Long-Term Effects of the Terrorist Attack in Beslan on Adolescent Survivors

Sir: The important study by Moscardino et al.[1] showed that adolescents who survived the Beslan terrorist attack (North Ossetia) did not report more overall levels of psychological distress (as measured with the Brief Symptom Inventory 18 and Strengths and Difficulties Questionnaire) 18 months after the event than a group of adolescents who were not in the school during the attack.

The authors conclude that these findings are in line with previous research suggesting that both directly and indirectly exposed children are at risk of developing adverse psychological symptoms after terrorism-induced trauma. However, a nonexposed control group was not included. Since the "normal" level of psychological distress among comparable nonexposed adolescents is unknown, this limitation severely hinders firm conclusions about the possible mid-term effects of the terrorist attack and may overestimate adverse affects.[2]

The cross-sectional nature of the study and the measures used prohibit any conclusion about the course or development of general psychological problems. Perhaps Moscardino and colleagues are right, but the reported data do not support their conclusion about the risk of developing adverse psychological symptoms. Of course, controlling for nonretrospective data on pre-event functioning is a powerful alternative, but in the case of such disasters, these data are hardly available.[3] The only thing we are sure of is that both groups reported comparable levels of general psychological distress 18 months postevent. In addition, the high ethical standard of the researchers prevented the assessment of posttraumatic stress disorder—although Galea et al.[4] showed that adverse effects of administering such measures might be very limited—and therefore it is unclear whether both groups are equally at risk for developing symptoms related specifically to the adverse event.

Although the nature of the trauma exposure was not comparable with that in the Beslan case, a 5-year longitudinal study[5] (using the electronic medical records of general practitioners) of health effects among adolescents in a discotheque fire showed that in the first year youth both with and without burns presented many symptoms, psychological as well as physical. After 1 year, the problems of youth without burns decreased to the level of a matched control group. Apart from the societal situation in Beslan, it may be expected that problems will diverge in time between exposed and nonexposed adolescents. Nonexposed youth from the same community may be subjected to "the hierarchy of suffering," meaning that there is less attention for their problems.

Furthermore, a group of families surviving the attack were hosted or relocated for a 6-week period 3 months after the event in a private residential structure in Trento, Italy. The authors were contacted to provide psychological assistance. Disaster studies suggest that relocation, even during a relatively short period, might be a risk factor for postevent psychological disturbances.[6] Being relocated with the expectation of returning after 6 weeks to a changed social system in which, according to one participant, "Now everyone follows his own path, not knowing which direction to take"[1(p858)] might be an important new source of stress. On the other hand, the 6-week period in Italy may have provided comfort, rest, and social support and helped to foster resilience and diminish stress,[7] as was probably the aim of the 6-week hosting. Possible participation of adolescents in both groups in this 6-week relocation was not presented in the article, nor part of the analyses, although it may confound outcomes.

According to the researchers, this study is part of an ongoing project on the mental health of Beslan's children and families. As stated in the article, the number of studies examining the long-term psychological effects of such attacks is limited. We hope that the authors are able to conduct a follow-up study in which the aforementioned issues can be addressed.

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

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Dr. Moscardino and Colleagues Reply

Sir: Van der Velden and Yzermans have raised several issues regarding the long-term psychological effects of the 2004 terrorist attack in Beslan on directly and indirectly exposed adolescent survivors. They express concern that the absence of a nonexposed control group and preattack data on participants' psychological functioning hinders any conclusion about the course or development of general psychological problems in this population.

