who, when switched from risperidone to olanzapine, normalized serum prolactin and testosterone levels and experienced resolution of sexual dysfunction.

Case report. Mr. A is a 40-year-old white man who fathered 2 children, now preschoolers, while prescribed low-dose loxapine. Following a switch to risperidone, he felt subjectively improved and experienced fewer motor side effects. Prolactin levels while taking risperidone, 3 mg b.i.d., were 73 and 102.3 µg/L, and while taking 5 mg/day, his prolactin level was 66 µg/L (reference range, 0-15 µg/L). Serum testosterone was subnormal at 5.3 and 7.6 nmol/L (reference range, 8-29 nmol/L). He revealed a history of complete loss of interest in sex and an almost total inability to obtain an erection on risperidone treatment. Risperidone was stopped and olanzapine started. Over a 3-month period, he experienced psychological improvement on olanzapine, 17.5 mg/day, along with progressive monthly reductions in prolactin values to 33, 21, and 15 µg/L and normalization of testosterone to 10.8, 11.1, and 12.1 nmol/L. His ability to obtain an erection returned by week 4, and his sexual interest gradually increased, although it had not returned to what he considered normal by month 3.

Decreased libido and erectile dysfunction may occur secondary to hyperprolactinemia and/or hypogonadism.⁴ Androgens also affect mental states, albeit in inconsistent ways that are often individual specific.⁵ Whether normalization of testosterone levels in this patient contributed to his mental improvement is an intriguing idea.

This is the second case report describing how a difference in the prolactin-elevating properties of 2 novel antipsychotics correlates with sexual functioning.⁶ Clinicians should actively question neuroleptic-treated patients about sexual side effects and consider whether an elevated prolactin level is contributing to a problem that may be eliminated by switching to a prolactin-sparing antipsychotic.

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