A Randomized Trial of Brief Cognitive-Behavioral Therapy for Prevention of Generalized Anxiety Disorder

Sir: Given its high prevalence and cost to society, generalized anxiety disorder (GAD) is a mental health problem that merits investigation of etiology, treatment, and prevention. We conducted a pilot study to investigate the efficacy of a preventative psychoeducational workshop for GAD with college students at risk for developing the disorder.

Method. A prevention workshop for GAD was developed based on empirically supported cognitive-behavioral treatments for GAD, and it was examined in college students who were screened using the Penn State Worry Questionnaire (PSWQ).[1] The trial was conducted at the University of Maine between September 2004 and November 2005. Participants were determined to be "at risk" for developing GAD if they manifested subclinical levels of GAD symptoms on the PSWQ as defined by a score that fell in the range between the cutoff score (62) recommended to identify people with GAD and 2 standard deviations below this cutoff score, 43.[2] The workshop was carried out over two 120-minute meetings during which education about anxiety and worry were provided and cognitive-behavioral strategies (e.g., self-monitoring, cognitive restructuring, progressive muscle relaxation, worry exposure, problem orientation/problem solving) for managing both were taught. Participants (N = 72; 48 women, 24 men) were randomly assigned to either an intervention (workshop, N = 35) or a no-treatment control condition (N = 37). An integral aspect of prevention research is examining the rate of incidence of a disorder over time in the sample of interest. We used the Generalized Anxiety Disorder Questionnaire-IV[3] to provide dichotomous data regarding presence or absence of GAD 1 year after workshop participation.

Results. Five participants (14%) in the control condition developed GAD by 12 months postintervention compared with 1 participant (3%) in the intervention condition. Fisher exact test of significance suggested different rates of GAD for at-risk participants in the intervention and control conditions (p = .11, 1-tailed). Because this analysis of our pilot study approached statistical significance, we determined that, in order to obtain statistical power of .80, a minimum 89 participants per condition would be required in a future study. Thus, although the sample size in our pilot study was too small to make a definitive judgment about prevention of GAD, more individuals in the control condition developed clinically significant symptoms by 12 months after baseline assessment than did individuals in the intervention condition.

Future GAD prevention research should address a number of factors in order to best ensure that incidence of the disorder is indeed prevented in a given sample. It is clear that certain conceptual and methodological issues, such as identification of risk factors (e.g., subclinical levels of psychopathology); empirically based, cost-efficient interventions; and participant-selection criteria, are imperative to consider when designing preventative interventions. The present study provided initial evidence of the feasibility of conducting prevention research for GAD. In an era of rising costs for health and mental health care, prevention programs for prevalent disorders such as GAD are important. A brief, psychoeducational intervention may be a usable format for disseminating a prevention program for this and other disorders.

The trial discussed above was conducted as part of Dr. Higgins' dissertation at the University of Maine, for which she received grant/research support from the University. The authors report no additional financial or other relationship relevant to the subject of this letter.

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Who Put the Tyramine in Mrs. Murphy's Fava Bean?

Sir: Music aficionados will, no doubt, recognize the parody on the title of Harry "The Hipster" Gibson's 1944 smash hit, "Who Put the Benzedrine in Mrs. Murphy's Ovaltine." Today, our concern is not Benzedrine and Ovaltine but, rather, why fava beans have attained the reputation of being one of those "tyramine-rich foods . . . to avoid" in the presence of monoamine oxidase inhibitors (MAOIs).[1(p87)] The product package inserts for EMSAM (selegiline transdermal system)[2] and Azilect (rasagiline)[3] contain warnings against ingesting tyramine-rich foods including "broad bean pods (fava bean pods)." The package insert for Parnate (tranylcypromine)[4] includes a contraindication to the use of high–tyramine content foods including "the pods of broad beans (fava beans)," as does the Marplan (isocarboxazid)[5] package insert. Even Wikipedia, the free Internet encyclopedia, states that "broad beans are rich in tyramine, and thus should be avoided by those taking [MAOIs]".[6] This statement is echoed on numerous other Web sites. The Nardil (phenelzine)[7] package insert is appropriately more circumspect, however, in contraindicating "the ingestion of foods with a high concentration of tyramine or dopamine."