Previous research has shown that adolescents who have had high levels of exposure to terrorism in terms of physical, temporal, and emotional proximity (e.g., loss of loved ones) are at increased risk of developing adverse reactions to trauma[1] and that youths who are indirectly exposed to a violent event may also manifest symptoms of anxiety and depression.[2] For example, Pfefferbaum et al.[3] found that children geographically distant from the Oklahoma City bombing who had not directly experienced an interpersonal loss reported posttraumatic stress disorder symptomatology and functional impairment. Shalev and colleagues[4] reported comparable rates of posttraumatic stress disorder and similar levels of distress symptoms among directly

and indirectly exposed groups of Israeli and Palestinian young adults exposed to continuous terror. Consistent with these findings, our study revealed that directly and indirectly exposed youths surviving the terrorist attack did not differ in overall psychological distress 18 months after the event. This pattern may be attributed to the large number of deaths caused by the attack, which exerted a particularly disrupting effect not only at the individual level, but also at the community level.[5]

Although we agree that comparing the 2 groups of Beslan adolescents without sampling youth located geographically distant from the attack is not an exhaustive approach, we do believe that our data are informative and could function as possible starting points for future research on adolescents affected by terrorism. Furthermore, we recently conducted a follow-up study to assess adolescents' psychological symptoms 1 year after the first evaluation. Interestingly, preliminary findings suggest that problems seem to diverge in time between directly and indirectly exposed groups as well as between girls and boys, thus supporting the idea that the initial comparable levels of psychological distress among both groups could follow different developmental trajectories.

Van der Velden and Yzermans raise a question about the possible effects of the 6-week hosting in Italy of affected families. As reported in our article, the extremely negative conditions of these families served as a basis for the present study, in which we conducted a large-scale assessment of adolescents' psychosocial adjustment addressing the major issues previously expressed by Beslan caregivers during open-ended interviews (see Moscardino et al.[5]). None of the children hosted in Trento, Italy, participated in the current study, as they were much younger than the target group.[6]

In conclusion, we acknowledge that the cross-sectional design of the study and the lack of a comparison group residing in a city that has not experienced the attack limit inferences about the developmental course of psychological distress among adolescents surviving terrorism. However, the aim of our follow-up study was to address these issues by providing longitudinal data that serve as the comparison (i.e., within-subject comparisons), thus avoiding the limitation of cross-sectional data. Given the public health significance of effective interventions for adolescent populations, further longitudinal studies are needed to better understand the psychological consequences of terrorism exposure at specific developmental stages and follow the course of impact over time.[7,8]

The original study was supported in part by the nongovernmental organization "Help Us Save the Children," Rovereto, Italy, and by the Faculty of Psychology, University of Padua, Italy. The authors report no additional financial or other relationship relevant to the subject of this letter.

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Self-Medication, Bipolar Disorders, and Stimulant Dependence

Sir: In the August 2008 issue of the *Journal*, Nejtek et al.[1] present findings that both quetiapine and risperidone produced improvement in manic, mixed, and depressive symptoms. In turn, symptom reduction was associated with reduced drug cravings in patients with co-occurring bipolar and stimulant dependence disorders, albeit not affecting drug use. These are important findings in that (1) there is an extraordinarily high incidence of co-occurrence of substance abuse in general associated with bipolar disorders and, in particular, a high co-occurrence of stimulant abuse; and (2) there are few if any specific effective psychopharmacologic treatments for stimulant dependence. Although in their study the reduction of psychiatric symptoms and craving did not seem to influence drug use, the study nevertheless demonstrates that successfully treating bipolar symptoms does produce important inroads on one of the important aspects of addiction, craving, involved in drug relapse and dependence.

In concluding remarks in their article, Nejtek et al. suggest that their results "offer no support for the self-medication hypothesis of Khantzian,"[1(p1265)] citing the 1985 article wherein the self-medication hypothesis (SMH) first articulated was first published.[2] In that article and in a subsequent update of the SMH,[3] beyond painful affects, difficulties with regulating self-esteem, relationships, and self-care were emphasized as important factors in influencing dependence on addictive substances. The distress associated with manic, mixed, and depressive symptoms is only one variable that drives addictive behavior. When other variables (such as self-esteem, relationships, and behavior) are targeted with added psychosocial interventions such as individual and group therapy, appreciable improvement in distress and drug use are observed.[4,5]

