Acupuncture for Major Depressive Disorder: Has Its Efficacy Been Disproved?

Sir: We appreciate the thoughtful design of the recently published study by Allen and colleagues.[1] It is essential to critically evaluate complementary and alternative therapies, and we believe this study has provided important data on the outcomes of treatment of major depressive disorder (MDD) using manual acupuncture. Given the need for innovative treatments of MDD, it is equally important that potentially efficacious interventions are not discarded prematurely. In this context, we question the authors' interpretation of their results.

1. Response and remission rates for both Traditional Chinese Medicine (TCM)–directed and non-TCM–directed acupuncture conditions compared favorably with those reported in antidepressant monotherapy trials and differed significantly from those associated with the wait list control. Similarly, those on the wait list showed significant improvement during the 8 weeks they received TCM-directed acupuncture. Thus, far from "failing to support the efficacy of TCM manual acupuncture as monotherapy for MDD," the results seem to support efficacy but rather raise important questions about the precise mechanisms through which acupuncture treatments, TCM- or non-TCM–directed, exert an impact on depressive symptoms.
2. The use of the terms *specific* and *nonspecific* in this report is based upon reference to TCM. Underscoring the difficulty of identifying an appropriate control procedure in studies of acupuncture for MDD, it is possible that points or combinations of points that were considered "nonspecific" for depression in this study might have been considered "specific" were this a study of other styles of traditional acupuncture, such as those from the Japanese, Korean, or French schools.[2] Likewise, acupuncture could be effective by as yet uncharacterized mechanisms different from those outlined in the TCM model. In such a case, certain points may be effective for certain conditions despite not fitting into the TCM model of illness and treatment. The study results raise the question of whether points considered "nonspecific" are, in fact, active for depression treatment or whether other factors associated with acupuncture visits (such as the physical interaction with the clinician, or patient expectations about treatment) accounted for the superiority of acupuncture treatment to the wait list control. Incorporating retractable "sham" needles, while not immune to methodological limitations, would be one way to further evaluate this question.

Dr. Alpert is a consultant to PamLab and Eli Lilly; has received grant/research support from PamLab, Eli Lilly, and Pfizer; and has received honoraria from Eli Lilly. Dr. Fava has received research support from Abbott, Alkermes, Aspect, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Lichtwer Pharma, Lorex, Novartis, Organon, PamLab, Pfizer, Pharmavite, Roche, Sanofi-Synthelabo, Solvay, and Wyeth-Ayerst; is an advisor/consultant for Aspect, AstraZeneca, Bayer, Biovail, BrainCells, Bristol-Myers Squibb, Cephalon, Compellis, Cypress, Dov, Eli Lilly, EPIX, Fabre-Kramer, Forest, GlaxoSmithKline, Grunenthal, Janssen, Jazz, Johnson & Johnson, Knoll, Lundbeck, MedAvante, Merck, Neuronetics, Novartis, Nutrition 21, Organon, PamLab, Pfizer, PharmaStar, Pharmavite, Roche, Sanofi-Synthlabo, Sepracor, Solvay, Somaxon, Somerset, and Wyeth-Ayerst; has participated in speakers boards for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Organon, Pfizer, PharmaStar, and Wyeth-Ayerst; and has equity holdings in Compellis and MedAvante. Drs. Yeung, Mischoulon, and Ma report no financial affiliations or other relationships relevant to the subject of this letter.

REFERENCES

1. Allen JJB, Schnyer RN, Chambers AS, et al. Acupuncture for depression: a randomized controlled trial. J Clin Psychiatry 2006;67:1665–1673
2. Editorial staff. Japan, China, South Korea work together to standardize acupuncture points. Acupuncture Today. March 2005;06. Available at http://www.acupuncturetoday.com/mpacms/at/article.php?id=30035. Accessibility verified June 7, 2007

Albert Yeung, M.D., Sc.D.
David Mischoulon, M.D., Ph.D.
Jonathan Alpert, M.D., Ph.D.
Yantao Ma, M.D.
Maurizio Fava, M.D.
Depression Clinical and Research Program
Massachusetts General Hospital
Boston, Massachusetts

Ms. Schnyer and Colleagues Reply

Sir: We thank our colleagues for their comments regarding our randomized controlled trial[1] of acupuncture in the treatment of depression. We would agree that the results of this single trial should not lead to the dismissal of acupuncture as a treatment for depression, and that further research in acupuncture for depression is warranted.

