Fluoxetine, Akathisia, and Suicidality: Is There a Causal Connection?

To the Editor.—We thank Drs Mann and Kapur[1] for their thoughtful and cogent treatment of the antidepressant-suicidality question. Their central neurochemical hypothesis was that fluoxetine (or any selective serotonergic reuptake blocker) might cause the presynaptic serotonergic neuron to temporarily decrease its firing rates. Such temporary serotonergic hypofunction would, in effect, leave the patient more susceptible to depression and subsequent suicidal ideation. The return of the depressive symptoms after experimental depletion of the serotonin precursor could be cited in support of this conjecture.[2] However, the reemergence of original depressive symptoms or "relapse" contrasts sharply with the presentation of our patients who became suicidal during treatment with fluoxetine.

We have now had experience with five such patients. All were women. None had a history of significant suicidal behavior; all described their distress as an intense and novel somatic-emotional state; all reported an urge to pace that paralleled the intensity of the distress; all experienced suicidal thoughts at the peak of their restless agitation; and all experienced a remission of their agitation, restlessness, pacing urge, and suicidality after the fluoxetine was discontinued. We describe herein five cases of what we think might be fluoxetine-induced akathisia accounting for suicidal ideation.

Report of Cases.—CASE 1.—A 39-year-old single white female actress presented with a lifelong history of dysthymia punctuated by numerous atypical stress-reactive depressive episodes. Stereotypically, these episodes consisted of hyperphagia, hypersomnia, feelings of rejection and worthlessness, and an increase in her long-term alcohol abuse. She had no history of mania, psychosis, obsessive-compulsive disorder, suicidal ideation, or panic. Her family history, however, was remarkable, with two first-degree relatives having committed suicide. She was first treated with imipramine hydrochloride in 1985 without effect. She was subsequently treated with 60 mg of phenelzine sulfate with a nearly complete amelioration of her atypical mood symptoms. This agent was discontinued after a hypertensive crisis. She began receiving fluoxetine at 20 mg per day, and within 2 weeks, developed anergia, increased hypersomnia, hyperphagia, restlessness marked with a desire to pace and an inability to find somatic comfort, and an "obsessional need" to kill herself. She made no attempt. This experience was qualitatively and quantitatively distinct from past episodes. Following the discontinuation of fluoxetine, the restlessness and suicidal ideation disappeared after about 10 days, but the atypical depressive symptoms persisted.

CASE 2.—A 24-year-old white woman first developed mild dysphoria with transient suicidal ideation at age 19 years. This episode was successfully treated with alprazolam. At age 23 years, she developed dysphoria, anergia, anorexia (with a 4.5-kg weight loss), anhedonia, and passing suicidal ideation. Fluoxetine (20 mg per day) was prescribed by her internist. Two and a half weeks later, she developed motor restlessness with a compulsive need to pace. She had no change in her level of suicidal ideation. Alprazolam on an as-needed basis was effective at relieving her complaints. Over the ensuing 3 months, she enjoyed a resolution of her depressive syndrome with a return of good psychosocial functioning and only occasional restlessness. After 4 months, she developed a marked sense of restlessness, pacing, insomnia, and obsessional suicidality. She was unable to recall any previous similar episode and stated that the suicidality was qualitatively different from her past ideations. She made no attempt and alprazolam was again partially effective at relieving both the restlessness and suicidal ideation. The fluoxetine was then discontinued with a complete resolution of her restlessness after about 2 weeks. She subsequently developed two milder episodes of restlessness and suicidal ideation (not as profound as that experienced during treatment with fluoxetine) while taking nortriptyline hydrochloride and trazodone hydrochloride.

CASE 3.—A 55-year-old divorced white woman had a history of recurrent depressive episodes since age 42 years. The episodes were marked by feelings of loss, sadness, abandonment, and rejection, and anorexia, weight loss, and diurnal variation. She did experience mild, predominantly passive suicidal ideation during her deepest depressive moments. In the summer of 1990 while taking 20 mg of fluoxetine per day and liothyronine sodium (Cytomel) for autoimmune hypothyroidism she increased the fluoxetine dose to 40 mg per day because of residual depressive symptoms. Within a few days she experienced a marked increase in anergia, incapacitation, restlessness—with the feeling that she was "jumping out of my skin," and ruminative thoughts to kill herself. She made no plan and described these feelings of restlessness and agitation as novel. The restlessness and suicidal ideation resolved with lorazepam. Her dose of fluoxetine was decreased back to 20 mg without a return of her restless-suicidal syndrome. Rechallenge with the 40-mg dose brought a recurrence of the syndrome that again responded to treatment with lorazepam and dosage reduction.

CASE 4.—A 27-year-old white woman presented with a long history of schizoaffective, predominantly manic-depressive type illness. In early 1990 she was being treated with fluphenazine hydrochloride (10 mg), carbamazepine (700 mg), benztropine mesylate (4 mg), and propranolol hydrochloride (40 mg). The last two agents were used to treat mild fluphenazine-induced akathisia. Fluoxetine (20 mg) was added because of depressive complaints and she had a very positive mood response within 4 weeks. At the patient's insistence, the fluoxetine dose was increased to 40 mg and within 2 weeks she developed unbearable akathisia that was "100 times worse than anything I've experienced before!" She was pacing incessantly, had a return of her auditory hallucinations, and transiently thought about suicide (she had no previous

history of suicidal ideation). Increasing the propranolol dose to 80 mg was ineffective but discontinuing the fluoxetine resulted in resolution of her akathisic complaint, auditory hallucinations, and occasional suicidal ideations.