That the authors conclude there is no support for the SMH is puzzling and unwarranted. Although they fail to find "direct evidence" that mood improvement did not reduce overall drug use, this finding alone does not support the conclusion that there is no support for the SMH. The reasons for continued drug use among substance-dependent individuals with or without symptomatology are complex. The SMH, more than anything else, emphasizes a range of painful subjective states that individuals self-medicate, that may or may not be associated with psychopathology. Studies such as the one by Nejtek et al. more often fail to code for or identify such subjective factors. In fact, when empirical studies using diagnostic criteria add measures that track for such subjective distress, they just as often identify self-medication factors to be operative.[6–8] Furthermore, beyond

important neurobiologic mechanisms that perpetuate continued drug use, there are psychological mechanisms to explain the repetitious self-defeating aspects of addiction, which in and of themselves are powerful and important.[9,10]

Dr. Khantzian is a stock shareholder in Merck, Johnson & Johnson, and Bristol-Myers Squibb. Dr. Albanese reports no financial or other relationship relevant to the subject of this letter.

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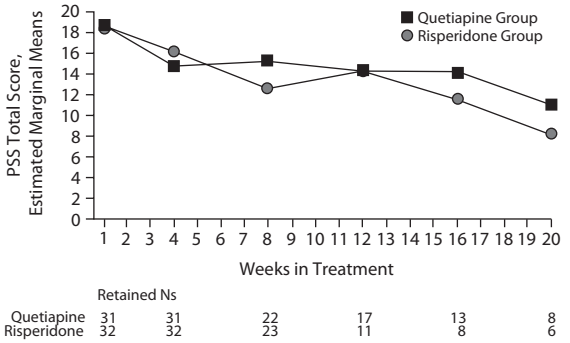
Dr. Nejtek and Colleagues Reply

Sir: We appreciate the opportunity to reply to the insightful comments of Drs. Khantzian and Albanese regarding the self-medication hypothesis and our recent findings published in August 2008.[1] We acknowledge that addiction etiology includes a domain of psychologically distressing subjective factors such as problems regulating self-esteem, relationships, and self-care, as stated by Khantzian and Albanese.

Nejtek et al.[1] used DSM-IV criteria for all subjects. Substance "dependence" includes persistent psychological problems and impaired social, occupational, and/or interpersonal functioning. DSM-IV criteria for bipolar disorder suggest a level of severity causing "marked impairment" evident in depressive and manic symptoms such as psychomotor agitation, sleep disturbances, excessive positive or negative self-worth, or irritability creating an "unequivocal and uncharacteristic change in functioning that is observed by others."[2] Thus, subjective factors involving self-esteem, relationships, and self-care are embedded within these specific DSM-IV diagnostic criteria.

Figure 1. Perceived Stress Scale (PSS) Total Scores at Weeks 1, 4, 8, 12, 16, and 20 in Quetiapine and Risperidone Groups[a]



[a]Type III tests of fixed effects: treatment (study) weeks: F = 5.34; df = 5,140.3; p < .0005; treatment (study) weeks by medication: F = 1.06; df = 5,140.3; p = .39.

Other instruments used weekly by Nejtek et al.[1] were the Young Mania Rating Scale[3] and the Inventory of Depressive Symptomatology,[4,5] which, together, captured subjective factors such as anxiety, irritability, self-esteem (high/low self-worth), relationships (sexual interest, problems with communication, interest in people/activities), and self-care (appetite, grooming). We expected to find a correlation between these subjective symptom improvements and reductions in drug use. However, the data revealed no direct evidence (i.e., statistical significance) that improvements in these subjective factors reduced drug use.

In Nejtek et al.,[1] we did not report scores from the Perceived Stress Scale,[6] as this scale was a secondary outcome not pertinent to our primary hypotheses concerning quetiapine or risperidone treatment for mood, drug craving, and drug use. As Drs. Khantzian and Albanese have brought subjective factors to the forefront, we have analyzed the role that perceived stress might have played in drug use and report secondary analyses using Perceived Stress Scale scores. The Perceived Stress Scale[6] is a 14-item tool that evaluates subjective factors related to coping with uncontrollable stressors. As Figure 1 illustrates, our longitudinal data show no statistical relationship between stress reduction and reduced drug use. The Perceived Stress Scale data mirror those from the Young Mania Rating Scale and the Inventory of Depressive Symptomatology as reported in Nejtek et al.,[1] which, as stated previously, include subjective factors of distress, self-esteem, relationships, and self-care.

