

## Response to Self-Injurious Behaviors in a Community Sample of Young Women

**Sir:** We would like to comment on the article by Favaro et al.<sup>1</sup> regarding self-injurious behaviors (SIBs) in a community sample of young women. Favaro et al.<sup>1</sup> presented a thorough piece of research with sound methodology and extremely insightful results regarding self-injury and its association to other self-harmful behaviors.

However, we were surprised that the authors argued that “the epidemiology of this phenomenon in the general population is unknown.”<sup>1(p122)</sup> Several recent studies with community and nonclinical samples, such as college students who self-injure, are available. A cursory search of the literature identified 39 studies that discuss community samples of adolescent and young adults who self-injure. These studies reported rates of SIB varying between 13.9% and 38%.<sup>2-6</sup>

In addition, the claim of Favaro et al.<sup>1</sup> that their study is “the first to investigate—and find—a connection between childhood abuse and compulsive SIB”<sup>1(p129)</sup> could be argued to be misleading as research on this topic is present in the existing literature.<sup>7,8</sup>

Given the rapid increase of articles on self-injurious behaviors in the literature, it is understandable how authors can miss some more recent studies. However, we believe that this study would have been more informative and of greater strength and validity had it included most recent available data.

*Drs. Plener and Kokaliari report no financial affiliations or other relationships relevant to the subject of this letter.*

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## Dr. Favaro and Colleagues Reply

**Sir:** We thank Drs. Plener and Kokaliari for their interest and appreciation of our article. We also thank them for understanding that it would have been impossible for us to cite articles that had not yet been published at the time our manuscript was submitted to *The Journal of Clinical Psychiatry*. Authors of research reports have to make a difficult—and sometimes debatable—choice as regards the citation of previous studies. Inevitably, even important articles may sometimes be omitted. However, as regards our recent article,<sup>1</sup> we can rule out the possibility that the omissions Plener and Kokaliari pointed out might affect the strength, validity, and quality of information of the study.

While acknowledging the contribution made by recent articles, we are still persuaded that “the epidemiology of this phenomenon in the general population is unknown.”<sup>1(p122)</sup> In the literature, we found no interview-based prevalence studies performed on samples representative of the general population. Although of unquestionable scientific value, all the articles that Plener and Kokaliari cited in their letter have at least 1 of the following limitations: (1) use of samples not representative of the general population, (2) use of self-reported measures, and/or (3) lack of a clear differentiation of self-injurious behavior (SIB) from suicide-related behaviors. Samples representative of the general population and use of interviews are considered essential requirements for reliable estimation of epidemiologic rates in psychiatry,<sup>2</sup> and the clear differentiation between self-injurious behavior and suicide-related behaviors is crucial because research in the field has demonstrated that suicidal acts and SIB are 2 distinct phenomena with different etiologies.<sup>3,4</sup> The articles cited by Plener and Kokaliari make an important contribution to the understanding of the phenomenon of impulsive self-harming behavior in high school and college students, but do not cover the lack of knowledge in the epidemiology of SIB. Our study represents an attempt to provide reliable prevalence estimates of the full spectrum of SIB. However, although 1 study about Italian young women is now available, to date no such studies are available about men or about other Western or non-Western countries. Our opinion is shared by Ross and Heath<sup>4</sup> and by Whitlock et al.,<sup>5</sup> who stated that “there exists no reliable estimate of the prevalence of SIB in the general, nonclinical, U.S. adolescent and young adult population.”<sup>5(p1940)</sup>

Concerning the second point, we would again like to emphasize that our study is “the first to investigate—and find—a connection between childhood abuse and compulsive SIB.”<sup>1(p129)</sup> In our article, we defined compulsive SIB as acts such as skin picking, self-biting, severe nail biting, and hair pulling. We found that the skin picking and self-biting were significantly associated with childhood abuse. Neither skin picking nor other compulsive SIB was mentioned in either of the articles that Plener and Kokaliari cited on this point.<sup>6,7</sup> Both articles found a significant association between childhood maltreatment/abuse and the risk of repeated acts of impulsive SIB. Perhaps Plener and Kokaliari mistook the term *compulsive* for a synonym of *repetitive*. In fact, it is noteworthy that studies exploring both compulsive and impulsive SIB are rare in the literature. We hope that our study stresses the importance of considering the full spectrum of SIB in future research.