Let us take a closer look at *Vicia faba*, aka the broad bean, horse bean, Windsor bean, field bean, tic bean, faba bean, and fava bean. It turns out that levodopa (L-dopa) was first isolated from *Vicia faba* seedlings in 1913 by Marcus Guggenheim.[8] In 1964, reports appeared describing hypertensive crises in 2 patients on treatment with MAOIs after ingesting broad beans. A patient taking pargyline, an MAOI, developed palpitations and severe headaches after eating whole, cooked broad beans. The pods alone had a similar effect, but not the seeds.[9] The other patient, on treatment with phenelzine, developed a severe

headache after eating fresh, young broad beans that had been sliced whole and boiled.[10] Hodge et al.[9] analyzed the bean pods and found that "Dopa was the predominant amino acid found, and the only one present with pressor activity." There was no significant amount of tyramine found.[9] In 1969, a discussion of interactions of MAOIs with foods and drugs noted that dopa "also occurs naturally in quite significant amounts in broad beans."[11(p150)]

Subsequently, a number of authors have correctly noted that dopa, not tyramine, is the guilty pressor substance in fava beans. Shulman et al.[12(p400)] assayed tyramine levels in over 100 foods; the finding for fava beans was "NIL" (none). In a 1989 table of foods interacting with MAOIs, *The Medical Letter* included fava beans as "foods not containing tyramine" but noted that they contain "dopamine, a pressor amine, particularly when overripe."[13] Sullivan and Shulman[14(p710)] also stated "dopamine, another pressor amine, is the active substance which is present in significant amounts in the bean pod and warrants an absolute restriction." McCabe and Tsuang[15(p180)] mention "the other pressor amine, levodopa or dopamine, is found in significant amounts in fava beans." Micromedex also implicates L-dopa (Thomson Micromedex, Greenwood Village, Colorado).

But wait! Moret et al.[16] found that fresh broad beans did contain tyramine in a concentration of about 1.0 mg/100 g of fresh weight. Also, Shalaby[17] found that germinated broad bean seeds contained tyramine—9.5 mg/kg to be exact. After cooking, however, no tyramine was detected in the seeds.

How much of an impact on blood pressure would these amounts of tyramine have? Bieck and Antonin[18] found that in 12 tranylcypromine-treated subjects, the mean oral tyramine dose required to increase systolic blood pressure by 30 mm Hg (the tyramine pressor test) was 8 mg. According to data from Moret et al.[16] and Shalaby,[17] someone taking an MAOI would have to eat almost a kilogram of *uncooked* broad beans for the tyramine content to have just a modest effect on blood pressure.

Do fava beans contain tyramine? The answer appears to be yes, if the beans are fresh and uncooked. Even then, the amount is unlikely to have a clinically meaningful effect on blood pressure in the presence of an MAOI. During cooking, tyramine is leached into the water and the cooked beans become tyramine-free. So, indeed, it is the dopamine (actually L-dopa) that should be of concern in Mrs. Murphy's fava bean. Nevertheless, both tyramine-rich and dopa-rich foods should be avoided with MAOIs.

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

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Management of Obsessive-Compulsive Disorder–Related Skin Picking With Gamma Knife Radiosurgical Anterior Capsulotomies: A Case Report

Sir: We present the case of a patient with severe skin picking who had not responded adequately to pharmacologic or behavioral therapy. He received bilateral anterior capsulotomies using gamma knife radiosurgery leading to improved behavior, reduction in skin picking with wound healing, and no adverse effects. The role of radiosurgery for severe obsessive-compulsive behavior is discussed.