We do not disagree with the basic philosophical rationale proposed by the self-medication hypothesis.[7,8] Conversely, the self-medication hypothesis suggests that if subjective factors of distress, self-esteem, relationships, and self-care could improve, then drug use should be reduced. Drs. Khantzian and Albanese also state that psychological problems are best resolved with psychosocial interventions. In Table 1 of Nejtek et al.,[1] we reported that 95% of the total number of patients received some type of behavioral therapy (i.e., intensive outpatient and/or 12-step programs) and 57% were engaged in residential treatment. Thus, pharmacotherapy was added to their existing therapeutic regimen.

In effect, the same subjective factors initiating drug use onset may not be the same factors that promote chronic drug

use resulting in drug dependence years later. Patients with protracted psychiatric disorders and co-occurring drug dependence have a continuous myriad of psychosocial, psychological, and complex neurobiologic mechanisms underlying *persistent* mood problems and drug use that together influence long-term prognostic outcomes. Our data remind clinicians to recognize that while pharmacotherapy may improve mood symptoms and behavioral therapy may improve psychological and/or psychosocial problems, drug use may remain dynamic, as altering persistent addiction behavior requires lifelong multimodal therapies.

The study referred to in this letter was funded with a clinical trials grant awarded to Dr. Nejtek by the Stanley Medical Research Institute. The research was also conducted with support from the Investigator-Sponsored Study Program of AstraZeneca, which provided the study drug, quetiapine. The authors report no additional financial or other support relevant to the subject of this letter.

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Switching Antipsychotic Medications: A 2-Year Chart-Review Study Exploring Patient Characteristics and Psychiatric Service Use of Schizophrenia Patients

Sir: Switching from first-generation antipsychotic medications (FGAs) to second-generation antipsychotic medications (SGAs) is common. This practice also occurs between SGAs, and occasionally from SGAs to FGAs.[1,2] Many controlled studies have examined the switch from FGAs to SGAs, but little research has been conducted to examine the process and outcomes of switching in naturalistic conditions.[3–5] Tempier and Pawliuk[6] found that switched patients used more psychiatric services than nonswitched individuals. The present study probes this finding and explores the determinants and effects of switching antipsychotic medications in patients with schizophrenia and related psychotic disorders.

Method. A chart review of 201 actively registered outpatients in a downtown Montreal psychiatric Continuing Care Clinic was conducted over a 2-year period from July 1, 2002 (T1), to July 1, 2004 (T2). Data were collected for T1, for 1 month prior to switching, for the date the switch or addition was initiated, and at T2. Patients had to have a primary DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or another schizophrenia spectrum disorder. Patients were grouped into those maintained on treatment with their antipsychotic medication (n = 156), those switched to a different antipsychotic (n = 23), or those given an additional antipsychotic (n = 22). Physician progress notes were reviewed to determine the reason(s) for switching or adding antipsychotics. The mean daily doses were translated into mean chlorpromazine-equivalent doses.[7] The use of adjuvant psychotropic medications (i.e., antidepressants, anxiolytics, anticholinergics, and mood stabilizers) was recorded and compared for changes between T1 and T2. This research protocol was cleared by the Director of Professional Services, Ethics Research Office of the McGill University Health Centre.

Psychiatric service use was measured by the following indexes: (1) number of visits to the Continuing Care Clinic, (2) emergency room visits, (3) admissions to partial hospitalization programs—the Rehabilitation Day Centre or the Transitional Day Hospital Program, (4) number of psychiatric hospitalizations and number of bed days spent at the McGill University Health Centre inpatient psychiatric unit, as well as the mode of hospitalization (i.e., whether voluntary or court-ordered).

Statistical analyses were undertaken with SPSS version 11.0 (SPSS Inc., Chicago, Ill.). General linear model 1-way analyses of variance were conducted to compare means of continuous variables between the 3 groups: maintenance, switched, and add-on. Multiple means comparison procedures were subsequently performed on significant outcomes determining which pairs of means differed. A 2-way contingency table generating a Pearson χ^2 test statistic was used to evaluate differences in proportions between the 3 groups for all categorical data. If the overall χ^2 test was significant, pairwise comparisons were conducted.