*Drs. Favaro, Ferrara, and Santonastaso report no financial affiliations or other relationships relevant to the subject of this letter.*

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### Aripiprazole and Perphenazine: No Difference

**Sir:** In their recent article, Kane et al.<sup>1</sup> present data from a large clinical trial that appear to show modest improvements with perphenazine and aripiprazole, but no significant differences between them, in patients with schizophrenia whose treatment resistance was objectively demonstrated by failure to show improvement in a 6-week trial with olanzapine or risperidone. In the abstract, the authors conclude only that aripiprazole and perphenazine can both improve symptoms in such patients, but at the end of the discussion, they assert that aripiprazole offers a more attractive option.

The study found no significant differences between these drugs on the first 8 outcome measures presented: (1) discontinuation rates, (2) reasons for discontinuation, (3) mean Positive and Negative Syndrome Scale (PANSS) change scores, (4) mean Clinical Global Impressions scale (CGI) change scores, (5) percentage with  $\geq 30\%$  PANSS improvement on last observation carried forward (LOCF) analysis, (6) percentage with  $\geq 30\%$  PANSS improvement on observed case (OC) analysis, (7) mean Quality of Life Scale (QLS) change scores, and (8) percentage with  $\geq 20\%$  QLS improvement on LOCF analysis. A significant difference at  $p < .05$  was found on a ninth measure: the percentage of patients with  $\geq 20\%$  improvement on the QLS in OC analysis. It thus appears that the authors applied an  $\alpha$  level of  $p < .05$  to at least 9 measures, 3 of which were based on the same data from the QLS. It is standard practice in clinical trials to identify a primary outcome and apply the  $\alpha$  of  $p < .05$  to that outcome. When multiple outcomes are tested, the possibility of finding a significant result by chance at  $p < .05$  increases by 5% with each additional test. With 9 tests, there is a 45% likelihood of finding a significant result at  $p < .05$  on 1 of the tests by chance alone. To avoid this error, a significance level closer to  $p < .007$  or at least  $p < .01$  can be applied, revealing that none of these differences are statistically significant.

The authors suggest that aripiprazole was better tolerated because of the significantly greater extrapyramidal symptoms (EPS) with perphenazine on 1 continuous measure. However, greater proportions of patients assigned to aripiprazole than to perphenazine discontinued due to adverse events (14% vs. 8%), and greater proportions of patients assigned to aripiprazole had at least one adverse event (21% vs. 17%). Table 4 shows that the total number of adverse events was less than 5% greater for patients on perphenazine treatment than for patients on aripiprazole treatment. Differences reported in the frequency of EPS-related events were not statistically significant by my calculation (19.4% vs. 13.7%,  $\chi^2 = 0.74$ ,  $df = 1$ ,  $p < 1.0$ ), nor were the differences in reported rates of akathisia or EPS itself. The authors bypass these categorical data and draw their conclusion from 1 of 3 continuous measures, the Simpson-Angus Scale, on which aripiprazole was superior to perphenazine at  $p < .04$ . There were no significant differences even at  $p < .05$  on the other 2 continuous EPS measures. Adjustment for the use of 3 continuous EPS measures would require an  $\alpha$  value of  $p < .016$ , revealing the Simpson-Angus Scale analysis differences not to be significant. Neither adjustment for multiple comparisons nor the finding of multiple nonsignificant differences is addressed. It is stated in the Discussion section without citation that perphenazine has greater risk of tardive dyskinesia, but as pointed out in a recent review, the relevant research on tardive dyskinesia risk with first-generation antipsychotics (FGAs) as compared to second-generation antipsychotics (SGAs) exclusively involves haloperidol at moderate to high doses and thus may not be generalizable.<sup>2</sup>

Researchers often hesitate to conclude that a study found no differences between treatments because of the adage that “one can never prove the null hypothesis.” Descriptive candor, however, warrants explicitly noting when there are no differences on an extensive array of measures even without making the further claim of having proven that there are no differences. The final conclusion of this industry-sponsored trial favors aripiprazole, and this seems inconsistent with both the extensive array of no-difference findings and with findings of studies such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,<sup>3</sup> which (like the study commented upon here) showed virtually no benefit on measures of symptoms of quality of life for atypical antipsychotics as compared to perphenazine.)