We don't agree, however, that our results support the *efficacy* of acupuncture as a monotherapy for depression. Yeung and colleagues' remarks pertain to the clinical effectiveness of the entire intervention package but not to the efficacy of acupuncture per se.[2] Demonstrating efficacy, the primary aim of our study, requires finding a significantly better outcome for the active rather than the control intervention. Our study found a nonsignificant trend in the reverse direction; thus efficacy was not demonstrated. Moreover, the low response rate of the specific intervention (22%) falls within the placebo response rate of other randomized controlled trials of depression[3] and is not significantly different from the response rate of the waitlist control (17%) after 8 weeks. Although response rates were higher after 16 weeks, patients receiving 16 weeks of "specific" acupuncture did not respond better than those receiving 8 weeks (following waitlist). Of course an average 12.4-point reduction in HAM-D_{17} score among completers across 16 weeks is not clinically trivial, and is descriptively similar to antidepressant monotherapy trials, but such findings address the effectiveness of the entire treatment package, including nonspecific therapeutic elements, and do not address efficacy.

Among other important methodological issues in acupuncture research highlighted in our discussion section is the issue of using invasive needling at valid acupuncture points as a credible control. Yeung and colleagues correctly note that points considered "nonspecific" for treatment of depression in one style of acupuncture may be "specific" in another style. Different point combinations and needling techniques may affect distinct depression pathways and may account for individual patient differences in response to treatment.[4] For this

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

reason, we were careful to point out that our results reflect exclusively the implementation of the specific approach[5] employed in this trial.

The retractable needling device noted by Yeung and colleagues provides an alternative control for the effects of needling but not necessarily the effects of acupuncture.[6] The choice of this device as a control assumes that precise anatomical point location and specific needle stimulation are the active ingredients of acupuncture treatment. Point location varies greatly across different acupuncture schools; traditionally, points are considered to be approximate landmarks that help find effective zones of physiologic access.[4] Some styles consider obtaining a strong sensation as essential to an effective treatment; others focus on promoting changes by using very shallow insertion and little or no stimulation. Although the retractable needle provides an important option in research, without modifications[7] its validity as a viable control is not generalizable across all acupuncture styles. Moreover, its use (1) is questionable in patients with previous acupuncture experience, (2) potentially impairs the clinical effectiveness of the authentic treatments (the use of the retractable needle requires some components of the device to be used as a counterpart in the active acupuncture arm, which limits skillful manipulation of the needles), (3) requires extensive training and careful monitoring of the clinicians, and (4) entails very high costs (about $5 a needle) (in our study, we used an average of 16 needles per treatment and provided 12 treatments, a cost of about $80 per treatment when using the retractable device and about $960 per patient randomly assigned to the control arm). The feasibility of its use as a placebo control should be tested, vis-à-vis the specific condition and the specific style of acupuncture to be investigated, before engaging in a phase 2 trial.

In the absence of a comprehensive model of the mechanism for acupuncture that integrates the diverse empirically demonstrated physiologic effects, it is all but impossible to design effective, universally valid controls because it is unknown exactly what must be controlled for or what accounts for specificity in acupuncture. Because of this complexity, the use of multiple research designs, each with particular controls, will ultimately strengthen the evidence base for acupuncture. The results of our study should be framed as a failure to find efficacy of Traditional Chinese Medicine (TCM)–style acupuncture compared to an active control that itself was not likely inert. Other studies that used the same control found evidence for efficacy of the same treatment approach in specific depressed population samples, such as pregnant women[8] and young women who experience a first depressive episode.[9] Much remains to be done to determine if the broad field of acupuncture can provide a valuable contribution as a monotherapy to the treatment of depression overall and for specific populations.

The study discussed in this letter was supported, in part, by grants from the National Institutes of Health (R21 RR09492, R01 MH56965, and R01 AT00001).

Dr. Moreno is a consultant to Cyberonics and Forest; has received grant/research support from Cyberonics; and has participated in speakers/advisory boards for Cyberonics, Wyeth-Ayerst, and Forest. Drs. Allen, Hitt, and Manber and Mss. Schnyer and Chambers report no additional financial affiliations or other relationships relevant to the subject of this letter.