Results. The 3 groups were found to be generally homogeneous in sociodemographic characteristics, such as age, age at psychiatric disorder onset, number of psychiatric admissions, and illness duration. Patients who had a change in medication regimen (via a switch or add-on) were hospitalized more often for psychiatric reasons within the year prior to T1. Having more hospitalizations is consistent with a previous study concluding that high levels of prior inpatient and outpatient service use is the single strongest predictor for switching antipsychotic medications.[8] The higher hospitalization rates among switched and add-on patients most likely indicate increased symptomatology, which may have played a role in the decision to change antipsychotic prescriptions. In addition, switched and add-on patients were more likely to be diagnosed with a personality disorder ($\chi^2 = 15.63$, df = 8, $p < .001$). Moreover, 35% (8/23) of switched patients had a substance abuse disorder diagnosis versus 16% (25/156) of those in the maintenance group and 14% (3/22) in the add-on group, although this difference was statistically greater versus the maintenance group only ($\chi^2 = 4.690$, df = 1, $p = .030$).

At T1, there were no significant differences in the mean chlorpromazine-equivalent daily doses or proportions of FGA or SGA monotherapy, polypharmacy, or depot antipsychotic prescriptions found between the 3 groups. However, a closer look at SGA prescriptions revealed that a significantly greater proportion of maintained patients (11%) were being treated with clozapine versus switched (0%; $t = 4.354$, $p = .0002$) but not versus add-on patients (9%; $t = 0.544$, $p = .589$). At T2, 2 patients in the switched group and 1 patient in the add-on group had been initiated on treatment with clozapine, making the difference from the maintenance group no longer significant. While the number of maintenance patients on polypharmacy treatment decreased by 23 percent between T1 and T2, the number of switched patients doubled. For add-on patients, prescriptions with more than 1 antipsychotic increased 350% from T1 to T2, indicating that the majority of patients who were initiated on treatment with an additional antipsychotic were maintained on treatment with 2 or more antipsychotics. Because of polypharmacy use, the add-on group was also receiving significantly higher doses than the maintenance group ($p = .009$).

Reasons for switching antipsychotics were lack of efficacy/symptom exacerbation (48%), adverse effects (17%), medication noncompliance (17%), and patient or family request (13%). The rationales for prescribing add-on antipsychotics were lack of efficacy/symptom exacerbation (73%), patient or family request (14%), medication noncompliance (9%), and adverse effects (5%). Clinical treatment guidelines[9,10] indicate that when physicians are dealing with poor responders or patients experiencing intolerable side effects, the first strategy to improve their treatment should be to optimize (increase or lower, respectively) their current antipsychotic dose. One month prior to switching, only one third of switched patients and one half of add-on patients whose medications were changed due to lack of efficacy/symptom exacerbation or adverse effects exhibited evidence of an attempt to optimize antipsychotic dose. The remainder of these patients were maintained on the same dosage as at T1.

Over the 2-year study period, the switched group visited the Continuing Care Clinic most often (mean = 30.61 times, SD = 17.48 times), followed by the add-on group (mean = 27.55 times, SD = 22.34 times) and finally the maintenance group (mean = 18.45 times, SD = 20.98 times). Both switched and add-on groups made significantly more clinic visits compared to the maintenance group ($p = .012$ and $p = .017$, respectively). Of switched and add-on patients, 74% (17/23) and 77% (17/22), respectively, made at least 1 visit to the emergency room as compared to only 19% (30/156) of maintained patients ($\chi^2 = 51.11$, $df = 2$, $p < .001$). In addition, 39% (9/23) of the switched group and 64% (14/22) of add-on patients had an overnight stay at the emergency room at least once in comparison to only 6% (10/156) of maintained patients ($\chi^2 = 55.78$, $df = 2$, $p < .001$). Regarding partial hospitalization use, 22% (5/23) of switched patients and 23% (5/22) of add-on patients were admitted to the Transitional Day Hospital Program compared to only 2% (3/156) of the maintenance group ($\chi^2 = 23.808$, $df = 2$, $p < .001$). In addition, 23% (5/22) of the add-on group were admitted to the Rehabilitation Day Centre during the study period in comparison to 7% (11/156) of the maintenance group ($\chi^2 = 5.792$, $df = 1$, $p = .016$) and 9% (2/23) of the switched group (not significant).

