

Resilience in the Aftermath of Terrorism and During Warzone Exposure: Is It Religiousness or Is It Number of Blood Relatives?

Sir: The carefully constructed study by Kaplan et al.¹ is a major contribution to the literature on stress resilience. The authors concluded that “Religiousness combined with common ideological convictions and social cohesion was associated with substantial resilience as compared to a secular metropolitan urban population.”^{1(p1146)} Kaplan et al. should also be lauded for emphasizing the limitations of this study. We would like to point out one additional confounding factor that Kaplan et al. should be able to examine using information already available or easily obtainable from their sample.

Strict adherents to several mainstream religions that frown on birth control usually have much larger families than secular individuals. A “subconscious awareness” that, if killed, one will still pass one’s genes on to the next generation may be associated with lower levels of anxiety during constant risk to personal survival (independent of the belief in an afterlife, for which religiousness is a proxy).

We predict that the number of first-degree blood relatives (as specifically measured by number of siblings and number of children) may explain part of the statistical correlation between self-reported religiousness and high stress resilience. This prediction is testable/falsifiable. One can carry out a multiple regression (or general linear model) in which the dependent variable is the resilience score and the independent variables are x_1 = number of siblings and x_2 = self-reported religiousness score. The interaction between x_1 and x_2 will be informative. A 3-dimensional plot (of x = number of sibling and offspring, y = self-reported religiousness, and z = resilience) can visualize the effects of interaction.

The biological/evolutionary “level of explanation” we present above is less dependent on subjective self-report and may make the findings of Kaplan et al. more generalizable. As we and others have argued (and as can be seen above), clinical hypotheses based on neuroevolutionary reasoning are eminently testable and may be useful in elucidating factors that underlie fear-circuitry-related symptomatology and stress resilience.^{2–13}

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Drs. Bracha and Hayashi report no other financial affiliation or relationships relevant to the subject of the letter.

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H. Stefan Bracha, M.D.

National Center for PTSD
Department of Veterans Affairs
Pacific Islands Health Care System
Spark M. Matsunaga Medical Center
Asia-Pacific Center for Biosecurity,
Disaster and Conflict Research
John A. Burns School of Medicine
University of Hawaii at Manoa
Kentaro Hayashi, Ph.D.
Department of Psychology
University of Hawaii at Manoa
Honolulu, Hawaii

Dr. Cohen and Colleagues Reply

Sir: We appreciate the comments of Drs. Bracha and Hayashi on our study of factors contributing to the resilience of civilian populations exposed to terror in Israel over the first 3 years of the El-Aqsa Intifada.

Drs. Bracha and Hayashi base their comments on well-established findings in animals that raise questions regarding a possible bio-evolutionary undertow to our findings. Animal populations have tended to display degrees of investment of effort in nurturing and rearing that are related to numbers of offspring and to environmental pressures. Regarding environmental pressures, inasmuch as security conditions (or foreseen risk levels for offspring) can certainly be perceived as a form of offspring investment, the idea presented by Drs. Bracha and Hayashi does, in fact, merit interest from a biological/evolutionary point of view.

We examined the data from our study population for a possible statistical relationship among number of children, religiousness, and resilience, but found no evidence of any correlation, linear or nonlinear, except for a tendency for secular

families from the Tel-Aviv area with a greater number of children to express greater stress symptoms than other groups.

The fact that we were unable to find any correlation is probably related to a number of factors, some general and others more specific to the case in point. Firstly, animal behavior and human behavior differ in degree of complexity; human behaviors are often motivated by abstract and metaphysical concepts that are difficult to compare. Secondly, the intricacies of the composition of the populations under discussion, especially in light of the highly charged and volatile geopolitico-religious nature of the conflict involved, as well as the implications that personal, community, and national motivating factors carried at the time of the study mandated the circumspection and care that we devoted to the limitations of our findings on a conceptual-ethical and practical level.

Humans have proven time and again that ideological motivation can supersede biological forces. In the very conflict under study, young people with no known psychopathology have proven to be willing to knowingly commit suicide for ideological and religio-political reasons.