One reason this report is especially noteworthy is that the Discussion includes a clear and cogent argument for greater use of FGAs like perphenazine in schizophrenia that is resistant to SGAs (p. 221). The authors remind us that, in earlier studies, SGAs were compared primarily to haloperidol in patients who had already failed treatment on FGA therapy and, in many if not most cases, they had failed on treatment with haloperidol itself. They thus had a somewhat better response to “something new” as compared to a drug or a drug class from which they had already failed to gain benefits. Now that the vast majority of patients are treated exclusively with SGAs, those who do not respond may be good candidates for a trial of FGAs like perphenazine. As the authors put it, “Results from the current study suggest that at least some typical agents may provide an effective alternative for some of these patients” (p. 221).

One of the common justifications for the marketing of large numbers of similar SGAs is the belief that some patients may have an individual response to 1 drug rather than another, even when there are no differences between drugs in head-to-head randomized trials. This rationale draws some support from the current study, since patients with virtually no response to olan-

zapine or risperidone showed a modest and equivalent response to aripiprazole and perphenazine. Following this logic, clinical practice might be better served if physicians exercised the option of selecting from all 20 or so FGA and SGA drugs currently on the market rather than just the 5 or 6 most expensive drugs that are still under patent and extensively advertised.

*Dr. Rosenheck has received research support from Eli Lilly, Janssen, AstraZeneca, and Wyeth and has been a consultant to GlaxoSmithKline, Bristol-Myers Squibb, and Janssen.*

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#### Dr. Kane and Colleagues Reply

**Sir:** In our study,<sup>1</sup> patients with schizophrenia who met historical criteria for treatment resistance were prospectively treated in an open trial with doses of risperidone or olanzapine that are usually effective in most patients with non-treatment-resistant schizophrenia. Patients who did not improve during a 6-week trial were randomized to aripiprazole or perphenazine treatment, and about 25% responded to either drug in terms of Positive and Negative Syndrome Scale scores or Clinical Global Impressions scale scores over the next 6 weeks. We suggested that we could not rule out the possibility that the improvement observed during the course of this study was not a true drug effect because of the absence of groups treated with subtherapeutic doses of aripiprazole or perphenazine or continuation treatment with risperidone or olanzapine. We, therefore, suggested that, from the point of view of efficacy, our results do not provide any basis for choosing between these 2 drugs in treatment-resistant patients who may have failed prior treatment with other atypicals. If clinicians chose to try an additional trial with another antipsychotic before initiating a trial with clozapine, the drug with the most evidence for efficacy in treatment-resistant patients,<sup>2,3</sup> then these 2 medications could be considered. Dr. Rosenheck's letter raises concern about our lack of correction of the secondary outcome measures for multiple comparisons, but the absence of such a correction is quite customary in clinical trials.

Although we stated, and reiterate here, that aripiprazole was better tolerated than perphenazine, we pointed out that for many adverse events noted in this trial, there were no significant differences between aripiprazole and perphenazine. In particular, the difference between the 2 treatments in all-cause discontinuation rates for adverse events was not statistically significant. However, there was evidence that for 2 important side effects, prolactin elevations and extrapyramidal symptoms

(EPS), aripiprazole was, indeed, better tolerated. Dr. Rosenheck suggests we made too much of the EPS difference because it was not evident in categorical measures, only in the key continuous measure, the Simpson-Angus Scale. The Simpson-Angus Scale is the most widely used measure of EPS in clinical trials. Categorical analyses are less capable of revealing differences than are those that analyze continuous variables, which EPS most certainly is. The EPS difference between the 2 drugs would have been even more marked had we not permitted the use of anticholinergic drugs. Anticholinergic drugs often interfere with cognitive function and are best avoided, as would be the case with aripiprazole. In the CATIE trial,<sup>4</sup> significantly more patients discontinued perphenazine due to EPS than discontinued the second-generation antipsychotics ( $p = .002$ ). We would argue that long-term treatment with conventional antipsychotic medications is also associated with a greater risk of tardive dyskinesia, though data for perphenazine specifically are lacking.<sup>5</sup>