In terms of psychiatric hospitalizations, a far greater proportion of switched (57%) and add-on (55%) patients were admitted compared to only 6% of the maintenance group ($\chi^2 = 58.69$, $df = 2$, $p < .001$). Of the hospitalized patients, the mean number of hospitalizations and cumulative bed days did not differ among the 3 groups. When the condition under which the hospitalization occurred was examined, a greater percentage in the switched group (62%) were committed involuntarily as compared to the maintenance (20%) and add-on (17%) groups ($\chi^2 = 6.84$, $p = .033$).

In order to control for individual medication effects, we also analyzed service use variables for maintenance group patients taking typical and atypical monotherapy and antipsychotic polypharmacy. A trend was found for the number of clinic visits patients made, with those receiving typical antipsychotics visiting the clinic the most (mean = 25.71 times, SD = 25.01 times) and those taking atypicals visiting the least (mean = 14.77 times, SD = 19.81 times) ($p = .049$). However, this finding is confounded by the fact that 68% of those on treatment with typical monotherapy were receiving depot medications and had to attend the clinic to receive their treatment. No other differences in service use existed among users of typical or atypical antipsychotics or antipsychotic polypharmacy.

The present study revealed important findings supporting several differences in clinical characteristics between maintenance, switched, or add-on groups: (1) a higher frequency of secondary personality disorder diagnoses among switched and add-on patients, (2) a higher frequency of involuntary hospitalizations (i.e., under a court order), and (3) higher frequency of substance abuse among switched patients. Previous studies revealed that schizophrenia patients with personality disorders had significantly longer inpatient stays[11] and were more likely to be noncompliant with treatment and have a decreased therapeutic response to medications[12] than those without secondary diagnoses.

Lack of drug efficacy accompanied by symptom exacerbation was the most commonly found reason for switching (48%) or adding (73%) antipsychotic medications. This finding is similar to those of previous studies that report this reason's proportion to be between 46%[13] and 67%.[14] The finding of few attempts to optimize current antipsychotic dosage 1 month prior to switching or adding is somewhat surprising. Clinicians have several options to consider when addressing a patient with suboptimal symptomatic and functional response. Optimizing treatment with the current antipsychotic should be undertaken prior to initiating a switch.[9,10] In fact, it may effectively render switching unnecessary.

Perhaps factors other than symptoms and functional capacity may have influenced a change in medication, such as greater contact with physicians, which allows for more monitoring of fluctuating symptoms.[8] It is likely that the switched and add-on patients' having more hospitalizations gave clinicians more opportunities to switch or add antipsychotic medications. Exogenous factors (i.e., not related to patient characteristics), such as the release of a new drug into the market, may also play a role in the prevalence of switching.

In summary, the results of this study support the argument that there is an association between antipsychotic medication disruption and the increased use of psychiatric services. However, this most likely reflects the existence of more severe symptomatology in switched and add-on patients and the probability that their problems continued to persist after there was a change in antipsychotic medication. It is important for physicians to understand the possible risks associated with switching antipsychotic medications and to exhaust other possibilities, particularly, dose optimization, prior to implementing a switch. The present study was limited by its retrospective design and the unavailability of functioning and/or symptom scores. Although information regarding reasons for switching was retrieved from physician progress notes, incorporating a symptom severity measure would allow for a more precise

comparison of the time course of symptoms between groups. Future research should examine whether add-on and switched patients form a homogeneous group or whether one group is more problematic than the other.

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

This work was conducted as part of Ms. Schneider's Master of Science (Psychiatry) thesis at McGill University.

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