REFERENCES

1. Allen JJB, Schnyer RN, Chambers AS, et al. Acupuncture for depression: a randomized controlled trial. J Clin Psychiatry 2006;67:1665–1673
2. Chambless DL, Hollon SD. Defining empirically supported therapies. J Consult Clin Psychol 1998;66:7–18
3. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 2002;287:1840–1847
4. Schnyer R, Birch S, MacPherson H. Acupuncture Practice as the Foundation for Clinical Evaluation. London, England: Elsevier; In press
5. Schnyer RN, Allen JJB, Hitt SK, et al. Acupuncture in the Treatment of Major Depression: A Manual for Research and Practice. London, England: Harcourt-Brace Churchill Livingstone; 2001
6. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. Lancet 1998;352:364–365
7. Wayne PM, Krebs DE, Macklin EA, et al. Acupuncture for upper-extremity rehabilitation in chronic stroke: a randomized sham-controlled study. Arch Phys Med Rehabil 2005;86:2248–2255
8. Manber R, Schnyer RN, Allen JJ, et al. Acupuncture: a promising treatment for depression during pregnancy. J Affect Disord 2004; 83:89–95
9. Allen JJB, Schnyer RN, Hitt SK. The efficacy of acupuncture in the treatment of major depression in women. Psychol Sci 1998;9: 397–401

Rosa N. Schnyer, L.Ac.
Department of Psychology
University of Arizona
Tucson, Arizona and
Osher Institute
Harvard Medical School
Boston, Massachusetts
Andrea S. Chambers, M.A.
Sabrina K. Hitt, Ph.D.
Department of Psychology
Francisco A. Moreno, M.D.
Department of Psychiatry
University of Arizona
Tucson, Arizona
Rachel Manber, Ph.D.
Stanford University
Stanford, California
John J. B. Allen, Ph.D.
Department of Psychology
University of Arizona
Tucson, Arizona

Sertraline Versus Venlafaxine XR in Major Depressive Disorder

Sir: A recent study by Shelton et al.[1] suggests that sertraline and venlafaxine XR have a comparable efficacy in treating major depressive disorder. The following comments would enable an improved understanding of this study.

Shelton et al.[1] stated that participants were outpatients but did not clarify what process was involved in such recruitment. Because several centers were involved in this study, a lack of specification of the recruitment process could affect valid interpretation of study findings, as selection bias could not be ruled out.

There is a need to comment about interrater reliability of outcome measures, as 8 centers participated in this study,[1] although treatment center was used as a covariate.

The authors define response as achievement of 1 or 2 on the Clinical Global Impressions-Improvement scale (CGI-I) or a ≥ 50% reduction in Hamilton Rating Scale for Depression (HAM-D) total score and remission as having a score of 1 or 2

on the CGI-I scale and a HAM-D score ≤ 7. In this background, use of CGI-I score appears to offer less contribution to improve the definitions of response and remission.

The primary outcome measure chosen was the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). One of the basic premises of this study was to test the theoretical principle that the dopaminergic system is linked with motivation and reward and that higher doses of sertraline that activate the dopaminergic system could yield a better quality of life. The fact that this study did not find a difference between sertraline and venlafaxine XR on the quality of life measure in depression, akin to another study,[2] could be explained by the observation[3] that venlafaxine has an ability to block dopamine reuptake at higher doses.

Regarding covariate analysis, consideration of baseline Q-LES-Q, HAM-D, CGI-I, CGI-Severity scale, and Hamilton Rating Scale for Anxiety scores as covariates was not needed, as initial analysis has clearly shown groups to have comparable scores on these measures. Further, the inclusion of a few variables that have relation to quality of life, such as education level, employment status, and family history of depression, as done in another study,[2] could have increased the generalizability of this study.[1]

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

REFERENCES

1. Shelton RC, Haman KL, Rapaport MH, et al. A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder. J Clin Psychiatry 2006;67:1674–1681
2. Sir A, D'Souza RF, Uguz S, et al. Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptoms. J Clin Psychiatry 2005;66:1312–1320
3. Stahl SM. Newer antidepressants and mood stabilizers. In: Essential Psychopharmacology. New York, NY: Cambridge University Press; 2005:245–295

Ana Lusicic, M.D.
Karuppiah Jagadheesan, M.D, F.R.A.N.Z.C.P.
Moreland Continuing Care Team
Coburg Campus
North Western Mental Health Service
Melbourne, Victoria, Australia