The message from our study was not to suggest that any and all treatment-resistant patients should be given a trial of perphenazine or aripiprazole. We perhaps did not state clearly enough that, if patients fail a single trial of an atypical antipsychotic agent such as olanzapine or risperidone, a second trial might be of perphenazine or aripiprazole. As most patients who are treatment resistant will have had trials of 2 or more atypical antipsychotic drugs for adequate duration and at adequate doses, clozapine would be the most likely choice for the majority of patients who meet the criteria for treatment resistance, as we have advocated elsewhere.<sup>3</sup>

Dr. Rosenheck's conclusion that clinicians should basically choose any drug from the so-called first- and second-generation drugs, which he views as completely equivalent, as long as the patient has not previously tried it, is not a view we share. This suggestion ignores differences between these 2 drug classes and ignores considerable differences within the group of atypical antipsychotic drugs on mechanism of action and metabolic side effects, and to some extent effectiveness in nonresponding patients as suggested in CATIE Phase II.<sup>6,7</sup>

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*Dr. Kane has served on speakers or advisory boards for AstraZeneca, Bristol-Myers Squibb, Pfizer, Eli Lilly, Janssen, and Wyeth. Dr. Meltzer has been a consultant to Janssen, Bristol-Myers Squibb, Eli Lilly, Pfizer, ACADIA, Solvay, and Memory; has received grant/research support from Janssen, Eli Lilly, Sepracor, ACADIA, Organon, and Memory; has served on speakers or advisory boards for Pfizer; is a stock shareholder in ACADIA; and has received other financial or material support from Janssen and AstraZeneca. Dr. Carson is an employee of Otsuka Pharmaceutical Development and Commercialization, Inc. Dr. McQuade is an employee of Otsuka Pharmaceutical Development and Commercialization, Inc., and is a stock shareholder in Bristol-Myers Squibb. Dr. Marcus is an employee of Bristol-Myers Squibb. Dr. Sanchez is an employee of and a stock shareholder in Bristol-Myers Squibb.*

*This letter was written by the authors on behalf of the Aripiprazole Study Group. Study investigators are listed at the end of the original article.*

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### **A Case of Aripiprazole-Related Tardive Akathisia and Its Treatment With Ropinirole**

**Sir:** Aripiprazole, like the other members of the class of atypical antipsychotics, is hypothesized to have a low risk of both acute and long-term extrapyramidal adverse effects. While only 1 case of tardive dyskinesia associated with aripiprazole thus far has been reported in the literature,<sup>1</sup> acute akathisia is commonly seen with this drug,<sup>2</sup> as can be the case with both typical and atypical antipsychotic medications. However, tardive akathisia remains a rare complication in the use of antipsychotics overall. The following report describes the case of a 55-year-old white woman who developed tardive akathisia while taking aripiprazole. We believe it is the first such case reported. Furthermore, we report successful control of the symptoms of tardive akathisia with the dopamine receptor agonist ropinirole.

**Case report.** Ms. A presented for outpatient treatment in June 2004 for ongoing symptoms of anxiety and depression. She carried DSM-IV diagnoses of generalized anxiety disorder, recurrent major depressive disorder, generalized social phobia, and obsessive-compulsive disorder. She had failed trials of a wide variety of available antidepressant medications due to either lack of benefit, or, more commonly, adverse effects. In particular, Ms. A had shown poor tolerance to most serotonergic

medications (selective serotonin reuptake inhibitors, buspirone, and several tricyclic antidepressants) due to either increased anxiety or restlessness, even with small starting doses. Her medication regimen at the time of presentation included bupropion sustained release, 100 mg daily; clonazepam, 0.5 mg daily; methylphenidate, 20 mg thrice daily for narcolepsy; and aripiprazole, 5 mg daily for the past 3 months.