As suggested, there is indeed a greater tendency for the more religious adherents to the Jewish faith, as well as other faiths, such as Catholicism, to conform to the dictum "go forth and multiply." This holds true for all areas of Israel, not only in the areas studied. Whether this dictum is related to evolutionary motivations is a matter of conjecture, far beyond the scope of our study.

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

**Hagit Cohen, Ph.D.
Michael A. Matar, M.D.
Zeev Kaplan, M.D.**

Ministry of Health Mental Health Center
Ben-Gurion University of the Negev
Beer-Sheva, Israel

Facial Hyperhidrosis–Induced Social Fear Alleviated With Topiramate

Sir: Primary hyperhidrosis is excessive uncontrollable sweating without any discernible cause. Social fears, induced by facial hyperhidrosis in a patient with panic disorder, responded to treatment with topiramate that reduced excessive sweating and alleviated the fear of embarrassment in social situations.

Case report. Mr. A, a 41-year-old, successful executive in good health, had suffered from panic disorder since childhood. Untreated panic attacks were associated with palpitations, profuse sweating in the face and upper body, "butterflies" in the stomach, poor concentration, and anxiety. Attacks occurred from once a fortnight to 5 times a day, both spontaneously and in social situations, and lasted for up to 2 hours. The attacks were followed by exhaustion. Excessive sweating was familial; his mother also sweated profusely, particularly when anxious.

Mr. A entered therapy at the age of 32 years and received clonazepam, 0.5 mg 1 to 3 times a day, and paroxetine, 20 mg/day, for 7 years. The medications were well tolerated, and they controlled symptoms of panic such as palpitations, shakiness, hyperventilation, and gastrointestinal symptoms, but not the conditioned responses of hyperhidrosis that occurred in

professionally demanding situations such as negotiations, confrontations with employees, or public speaking. The profuse facial sweating was highly embarrassing and interfered with his functions as an executive because it was noticed by others, who made teasing comments. Cognitive-behavioral therapy and a brief trial of mitrazapine did not reduce the hyperhidrosis. Therefore, the patient considered undergoing thoracic sympathectomy.

In an effort to avoid such a radical intervention, a trial of topiramate, added to his current regimen of paroxetine and clonazepam, was initiated. Topiramate was started at 50 mg/day and after 2 weeks was increased to 100 mg twice daily. After 2 weeks on a dose of 100 mg twice a day, Mr. A noticed some decrease in sweating. Topiramate was then increased to 200 mg twice a day, and sweating decreased to a tolerable level throughout the whole day. The patient is now able to conduct demanding social interactions without embarrassment. He remains free of panic attacks and experiences only mild episodes of hyperhidrosis once or twice a month. He is satisfied with the results in spite of some tiredness and mild cognitive slowing.

Topiramate was chosen because it reduces sweating and has been successful in the treatment of palmar-plantar hyperhidrosis.¹ Topiramate seems to block sweating at the level of the sweat glands. The mechanism underlying this effect is not fully understood but may be caused through inhibition of carbonic anhydrase isoenzymes localized in sweat glands.²

The incidence of hyperhidrosis in younger people is 0.6% to 1.0%, with 25% familial involvement.³ It may occur as generalized or localized, with the latter type usually beginning in childhood or adolescence. While the choice of treatments for axillar and palmar-plantar hyperhidrosis includes topical agents, ionophoresis, injections of botulin toxin, and thoracic endoscopic sympathectomy, facial hyperhidrosis usually requires sympathectomy with surgical destruction of the first and second sympathetic thoracic ganglia. However, the success rate for facial hyperhidrosis is lower than for other types of hyperhidrosis.⁴

Sympathectomy is a major intervention, and the results in facial hyperhidrosis are frequently unsatisfactory. Alternative physical treatments have not been successful in this condition. Per the findings of the case reported here, topiramate can be useful in alleviating social embarrassment caused by hyperhidrosis.

Dr. Hoehn-Saric reports no financial affiliation relevant to the subject of this letter.

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Rudolf Hoehn-Saric, M.D.