Dr. Shelton Replies

Sir: The point regarding the nature of the recruited sample in our study, "A Randomized, Double-Blind, Active-Control Study of Sertraline Versus Venlafaxine XR in Major Depressive Disorder," raised by Drs. Lusicic and Jagadheesan is well taken. The participating sites were outpatient clinics affiliated with large, tertiary-care referral centers, or large community clinics that were experienced in clinical trials. Patients were recruited from those who presented for care in the centers, by self- or word-of-mouth referrals, or in response to advertisements regarding the study. Such recruitment may have resulted in the selection of a sample biased in any of several different ways. This might have mitigated differences between the treatments in much the same way as has been seen in placebo-controlled trials in the past. Since placebo response was not determined, we cannot comment on potential placebo effects in the trial. However, the results were quite similar to those shown in prior trials.

The authors also raised concerns about interrater reliability. Interrater reliability was determined at the initiation of the study and exceeded 0.90. As noted in their letter, however, we enter site as a covariate in the analyses to help to control for any differences between centers.

The authors also question the value of using the Clinical Global Impressions (CGI) scores in improving the determination of response and remission rates. The purpose of using the CGI in this manner was intended to control for any underreporting of symptoms by patients in the study. The observations of clinicians served to check any tendency for patients to report improvements in mood that were not consistent with clinical observations. Such underreporting would serve to inflate the rates of response and remission, an undesirable result. Combining endpoint scores with CGI values has been used in other trials in the past.

A question was also raised as to whether venlafaxine represents a dopamine reuptake inhibitor at higher doses, given the core premise of the study. Even at high doses, the effects of venlafaxine on dopamine reuptake are questionable. An examination of the binding affinity for the dopamine transporter (DAT) in this regard is telling. The dissociation constant (K_d) of sertraline for DAT is approximately 25 nanomolar (nM); by contrast, K_d = 9300 nM for venlafaxine, indicating extremely low potency.[1] Certainly, however, in the dosing range used in this study (up to 225 mg/day), venlafaxine would not be expected to have significant effects on dopamine uptake. However, the authors correctly note that we did not find support for a difference of the quality of life, enjoyment, and satisfaction between sertraline and venlafaxine. The results indicate that either sertraline does not have clinically meaningful effects on dopamine reuptake, or quality of life scales may not effectively measure a separate dimension of motivational drive that could be affected by dopamine.[2,3]

The question raised regarding covariates is perplexing, since the rating scales mentioned by the authors were not entered as covariate in the main analyses. It is always possible to enter more variables as covariates. The point regarding covariates is accurate; in the absence of significant baseline differences between groups, the use of baseline scores as covariates is not required. However, it can be done to account for nonsignificant baseline differences that may still have an influence on the statistical outcome.

The study discussed in this letter was funded by Pfizer Inc, New York, N.Y.

Dr. Shelton has received grant/research support from Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, Sanofi, Wyeth-Ayerst, AstraZeneca, and Abbott; is a paid consultant to Pfizer and Janssen; and has participated in speakers bureaus for Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, GlaxoSmithKline, Solvay, Wyeth-Ayerst, and Abbott.

REFERENCES

1. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997;340:249–258
2. Gorman JM, Sullivan G. Noradrenergic approaches to antidepressant therapy. J Clin Psychiatry 2000;61(suppl 1): 13–16
3. Shelton RC, Tomarken AJ. Can recovery from depression be achieved? Psychiatr Serv 2001;52:1469–1478

Richard C. Shelton, M.D.
Department of Psychiatry
Vanderbilt University Medical Center
Nashville, Tennessee

A Case of Unexpected and Selective Remission of a 20-Year History of Ephedrine Dependence Following Treatment With Low-Dose Aripiprazole

Sir: Unlike cocaine and methamphetamine dependence, ephedrine dependence is not well studied; however, clinicians who treat eating disordered patients recognize it as a common phenomenon. To date, there are no medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of stimulant dependence. Here we describe the case of a patient who experienced unexpected remission of a 20-year history of ephedrine dependence following treatment with low-dose aripiprazole.