During the course of treatment over the next several months, Ms. A was tried on several medications in attempts to reduce her anxiety and depression. First, because Ms. A reported some previous benefit from the aripiprazole, the dose was titrated up to 7.5 mg daily for 2 weeks and then to 10 mg daily. This approach produced no noticeable improvement, and Ms. A reported restlessness and insomnia, both of which subsided when, after 2 weeks, the dose was reduced back to 5 mg daily.

Six weeks later, duloxetine was initiated at 30 mg daily and was taken for about 1 month before the dose was titrated up to 60 mg. About 1 month later, Ms. A reported severe restlessness and inner tension. Upon examination, she was noticeably uncomfortable, exhibiting generalized restlessness, particularly in her legs, moving them frequently from one position to another. She could voluntarily control the movements but found it uncomfortable. She had no other abnormal movements, including no signs of parkinsonism or dyskinesia. Upon further inquiry, Ms. A realized that she had been experiencing the akathisia at milder levels since starting the aripiprazole. She mistook the akathisia for anxiety, but, with the worsening of the akathisia, she became able to differentiate it from anxiety. The aripiprazole was discontinued immediately but without improvement. Similarly, over the next few weeks, duloxetine, bupropion sustained release, and methylphenidate were discontinued, also without benefit. The latter 2 medications were reinstated after about 2 weeks, as they had provided benefit for years prior to the development of these symptoms.

Trials of many medications purported to help ameliorate symptoms of akathisia were instituted over the next several months, including (in sequential order, with some overlap) higher doses of clonazepam (up to 1 mg thrice daily for about 3 months), propranolol (up to 20 mg thrice daily for 1 month), diphenhydramine (up to 50 mg thrice daily for several days [too sedating]), and benztropine (up to 2 mg thrice daily for 3 months). While obtaining modest relief, particularly with the more sedating medications taken at bedtime, Ms. A continued to have almost constant severe akathisia. Thorough examinations by her primary care physician and a neurologist specializing in movement disorders, including laboratory evaluations, found no evidence for etiology of the restlessness other than akathisia. The results of these evaluations, in addition to the persistence of akathisia for months after discontinuation of the causative agent(s), supported the diagnosis of tardive akathisia.

After the benztropine trial was discontinued, a 2-month trial of quetiapine provided moderate relief limited by sedation at 200 mg/day. After quetiapine was discontinued, a trial of reserpine was started and proved to be the most helpful of all previous medications that were tried, providing about 50% relief at maximal doses of 9 mg daily, without adverse effects such as depression. Unfortunately, Ms. A appeared to develop a tolerance to the beneficial effects of the reserpine, as her akathisia gradually worsened over the several months that she was maintained at this dose.

In May 2005, ropinirole, a dopamine agonist, was approved by the U.S. Food and Drug Administration for the treatment of restless legs syndrome. Because restless legs syndrome shares many of the features of akathisia, a rationale existed for trying

it in this patient. After discontinuation of reserpine, ropinirole was started at 2 mg/day and titrated upward. Ms. A experienced a dose-dependent improvement in her akathisia, with almost complete amelioration of her symptoms at a daily dose of 18 mg divided into several doses during the day. However, the akathisia was still present more than 18 months after discontinuation of the potential offending agents as its symptoms reappeared when she attempted to decrease the dose of ropinirole, a result that supports the diagnosis of tardive akathisia as well as the efficacy of ropinirole for its treatment.

To our knowledge, this is the first report of a case of tardive akathisia associated with aripiprazole. Aripiprazole appeared causally related to the tardive akathisia due to (1) the irreversibility of the akathisia in relation to aripiprazole therapy, and (2) the greater prior probability of antipsychotics versus serotonergic medication as the causative agent (guilt by association).