Pathologic skin picking is classified as an impulse-control disorder not otherwise specified in the DSM-IV. It is a repetitive, body-focused disorder that can have considerable overlap and show features of other psychiatric illnesses, such as obsessive-compulsive disorder (OCD), body dysmorphic disorder, and trichotillomania.[1–3] It can be a common condition and has been reported to occur in 2% of the population.[1] The medical morbidity of this condition can be significant, with such complications as scarring and dermatologic infections.[4] When the skin picking is severe, life-threatening complications have been reported.[1] The diagnosis of OCD can be made in approximately 50% of skin-picking patients.[5] Other associated diagnoses include alcohol abuse (39%), body dysmorphic disorder (32%), and trichotillomania (23%).[1] Management of patients with severe skin picking or self-mutilation typically includes medical therapy consistent with OCD-related illness, such as medications and behavioral therapy.[6,7] In rare instances, intractable OCD may be treated with surgery, such as limbic leucotomy.[8]

There is a recent interest in the use of neuromodulation with anterior internal capsule deep brain stimulation for patients with OCD.[9,10] However, in a patient with severe skin picking, implantation of stimulation hardware is not feasible. In this report, we detail the results of gamma knife radiosurgical anterior

Figure 1. (A) Appearance of the Anterior Neck Following Skin Grafting (B) Appearance of the Active Site of Skin Picking Over the Upper Back

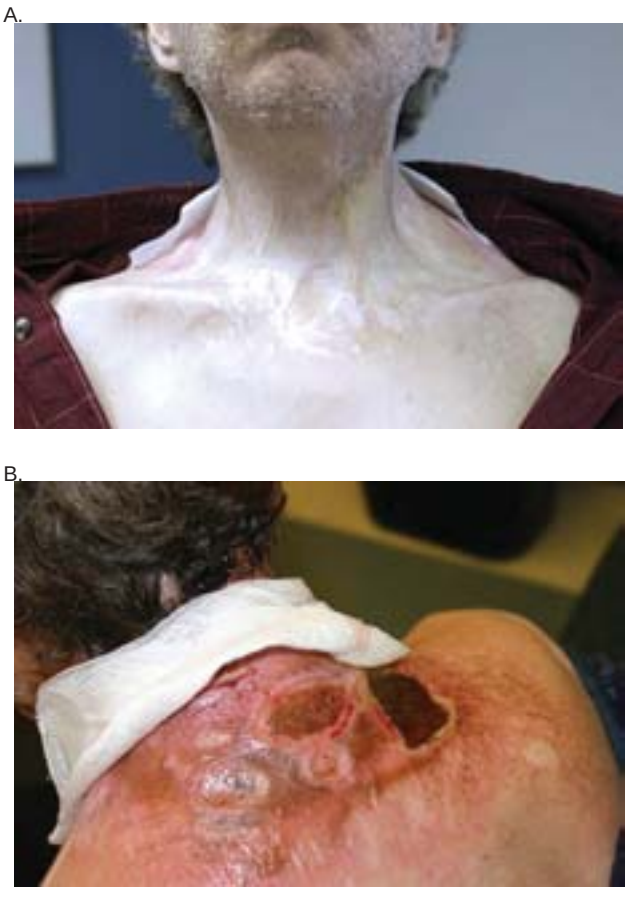
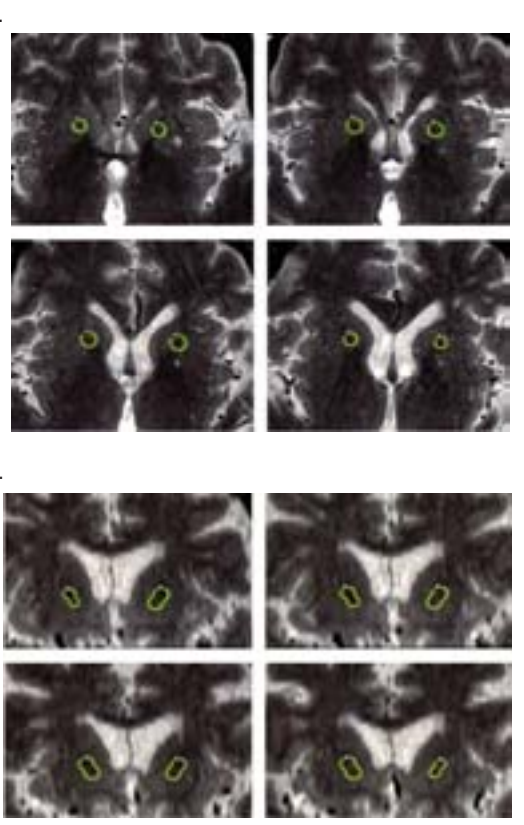