Case report. Ms. A, a 37-year-old woman with eating disorder not otherwise specified and major depressive disorder (both diagnosed per DSM-IV-TR criteria), initially presented in 2005 to the University Mental Health Center forced into treatment by her probation officer after a routine urine drug screen was positive for methamphetamine. Ms. A adamantly denied having ever used methamphetamine, but acknowledged a 20-year history of abusing over-the-counter medications to maintain her weight. (Subsequent hair analysis confirmed the presence of ephedrine but not methamphetamine.)

Ms. A reported having an eating disorder since the age of 17 years, characterized by binge eating and vomiting as well as overuse of laxatives and over-the-counter stimulants. Other problems included recurrent episodes of major depression, impulsive and compulsive shopping, and forgery. The forgery resulted in her arrest, conviction, time in jail, and subsequent probation. Ms. A also described a 20-year history of use of as much as 1.5 mg of ephedrine daily. During this period, her ephedrine dependence continued despite comprehensive psychiatric care including inpatient hospitalization and outpatient medication management (bupropion, sertraline, lithium, paroxetine, and venlafaxine) as well as individual psychotherapy and group psychotherapy, the latter specific to dual diagnoses.

At the time of presentation, Ms. A's problems included significant depression, daily vomiting, impulsive and compulsive spending, and ephedrine dependence. Her body mass index was 18.5 kg/m^2. To the best of our ability, we ruled out bipolar spectrum disorder. To address her presenting problems, we prescribed 40 mg/day of fluoxetine and gradually increased the dose to 80 mg/day. She also received cognitive-behavioral therapy. During 6 months on this program, her depression remitted completely; however, her daily vomiting, impulsive/compulsive shopping, and ephedrine dependence continued unabated.

Ms. A's insight into the problems surrounding her ephedrine dependence was limited. Although she was concerned about the possibility of not being present to raise her young children due to the ongoing risk of legal incarceration, she refused to consider the risk of cardiac complications that could result from excessive ephedrine intake. In addition, she continued to use ephedrine despite having to spend 3 nights in the county jail after a second urine drug screen was positive for methamphetamine. (This was again proved to be a false positive with hair analysis.)

Since one small open-label trial of aripiprazole in obsessive-compulsive–disordered patients suggested that aripiprazole might be effective for controlling compulsions,[1] we hypothesized that this medication might be of value for her. Not unexpectedly, Ms. A expressed significant concerns about the potential for weight gain as mentioned in the drug's package insert. However, after we reviewed with her information suggesting that the risk of weight gain was small,[2,3] she consented for off-label use of aripiprazole. Accordingly, we prescribed 2.5 mg of aripiprazole daily to augment the 80 mg/day of fluoxetine.

Over the course of the next 8 weeks, during which time Ms. A adhered to this medication regimen, her spending behaviors as well as her bingeing and vomiting did not change significantly. Surprisingly, however, during that same time period she completely tapered herself off ephedrine. When asked to explain why she had stopping using ephedrine, Ms. A reported, "It wasn't doing anything for me anymore." She further explained that for years ephedrine had helped her maintain a very high energy level, but while taking aripiprazole, she was able to get the same activities accomplished without taking ephedrine. After the initial 8 weeks, Ms. A elected to discontinue aripiprazole, as she was still concerned about gaining weight. She reported feeling that her clothes were tighter (although she refused to step on a scale) and attributed the weight gain to taking aripiprazole, rather than to stopping ephedrine. At the present time, 5 months after she first took aripiprazole, Ms. A continues to be ephedrine-free and now meets criteria for ephedrine dependence in early full remission; remission has currently lasted for 4 months.

Literature concerning the pharmacologic treatment of stimulant dependence is limited. Dopamine partial agonists such as aripiprazole have been on the U.S. market only since 2003 with primary FDA indications for schizophrenia, bipolar mania, and bipolar mixed episodes. However, aripiprazole has been suggested as a potential pharmacotherapy for substance dependence. As early as 2000, Childress and O'Brien[4] postulated that because dopamine partial agonists, including medications such as aripiprazole, have unique agonist/antagonist effects on dopamine receptors, they might be useful in treating withdrawal and craving symptoms seen in cocaine-dependent patients. Expounding on that theory, Feltenstein and colleagues[5] tested how aripiprazole affected cocaine-dependent rats when the rats were presented with an opportunity to use cocaine. Their results suggested that rats who took aripiprazole showed fewer cocaine-dependent behaviors than controls. Lile and colleagues[6–8] published the results of 3 different trials of aripiprazole during 2005 and 2006, suggesting that aripiprazole can help attenuate the effects of *d*-amphetamine on human subjects as well.