Department of Psychiatry and Behavioral Sciences
Johns Hopkins School of Medicine
Baltimore, Maryland

Tolerability of High-Dose Aripiprazole in Treatment-Refractory Schizophrenic Patients

Sir: Aripiprazole is a new antipsychotic that works as a partial agonist/antagonist at dopamine D_2 and serotonin 5-HT_{1A} receptors and has a favorable side effect profile.¹ The maximum manufacturer-recommended dose in the United States is 30 mg/day, although patients with a history of antipsychotic nonresponse are likely to be treated with aripiprazole doses over 30 mg. Review of the literature found 1 safety study of 40 patients with stable schizophrenia or schizoaffective disorder who were administered aripiprazole 30 to 90 mg with no dose-dependent increases of adverse events.² We report on the tolerability of aripiprazole at doses of over 30 mg daily in 4 inpatients diagnosed with schizophrenia or schizoaffective disorder who had an extensive history of treatment nonresponse to both typical and atypical antipsychotics and lengthy inpatient stays.

Case 1. Mr. A, a 42-year-old African American man with schizoaffective disorder, bipolar type, and diabetes, was admitted in 2002 for decompensation due to medication noncompliance. At the time of admission, Mr. A was dressed neatly but appeared tense, with no eye contact. His affect was constricted, and he was illogical, circumstantial, disorganized, and religiously preoccupied, with persecutory delusions. He had not improved with monotherapy of risperidone 4 mg or ziprasidone 160 mg.

After 2 months of treatment with aripiprazole 30 mg/day, Mr. A continued to have residual paranoia, and his aripiprazole dose was increased to 60 mg/day (by 5 mg/week). The patient responded to treatment with aripiprazole and participates at present in the patient work program and discharge planning. His heart rate and blood pressure were unchanged at doses of aripiprazole over 30 mg/day. His weight remained stable. He did not experience elevated blood sugar levels and therefore did not need additional insulin coverage, and his standing oral antihyperglycemic medications did not require change. His hemoglobin A_{1c} level remained stable. Mr. A had an elevated prolactin level of 42 μ g/L during previous treatment with ziprasidone, which decreased to a normal level of 7 μ g/L after 9 weeks on aripiprazole treatment (7 weeks after ziprasidone was discontinued). He has not exhibited extrapyramidal side effects while on treatment with 60 mg/day of aripiprazole.

Case 2. Mr. B, a 44-year-old Hispanic man with schizophrenia, disorganized type, and a history of violence, sexual assaults, and persistent psychotic symptoms, was admitted in 2000. He had been treated with haloperidol (20 mg/day), fluphenazine (20 mg/day), mesoridazine (150 mg/day), thioridazine (up to 800 mg/day), olanzapine (up to 35 mg/day for 10 months), quetiapine (up to 1200 mg/day for 6 months), lithium (600 to 900 mg/day), valproic acid (up to 1750 mg/day), gabapentin (up to 3600/day), fluoxetine (40 mg/day), paroxetine (20 mg/day), and clonidine (up to 8 mg/day) with varying success. He also underwent a clozapine trial that was discontinued due to neutropenia. Mr. B's hospital course was complicated by his water-seeking behavior, which resulted in polydipsia, hyponatremia, and acute illness requiring medical intervention.

After failure of combined therapy with ziprasidone 160 mg/day and olanzapine 40 mg/day, with lithium 300 mg 3 times per day and valproic acid 2000 mg/day, Mr. B was cross-tapered to aripiprazole 30 mg/day while continuing to receive lithium 900 mg/day and valproic acid 2000 mg/day. Aripiprazole was titrated upward by 5 mg every 5 to 7 weeks to 45 mg/day, but Mr. B continued to remain quite disorganized, incoherent, and preoccupied with internal stimuli. He was hostile in groups and

would kiss and grope female patients. After he twice required emergency administration of intramuscular (IM) haloperidol 5 mg after 18 days on treatment with aripiprazole 45 mg/day for continued psychotic and agitated behavior, aripiprazole was discontinued and haloperidol was restarted.