Figure 2. Axial (A) and Coronal (B) Gamma Knife Radiosurgical Dose Plans for Anterior Capsulotomy



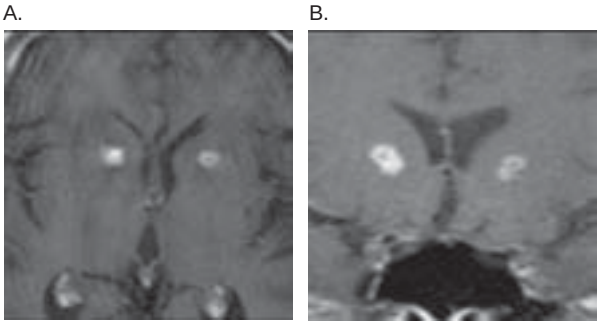
capsulotomies for a patient with severe mutilation. This study was approved by the Institution Review Board of the University of Pittsburgh. The patient provided his own informed consent.

Case report. Mr. A, a 55-year-old, married, male engineer, had a 25-year history of skin picking with increasingly severe self-injury when he first presented to our hospital facility in 2002, after having been cared for at other regional facilities for several years. His behavior was focused mainly on the head and neck. He did not have a history of trichotillomania, but he had some features of OCD, such as obsessional slowing. He had used scissors and other instruments to cut and gouge his skin and had required skin grafts on numerous occasions, which he had either removed or damaged. He was chronically anemic due to blood loss. An anterior neck skin graft (January 2006) had been eventually successful (Figure 1A), and the patient turned his attention to picking the skin over the upper back (Figure 1B). He had worked as an engineering technician for almost 3 decades prior to going on disability. He was a conscientious worker and, although married, was socially isolated. He had received multiple medication trials with antidepressants, atypical antipsychotic agents, naltrexone, and gabapentin. He had tried and failed numerous courses of outpatient behavioral therapy and one course of intensive outpatient therapy. Prior to surgery, he was taking clomipramine (50 mg p.o. q.h.s.), quetiapine (300 mg p.o. q.h.s.), and divalproex sodium (500 mg p.o. t.i.d.). The patient had also taken fluvoxamine 300 mg once daily. As per our behavioral disorders protocol, he underwent 2 separate psychiatric evaluations prior to the recommendation of surgery. A second assessment recommended a trial of high-dose olanzapine (20 mg p.o. q.h.s.) for 3 months, which was completed but did not provide benefit. The time from the first neurosurgical assessment (February 2005) to the procedure was 14 months. Prior to surgery, his Yale-Brown Obsessive Compulsive Scale (YBOCS)[11] score was 39 of a possible 40 points.

He underwent outpatient gamma knife radiosurgery to create bilateral anterior capsulotomies.[12,13] After stereotactic frame placement under local anesthesia, high-resolution contrast-enhanced volume-acquisition images through the basal ganglia and long relaxation time sequences allowed imaging of the anterior limb of the internal capsule. The chosen target was 50% of the distance along the putaminal border as it intersected with the anterior limb. Two 4 mm isocenters were used to create an oval radiosurgical volume on each side. Within the inferior aspect of the anterior limb, the 50% isodose volume reached the border of the nucleus accumbens region (Figure 2). Thus, both axial and coronal image planning were crucial. We did not use coordinates based on the anterior-posterior commissural line, as direct targeting methods had been advocated previously.[14] A maximum radiosurgery dose of 140 Gy was delivered to each target. The patient was discharged home the same afternoon.