Several studies have demonstrated that patients with eating disorders not infrequently use amphetamines and other stimulants to maintain weight loss.[9,10] These stimulants also provide patients with a perceived energy boost to combat the fatigue associated with limited food intake. Although to date the FDA has not approved any pharmacologic treatment of stimulant dependence, the articles cited above propose a potential role for aripiprazole in the treatment of cocaine and *d*-amphetamine dependence. In this regard, it seems reasonable to extrapolate that aripiprazole may be of value for patients with dependence on over-the-counter stimulants as well. Ms. A's case offers anecdotal evidence that low-dose aripiprazole may prove to be a viable pharmacotherapy to address ephedrine dependence. Given aripiprazole's low side effect profile and low threat of the serious weight gain seen with many other psychotropics, this agent might be well suited to treat ephedrine dependence in eating-disordered patients. Large case series and, ultimately, randomized controlled trials of aripiprazole in ephedrine abusers may demonstrate a role for aripiprazole in curbing ephedrine abuse and dependence, especially in eating-disordered patients.

Dr. Arnold and Dr. Yager deny any conflicts of interest.

The authors thank Caroline Bonham, M.D., Chad Woofter, M.D., and Christopher Abbott, M.D., as well as Residency Training Director David

Graeber, M.D., for their thoughtful review and comments on this case report. The individuals acknowledged have no financial affiliation or other relationship relevant to the subject of this letter.

REFERENCES

1. Connor KM, Payne VM, Gadde KM, et al. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. J Clin Psychiatry 2005;66:49–51
2. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005;19(suppl 1):1–93
3. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. Can J Psychiatry 2006;51:480–491
4. Childress AR, O'Brien CP. Dopamine receptor partial agonists could address the duality of cocaine craving. Trends Pharmacol Sci 2000; 21:6–9
5. Feltenstein MW, Altar CA, See RE. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. Biol Psychiatry 2007;61:582–590
6. Lile JA, Stoops WW, Vansickel AR, et al. Aripiprazole attenuates the discriminative-stimulus and subject-rated effects of d-amphetamine in humans. Neuropsychopharmacology 2005;30:2103–2114
7. Stoops WW. Aripiprazole as a potential pharmacotherapy for stimulant dependence: human laboratory studies with d-amphetamine. Exp Clin Psychopharmacol 2006;14:413–421
8. Stoops WW, Lile JA, Glaser PE, et al. A low dose of aripiprazole attenuates the subject-rated effects of d-amphetamine. Drug Alcohol Depend 2006;84:206–209
9. Widerman MW, Pryor T. Substance use among women with eating disorders. Int J Eat Disord 1996;20:163–168
10. Piran N, Robinson SR. Associations between disordered eating behaviors and licit and illicit substance use and abuse in a university sample. Addict Behav 2006;31:1761–1775

Karen K. Arnold, M.D.
Joel Yager, M.D.
Department of Psychiatry
University of New Mexico
Albuquerque, New Mexico

Sponsored Clinical Trials and Bias

Sir: I read with great interest your editorial[1] and the 2 letters from the February 2007 issue of your journal[2,3] highlighting the important concern about the source of funding influence on the outcome of interest.

In addition to the recent review by Heres et al.[4] that you refer to in your editorial,[1] the relationship between funding source and study outcome, which is so beautifully illustrated by the exchange between your 2 correspondents,[2,3] was investigated in several other published studies.[5–15] With one exception,[11] these studies showed that industry support was uniformly associated with positive study outcome for the sponsored intervention either as a trend[8] or, most times, at significant levels.[5,6,9,10,12–15] The association between funding and outcome is by no means a new development, as the first publication addressing the issue goes back to the 1980s.[6] Also, the impact of sponsorship is not limited to any one medical specialty, and it has in fact been much more thoroughly investigated in specialties other than psychiatry.[5,6,9,10,12,14,15]

How big can this undue influence be? According to Safer,[7] 89% to 98% of comparative drug treatment studies funded by pharmaceutical companies yield results that are favorable to their company's product; more specifically, Heres et al.,[4] in a recent review of second-generation neuroleptic trials, found that in 90% of the analyzed studies the reported outcome was in favor of the sponsor's drug.