Also, to our knowledge, this is the first report of a case of the effective treatment of tardive akathisia with ropinirole. With tardive akathisia, there are no controlled studies and few other data to guide pharmacologic intervention, making its treatment problematic. However, this report now provides at least anecdotal evidence for the use of ropinirole as a new intervention for the disabling symptoms of tardive akathisia. More generally, this case highlights the need for clinicians to carefully consider the risk-to-benefit ratio for antipsychotic medications and not to assume that because an antipsychotic is "atypical" it is free from risk of clinically significant movement disorders.

*Dr. Hettema has no financial affiliations or other relationships relevant to this topic of this letter. Dr. Ross serves on the speakers board for AstraZeneca.*

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### Aripiprazole Treatment of Patients With Borderline Personality Disorder

**Sir:** Aripiprazole, a U.S. Food and Drug Administration–approved drug, has been shown to be more effective than placebo for schizophrenia<sup>1,2</sup> and bipolar disorder<sup>3</sup>; however, our 2004/2005 controlled trial is the only one to our knowledge to assess aripiprazole in the treatment of DSM-IV borderline personality disorder.<sup>4</sup> We observed significant changes,<sup>4</sup> and, after the blind was broken at the end of that study, I conducted the present, 18-month follow-up observation of the same patients to evaluate the longer-term influence of aripiprazole.

**Method.** The patients in the first study were treated daily for 8 weeks with 15 mg of aripiprazole (N = 26: 21 females and

5 males) or placebo (N = 26: 22 females and 4 males) and tested weekly with the Symptom-Checklist (SCL-90-R),<sup>5</sup> the Hamilton Rating Scale for Depression (HAM-D),<sup>6</sup> the Hamilton Rating Scale for Anxiety (HAM-A),<sup>7</sup> and the State-Trait Anger Expression Inventory (STAXI).<sup>8</sup> In the present institutional review board–approved follow-up study in which all participants provided informed consent, the intervention group continued with 15 mg aripiprazole daily as a monotherapy, and the previous placebo group received no further placebo intervention since the blind was already broken. The use of any kind of new psychiatric medication also constituted an exclusion criterion for the placebo group during the 18-month follow-up. The subjects were tested with the same instruments twice a year, and, after 18 months, they were tested and physically examined 1 last time. Thirteen patients dropped out (aripiprazole group, N = 4; previous placebo group, N = 9).

Data were evaluated with the statistical program SPSS, Version 12 (SPSS Inc., Chicago, Ill.), using intent-to-treat analysis. The data were normally distributed (Shapiro-Wilk test). I performed a 2-factor repeated-measures analysis of variance, defining the treatment condition as the between-subject factor and the measurements in time as the within-subject factor, and adjusted the results with the Greenhouse-Geisser epsilon whenever assumptions for the repeated-measures analysis were not given. In order to determine the differences at the initial and final points, I conducted multiple comparisons, using contrasts for each treatment condition. The significance levels were adjusted with the Bonferroni correction.

**Results.** At 18-month follow-up, significant changes resulted in the aripiprazole group on the SCL-90-R (group × time effect, all  $p < .01$ ; group effect, all  $p < .01$ ), HAM-D (group × time effect,  $p < .01$ ; group effect,  $p < .01$ ), HAM-A (group × time effect,  $p < .01$ ; group effect,  $p < .01$ ), and STAXI (group × time effect, all  $p < .01$ ; group effect, all  $p < .01$ ), indicating a reduction in global psychological stress, aggression, and depression. The previous placebo group had 2 suicide attempts but the aripiprazole group had none.

Headache, insomnia, nausea, numbness, constipation, and anxiety, aripiprazole's most frequent side effects,<sup>1–3</sup> as well as occasional self-injury, were observed in the aripiprazole group, which corroborates the previous study.<sup>4</sup> As in the previous study,<sup>4</sup> I observed no significant weight change.<sup>1,2</sup>

Improvement in the aripiprazole-treated group continued over time, and the medication was relatively well tolerated. These findings not only corroborate previous reports,<sup>3,4,9</sup> but they also expand the scope of symptoms that can be treated by aripiprazole.

Aripiprazole appears to be relatively safe and effective in the longer-term treatment of borderline personality disorder. The positive treatment effect found in the first controlled study<sup>4</sup> could be replicated in this observational follow-up study.

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