Serial imaging studies at 2.5 and 7 months and at 12 months (Figure 3) showed oval volumes of contrast uptake within the anterior limb of the internal capsule, with a small volume of

Figure 3. Axial (A) and Coronal (B) Magnetic Resonance Images 1 Year After Radiosurgery



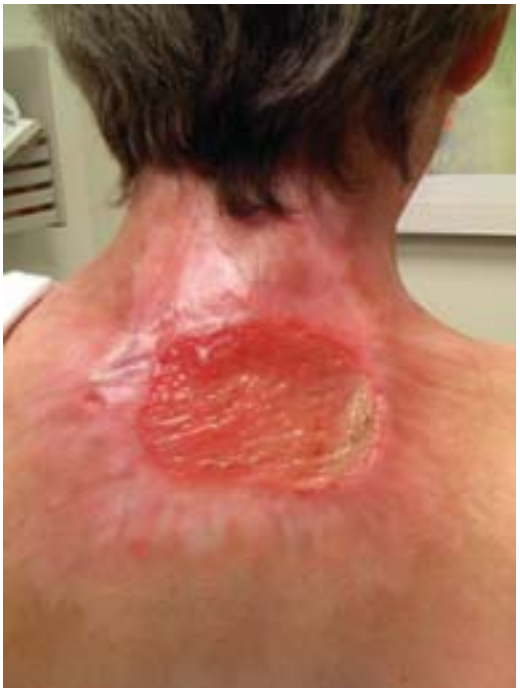
regional FLAIR (fluid attenuated inversion recovery) signal change. Clinical follow-up assessments showed the following: At 2½ months, his wife noted that he was much more agreeable and appreciative, paying her compliments. He was joining the family for meals and was much less argumentative regarding his care. His YBOCS score remained at 39/40. Skin picking began to lessen. By 7 months, the patient was noted to be much more agreeable to treatment, and his medication seemed to work better. He was now driving his daughter to school and was interested in family activities at home. Ritualistic behavior had lessened. His YBOCS score was reduced to 32. He was admitted for inpatient therapy (from month 7 to month 9 after radiosurgery). The facility had not agreed to provide inpatient care until he had undergone surgery. At 12 months, his YBOCS score was reduced to 22, and at 17 months, it was reduced to 8/40. Neuropsychological testing 14 months after radiosurgery (compared to the preradiosurgery assessment) showed that the patient was performing at or above his preradiosurgical level, especially in psychomotor speed. He had normal frontal lobe performance with some impulsivity and perseveration. Memory testing showed normal encoding. Over time, his skin began to heal as picking lessened. The appearance of his upper back at 17 months is shown (Figure 4). At 30 months, his YBOCS score was 4.

Imaging studies in OCD note effects in the orbital frontal cortex, anterior cingulate region, caudate nucleus, and thalamus. The utility of radiosurgery in the anterior limb of the internal capsule has been described previously in older studies from the Karolinska Institut showing target effects but without details on clinical outcomes.[12–14] Current studies support models of cortico-striato-thalamo-cortical dysfunction providing a basis for modulation or effects on this circuitry. The anterior internal capsule should be an appropriate target for such modulation.

Studies at Brown University[10] showed efficacy using conservative response criteria (a 35% reduction in the YBOCS score in approximately half of patients with intractable OCD). The gamma knife radiosurgery procedure was well tolerated. The initial results using single isocenter lesions were not successful, and thus a larger oval-shaped radiosurgical volume with two 4 mm isocenters was recommended.[10] Indeed, the shape of this radiosurgical volume may mimic the stimulation volume with a deep brain stimulation electrode. Typically, the radiosurgery effect develops over several months, and tissue necrosis at the target should occur by 2 to 4 months. The imaging and clinical effects on this patient developed over time, with improvement continuing past 1 year.

Although there may be benefits to placements of a deep brain stimulation system, including reversibility and adjustability, there have been reports of significant problems associated with battery failure since current use is typically high. Ideally, a procedure that would be long-lasting and not reliant upon the function of implanted hardware might be a better solution. With the creation of a lesion by either radiosurgical or radiofrequency technique, the effect is permanent but, of course, is not adjustable. The success rate of lesioning has not been studied in large numbers of patients. However, for a patient with compulsive skin picking, the placement of deep brain stimulation electrodes, cables, and pulse generators was contraindicated.

Figure 4. Appearance of the Patient's Upper Back 17 Months Following Radiosurgery



In summary, radiosurgical anterior capsulotomy can provide benefit in a patient with obsessive-compulsive disorder and in this patient led to improvement in social and thought behaviors, as well as in the physical manifestation of the disease.

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