Case 3. Ms. C, a 37-year-old African American woman with schizoaffective disorder, bipolar type, was admitted in 2000, noncompliant with medications, disheveled, menacing, and illogical. She exhibited a labile affect, endorsed command auditory hallucinations and paranoid delusions, and was slapping her children and strangers on the street. After admission, Ms. C was continued on haloperidol treatment, which was converted from daily oral haloperidol to monthly IM depot injections of haloperidol decanoate. Olanzapine was added to this regimen and slowly titrated to 40 mg/day, and valproic acid was added and titrated to 2000 mg/day. The patient also underwent brief trials of antidepressants (sertraline, mirtazapine, and venlafaxine). During 3 years on treatment with various permutations of the above medications, the patient continued to be symptomatic.

Ms. C was titrated to an aripiprazole dose of 30 mg/day in addition to her prior treatment with olanzapine 40 mg/day and valproic acid 2000 mg/day. She continued exhibiting negative symptoms of schizophrenia. Her aripiprazole dose was increased above 30 mg by 5 mg every 4 to 6 weeks as olanzapine was tapered off. Ms. C was continued on aripiprazole 60 mg/day and valproic acid 2000 mg/day. Two months later, when she began to require emergency medication for catatonic behavior, i.e., standing for long periods of time to the point of lower extremity edema, refusing to sit, not attending to activities of daily living, and bizarre posturing, aripiprazole was tapered and ziprasidone treatment was started, with moderate improvement of the catatonic behaviors.

Case 4. Mr. D, a 46-year-old African American man with schizophrenia, paranoid type, was admitted from the outpatient clinic in 1991 for auditory hallucinations, angry outbursts, disorganization, and isolative behavior. During this hospitalization, Mr. D underwent unsuccessful trials of fluphenazine (up to 15 mg/day), fluphenazine decanoate (up to 62.5 mg every 2 weeks), haloperidol decanoate (up to 200 mg every 4 weeks), clozapine (up to 750 mg/day), olanzapine (up to 40 mg/day), depot risperidone (up to 75 mg IM every 2 weeks) combined with thiothixene (up to 30 mg/day), and oral risperidone (up to 6 mg/day). Trials of antidepressants (sertraline, paroxetine, and bupropion) were also combined with antipsychotics without beneficial results. Mr. D was unpredictably hostile, internally preoccupied, and withdrawn, with barely adequate activities of daily living prior to initiation of aripiprazole.

After 1 previous failure of aripiprazole 30 mg/day, it was initiated in addition to risperidone 4 mg/day. Mr. D's aripiprazole dose was increased over 4 months to the target dose of 60 mg/day, and risperidone was then tapered. After 1 month of monotherapy with aripiprazole 60 mg/day, the patient was placed on continuous observation for potential dangerousness and received emergency medication of IM lorazepam 2 mg after punching a ward nurse in the face when approached for having entered a female patient's room looking for his clothes. During the following month, 2 more episodes requiring IM ziprasidone 20 mg occurred: an episode of screaming and an episode in which he exposed his penis in group; aripiprazole was discontinued and haloperidol decanoate was started.

In our 4 patients treated with aripiprazole 35 to 60 mg/day, the following observations were noted: weight reduction in 3 patients, with no change of weight in the fourth patient; insomnia in 1 patient (Mr. A, adequately treated with diphenhydramine 50 mg); and no extrapyramidal side effects in any of the

patients. All patients had blood pressure, heart rate, and electrocardiogram (QTc) monitoring and measures of lipid and glucose levels, and all but 1 had measures of prolactin levels; no changes were observed. In 1 patient previously treated with ziprasidone, prolactin level returned to normal from an elevated state. For the diabetic patient, his diabetes treatment regimen and hemoglobin A_{1c} level remained stable.

Of the 4 patients presented, only 1 improved enough to allow discharge planning. Mr. A showed a dose-dependent response with greater improvement noticed at aripiprazole doses of 35 mg/day and higher. While it seems that aripiprazole is well tolerated at doses up to 60 mg/day, the ability to draw conclusions regarding efficacy in this population of treatment-resistant schizophrenic patients is limited given that patients were not clinically rated.