These are clearly impressive numbers. The question is, What does this mean for a busy clinician who oftentimes tends to jump from the title of a paper and its abstract right to the conclusions, entirely skipping the method section? Read the literature with a critical eye, you propose.[1]

Unfortunately, I am afraid that the educated skepticism that you thoughtfully recommend[1] for the medical journal readers, despite its appeal, is not a realistic solution. Even if one would have adequate time, which is seldom the case in a busy practice, the level of statistical sophistication that is required for one to discern between the many issues that can misrepresent a certain outcome needs to be above the level of just "educated skepticism." The reality is that most clinicians are intimidated by p and chi-square, 1-tailed versus 2-tailed tests, noninferiority versus superiority trial designs, last observation carried forward, or equivalence margins—to mention only a few of the statistical concepts discussed in your correspondents' letters.[2,3]

In this context, I believe that the burden for a skeptical read needs to stay with the journal and the peer reviewers. To better inform their readers, journals might consider adding companion critical abstracts summarizing the "skeptical read" findings for each and every published paper. In this era of electronic media, such abstracts can be easily made available in the journals' electronic editions, as Web links included with the text of the paper. Other than informing, such an addition would also have the major benefit of further educating and, as such, providing a solid foundation for that desirable state of "healthy skepticism" that you have kindly proposed.

Dr. Preda reports no financial affiliations or other relationships relevant to the subject of this letter.

REFERENCES

1. Gelenberg AJ, Freeman MP. The art (and blood sport) of psychopharmacology research: who has a dog in the fight? J Clin Psychiatry 2007;68:185
2. Gharabawi GM, Bossie CA, Pandina GJ, et al. A discussion of 2 double-blind studies comparing risperidone and quetiapine in patients with schizophrenia [letter]. J Clin Psychiatry 2007;68:333
3. Sweitzer DE, Lazarus A, Brecher M. A discussion of 2 double-blind studies comparing risperidone and quetiapine in patients with schizophrenia [reply]. J Clin Psychiatry 2007;68:334
4. Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006;163:185–194
5. Yaphe J, Edman R, Knishkowy B, et al. The association between funding by commercial interests and study outcome in randomized controlled drug trials. Fam Pract 2001;18:565–568
6. Davidson RA. Source of funding and outcome of clinical trials. J Gen Intern Med 1986;1:155–158
7. Safer DJ. Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. J Nerv Ment Dis 2002;190: 583–592
8. Djulbegovic B, Lacevic M, Cantor A, et al. The uncertainty principle and industry-sponsored research. Lancet 2000;356:635–638
9. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. Arch Intern Med 1994;154:157–163
10. Ridker PM, Torres J. Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000–2005. JAMA 2006;295:2270–2274
11. Clifford TJ, Barrowman NJ, Moher D. Funding source, trial outcome and reporting quality: are they related? results of a pilot study. BMC Health Serv Res 2002;2:18
12. Cho MK, Bero LA. The quality of drug studies published in

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

symposium proceedings. Ann Intern Med 1996;124:485–489
13. Lexchin J, Bero LA, Djulbegovic B, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003;326:1167–1170
14. Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. BMJ 2002;325:249
15. Friedberg M, Saffran B, Stinson TJ, et al. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. JAMA 1999;282:1453–1457

Adrian Preda, M.D.
Department of Psychiatry & Human Behavior
University of California, Irvine School of Medicine
Orange, California

The Editors Reply

We appreciate Dr. Preda's thoughtful comments on our editorial. We agree that journal editors and peer reviewers are responsible for a large part of the process of ensuring the dissemination of clinically relevant and scientifically valid articles to our readers. As journal editors, we consider this a great responsibility. Clinicians will adapt their practices after reading published literature, and published reports will influence future research. Many practicing clinicians would share the opinion that it is a burden to sort through papers and determine what the take-home messages are from the statistical analyses. A serious debt is owed to the many generous peer reviewers who serve our field. While the editorial and peer review process is not perfect, it has historically served us well. It allows for the careful examination of manuscripts by the fields' experts, with a critical evaluation and revision of literature before publication. We are dedicated to increasing transparency in the area of conflict of interest. Editors, reviewers, authors, and health care providers share the responsibility to creatively explore ways that the field of psychiatry can move forward in scientifically sound, efficient, and clinically meaningful ways.

Alan J. Gelenberg, M.D., Editor in Chief
Marlene P. Freeman, M.D., Deputy Editor