CASE 5.—A 45-year-old white woman presented with a long history of an atypical depressive disorder. Trials of nortriptyline, tranylcypromine sulfate, desipramine hydrochloride, trazodone, levothyroxine sodium, and lithium carbonate had been variably successful. In the middle of 1988, treatment with fluoxetine at 20 mg per day was started and within 3 weeks, she felt "better than I can remember." At the patient's insistence, the fluoxetine dose was increased to 40 mg, and after 2 weeks, she became agitated, frantic, insomnic, and restless and unable to keep still. She would take frequent long showers, pace, have her husband rub her back, and begged for relief. She would occasionally think of killing herself to gain relief. She was certain that this was a novel somatic-emotional state for her. The syndrome disappeared several days after discontinuing the fluoxetine and she is now well maintained on one third of a 20-mg capsule of fluoxetine per day.

Comment.—In the neuroleptic-treated population, akathisia has been associated with psychotic exacerbation and deterioration, medication noncompliance, and homicidal and suicidal behaviors.[3,4] It is also thought to be a correlate of resistance to treatment and poor outcome.[5]

As Drs Mann and Kapur noted, akathisia has been reported to occur during treatment with fluoxetine[6] and other typical tricyclic antidepressants.[7] Our cases appear to confirm that certain subjects experience akathisia while taking fluoxetine and that this effect is dose-related in the individual patient (cases 1, 4, and 5). Further, like the akathisia in the neuroleptic-treated schizophrenic population, "fluoxetine akathisia" can apparently be associated with suicidal ideation, sometimes of ruminative intensity. Cases 2 and 3 seem to indicate that conventional antiakathisic treatments, in these cases benzodiazepines, may be of benefit in this population.

Examining large, placebo-controlled databases for treatment-emergent suicidal ideation is not likely to be instructive because the active treatment, even if it causes suicidal ideation in a subgroup, also *suppresses* it. As long as the treatment (fluoxetine) suppresses more suicidal ideation than it induces, it will compare favorably with the placebo group. As to the brain mechanism by which tricyclics or neuroleptics generate this subjective state of distress and motoric agitation, we still have many puzzles to disentangle.

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Thyroid Function and Partial Sleep Deprivation Response

To the Editor.—Baumgartner et al[1,2] have recently documented higher thyroxine, free thyroxine, and reverse triiodothyronine levels in patients with depression who responded to total sleep deprivation (TSD) vs nonresponders.

Sleep deprivation, both partial and total, remains the only antidepressant intervention with a same-day beneficial effect. Originally reported by Pflug and Tolle, the antidepressant effects of one night of TSD have subsequently been confirmed in more than five dozen studies.[3,4] Partial sleep deprivation (PSD), which involves awakening the subject at 2 AM, appears to produce similar effects.[5] Partial sleep deprivation is a more tolerable procedure for the patient and, therefore, may be preferable to TSD. To date, however, there have been no direct comparative trials between PSD and TSD. While two other manipulations of the sleep-wake cycle (phase-advance of the sleep period and selective rapid eye movement deprivation) have been shown to improve major depression symptoms, the time course and duration of these latter two manipulations are quite different from those of PSD and TSD, suggesting different mechanisms may be mediating the effects.[6,7] Thus, while PSD and TSD appear to produce similar effects that may be mediated through similar mechanisms, there has been little investigation into the comparison of TSD with PSD.

Patients and Methods.—Alterations of the hypothalamic-pituitary-thyroid axis are well-documented features of depression.[8] As part of our ongoing investigations of the neuroendocrine and circadian effects of PSD in depression, we report herein the results of thyroid function assessment in 42 patients with depression undergoing PSD. Subjects consisted of 29 women and 13 men, aged 20 to 77 years, who satisfied Research Diagnostic Criteria for unipolar depression (n=27), bipolar I depression (n=11), or bipolar II depression (n=4). All patients underwent one night of PSD. The protocol for PSD has been used in our unit in previously published studies.[9] Our response criteria are similar to those used by Baumgartner et al.[1,2] As part of the baseline evaluation of patients with major depression admitted to our unit, baseline thyroid function test samples are drawn between 7 and 8 AM within the first 24 hours of admission. To monitor sleep of patients in our units, nursing staff made rounds every half hour during the night and recorded the total number of hours asleep. The duration of sleep recorded by nursing staff for 3 days before the PSD trial was averaged.

Categorical data were analyzed using χ^2 or Fisher's Exact Test, as appropriate. Two-tailed *t* tests were used for group comparisons (responders vs nonresponders).

As shown in the Table, there were no significant differences between responders and nonresponders at baseline in regard to sex, age, severity of depression, or duration of sleep. Patients with bipolar I depression responded more frequently than patients with unipolar or bipolar II depression, as previously re-