Dr. Lindenmayer has been a consultant for Eli Lilly, Novartis, and Bristol-Myers Squibb; has received grant support from Eli Lilly, Janssen, AstraZeneca, and Pfizer; and has been on the speakers bureaus of Johnson & Johnson, Eli Lilly, Janssen, AstraZeneca, and Bristol-Myers Squibb. Dr. Crossman reports no financial affiliation or other relationship relevant to the subject of this letter.

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Andrya M. Crossman, M.D.
Jean-Pierre Lindenmayer, M.D.
 Department of Psychiatry
 New York University School of Medicine
 New York, New York

Risperidone and Lamotrigine: No Evidence of a Drug Interaction

Sir: It has been suggested that adding lamotrigine to an ongoing treatment with risperidone and clozapine might significantly increase the serum concentration of risperidone.¹ However, lamotrigine is not known to inhibit the cytochrome P450 (CYP) enzymes CYP2D6 or CYP3A4, which are the major enzymes involved in the metabolism of risperidone.²

To extend the knowledge about this possible drug interaction, we performed a retrospective analysis on data obtained from our routine therapeutic drug monitoring database for risperidone and its active metabolite 9-hydroxyrisperidone. We identified 15 risperidone-treated patients (10 female and 5 male) who had been taking lamotrigine in doses from 50 to 425 mg/day concomitantly. The mean age was 33.8 years, and the mean time interval from ingestion of the last dose to blood sampling was 12.1 hours. Serum concentrations of lamotrigine monitored simultaneously indicated a good adherence to the treatment. The mean concentration/dose (C/D) ratio of risperidone (calculated with the sum of risperidone plus 9-hydroxyrisperidone in the numerator) was 9.4 (ng/mL)/(mg/day) (range, 3.8–14.7), and the mean risperidone/9-hydroxyrisperidone ratio was 0.56 (range, 0–2.2).

For comparison, samples from 211 patients (103 female, 108 male; mean age = 40.2 years) treated with risperidone but not

with lamotrigine or other drugs known to interact pharmacokinetically with risperidone were also reviewed. In this group, the mean time from ingestion of the last dose to sampling was 12.3 hours. The mean C/D ratio was 9.8 (ng/mL)/(mg/day) (range, 0.42–31.0), and the mean risperidone/9-hydroxyrisperidone ratio was 0.59 (range, 0–5.1).

In 5 of the 15 patients taking lamotrigine concomitantly, risperidone concentrations had also been measured when the patients had not been treated with lamotrigine. In these patients, the alterations in the serum concentration of risperidone plus 9-hydroxyrisperidone when lamotrigine was added were +73.6%, +2.2%, –29.6%, –40.0%, and –40.5%, respectively. Thus, on average, the serum levels in these 5 patients had decreased by 7% when lamotrigine was added. On the basis of the large variability in the alterations when lamotrigine was added, it cannot be excluded that a larger sample would have revealed a possible bimodal distribution. However, on the other hand, the considerable intraindividual variability is consistent with previous findings demonstrating that the average intraindividual variations in the serum concentration of antipsychotics with short elimination half-lives such as risperidone and quetiapine are about 50%, irrespective of whether or not another drug is added.³

Our findings do not support the suggestion that lamotrigine increases the serum levels of risperidone,¹ as both the C/D ratios and the risperidone/9-hydroxyrisperidone ratios were strikingly similar between the patients taking and not taking lamotrigine. In a recently published study, risperidone was shown not to influence the serum concentrations of lamotrigine.⁴ We suggest that, from a pharmacokinetic point of view, these drugs can be safely combined.

The authors have no conflicts of interest in connection with this letter.

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Ingrid Castberg, M.D.
Olav Spigset, M.D., Ph.D.
 Department of Clinical Pharmacology
 St. Olav's University Hospital
 Trondheim, Norway

Levetiracetam-Induced Depression in a Healthy Adult

Sir: Levetiracetam is a novel U.S. Food and Drug Administration (FDA)-approved antiepileptic drug reported to have a high degree of efficacy and tolerability in patients with epilepsy. The most common side effects reported in trials of levetiracetam for adjunct treatment of seizures include fatigue, somnolence, and dizziness.¹ In a meta-analysis of adverse events in placebo-controlled studies in epilepsy, depression occurred at a rate of 4% in 769 individuals taking levetiracetam versus 2% in 439 individuals taking placebo; suicide attempts

were also higher among individuals taking levetiracetam versus placebo (0.5% and 0.0%, respectively).²

Pilot studies have recently been completed to explore the potential utility of levetiracetam in the treatment of affective disorders, and both preclinical data³ and clinical trials^{4,5} suggest that it may be an effective treatment for bipolar spectrum disorders. Preclinical data show a significant decrease in motor hyperactivity in rats treated with levetiracetam, suggesting a potential role for the drug in the treatment of mania.³ Soria and Remedi⁴ reported that levetiracetam monotherapy was an effective mood stabilizer for 13 of 15 elderly patients with bipolar II disorder, and Grunze and colleagues⁵ found that 70% of patients with bipolar I disorder responded to adjunct levetiracetam in an open-label crossover study.

We report a case of a medically and psychiatrically healthy woman who developed symptoms consistent with major depressive disorder during the course of taking levetiracetam while participating in a research protocol designed to examine the effects of the drug on several measures of stress responsivity.

Case report. Ms. A was a 28-year-old married Latina woman who had no significant medical history and was free of all medications. She gave voluntary written informed consent to participate in a research protocol, which was approved by the Butler Hospital Institutional Review Board. The Structured Clinical Interview for DSM-IV-TR⁶ revealed that she did not meet criteria for any current or lifetime Axis I psychiatric disorder. Her baseline score on the Inventory of Depressive Symptomatology-Self Report version (IDS-SR)⁷ was 7. Review of systems, physical examination, routine blood and urine chemistries, urine toxicology, and electrocardiogram were all unremarkable. Ms. A's family psychiatric history was notable for major depression in her mother and for generalized anxiety disorder in her sister.

In June 2005, Ms. A was started on open-label levetiracetam 250 mg b.i.d., with titration to 500 mg b.i.d. after 1 week. She experienced mild side effects, including headache and drowsiness, but was able to tolerate them and continue in the protocol. Upon further dose increase to 750 mg b.i.d. at week 3, Ms. A experienced the onset of depressed mood, anxiety, insomnia, negative and hopeless rumination, decreased appetite, passive suicidal ideation, and frequent crying. This syndrome persisted and worsened over 1 week of treatment with levetiracetam 1500 mg/day, at which time she contacted research staff and was advised to lower the dose and come to the clinic for evaluation. Upon lowering the dosage, she experienced rapid and significant relief of the depressive symptoms, but still achieved an IDS-SR score of 23 during the clinic visit several days later.

Ms. A reported that when the depression was first evolving, she did not understand why she was feeling so sad, noting that there were no major stressors or losses in her life to explain her feelings. She had commented to her sister that she wondered if she were "going crazy," but there was no evidence of psychotic symptoms. She ultimately elected to continue in the protocol at the lower levetiracetam dose of 500 mg b.i.d., at which she experienced full relief of depressive symptoms and achieved an IDS-SR score of 2.

We prospectively observed a medically and psychiatrically healthy woman develop symptoms consistent with major de-

pressive disorder during 3 weeks of open-label titration of levetiracetam to a daily dosage of 1500 mg in the context of a research protocol. Upon decrease of the dose, her depressive syndrome resolved fully. The mechanism of this side effect is not known, and the extent to which the phenomenon described in this case report of a healthy adult applies to treatment of psychiatrically ill patients remains to be elucidated in future studies. However, in light of current interest in levetiracetam as a possible treatment for mood disorders, this finding underscores the importance of careful monitoring of the drug's behavioral effects.

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Lauren M. Wier, B.S.
Sandra B. Tavares, R.N.
Audrey R. Tyrka, M.D., Ph.D.
Lawrence H. Price, M.D.
Linda L. Carpenter, M.D.

Butler Hospital Mood Disorders Research Program/
 Department of Psychiatry and Human Behavior
 Brown Medical School
 Providence, Rhode Island