these descriptions were featured as acceptable solutions to a complex problem.

As a final note, we would like to mention the significance of the rationale of ancient physicians. In order to avoid unnecessary and potentially harmful medical practices, Sabuncuoglu suggested the following advise to junior doctors: "You should not intervene, when the outcome is unpredictable." We feel that schizophrenia is one of those conditions to which Sabuncuoglu's principle is applicable, during his time as well as today.

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Manic Switching in Patients Receiving Duloxetine

TO THE EDITOR: Duloxetine is a dual antidepressant. According to Viktrup et al. (1), duloxetine does not induce mania or hypomania in women without a history of major depression. Moreover, pooled data by Dunner et al. (2) show that the estimated risk of duloxetine-related manic switching is 0.1% to 0.2% in patients with major depression. However, the methodological limitations of the study conducted by Dunner et al. as well as the scarcity of other sources of information lead us to believe that the actual risk of manic switching with duloxetine remains unknown. We present two clinical cases in which manic switching occurred after treatment with duloxetine.

A 58-year-old man with a 2-month major depressive episode was seen in our outpatient clinic. There were no psychiatric antecedents, and both the patient and his family denied any episodes suggesting mania or hypomania. The patient did not have a family history of bipolar disorder, and his medical history was unremarkable.

Treatment with paroxetine (40 mg daily) resulted in initial partial remission, followed by severe relapse. Duloxetine (60 mg daily) was substituted and rapid recovery was obtained. Four months later—while still on duloxetine—admission was necessary because the patient experienced a manic syndrome with psychotic features. General examination and routine studies (rapid plasma reagin, human immunodeficiency virus, thyroid function, blood chemistry, and computed tomography scan) showed results within normal limits.

The second patient was a 40-year-old woman who had previously showed symptoms of bulimia and alcohol abuse. She also had interspersed periods of increased activity with times of more inhibition, for which medical care was never required. Several months before, she suffered a transient, acute psychotic episode that required hospital admission and short treatment with an atypical antipsychotic. Her status at the time included anhedonia, hypersomnia, anergy, difficulty in concentrating, and a sense of worthlessness. Six weeks after beginning treatment with duloxetine, the patient's mood improved. Nevertheless, after 3 months of treatment (120 mg daily), a sudden manic episode with psychotic symptoms was diagnosed, and inpatient management was required.

An increased risk of manic switching with venlafaxine (3), which is also a dual agent, has been reported. Although anecdotal, our two case studies warn against the risk of duloxetine. In both our patients, episodes were extremely severe. One patient had been treated with a selective serotonin reuptake inhibitor, but only after treatment with duloxetine did manic switching occur.

In our opinion, clinicians should carefully observe early warning signs of mania in patients with seemingly unipolar depressive disorders who are undergoing treatment with dual antidepressants.

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Hyperprolactinemia and Galactorrhea Induced by Serotonin and Norepinephrine Reuptake Inhibiting Antidepressants

TO THE EDITOR: Venlafaxine and duloxetine are serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants. Endocrine and reproductive side effects of these medications are rare, and, to our knowledge, there is only one published report of breast discharge with measured prolactin levels (1). We report a case of galactorrhea and nonmenstrual-related spotting with venlafaxine and duloxetine that was associated with concomitant dose-related elevated prolactin levels.

"Mrs. S" was a 40-year-old Caucasian female with three children and without any history of endocrine or reproductive pathology who had been receiving vitamins only and presented with dysthymic disorder. She had past failures (1 year each) of sertraline (50 mg daily) and fluoxetine (20 mg daily), without any subjective endocrine changes. She was titrated to venlafaxine extended release (225 mg daily) with partial improvement in depression but with development of dry mouth and constipation. The addition of bupropion extended release (300 mg daily) improved her mood further. Simultaneously, she developed bilateral breast discharge and nonmenstrual spotting. Magnetic resonance imaging of the patient's pituitary gland was normal. Gynecologic and endocrine evalua-

tions, including physical examination and laboratory studies, revealed no abnormality outside of an elevated prolactin level of 39.7 ng/ml. It was thought that this was related to the effect of venlafaxine on serotonin elevating prolactin, and thus bupropion extended release was increased to 450 mg daily, which resolved her depression. Venlafaxine was decreased over several weeks, and dry mouth, constipation, and vaginal spotting were eliminated. The patient's breast discharge persisted, although her prolactin level was normalized at 12.5 ng/ml. Because her mood worsened, venlafaxine was discontinued and replaced with duloxetine 60 mg daily. Her mood remained impaired, but her breast discharge increased and her prolactin level rose from 10.8 ng/ml to 28.2 ng/ml within 1 month. Duloxetine was discontinued and replaced with modafinil to address the patient's complaint of fatigue, with subsequent remission of her depression. Over the next 7 weeks, her breast discharge discontinued and her prolactin level decreased to 5.1 ng/ml. Receiving a combination of bupropion extended release (450 mg daily) and modafinil (100 mg daily), the patient's depression has been under control for 1 year.

To our knowledge, this is the first report of SNRI-induced, dose dependent, nonmenstrual, vaginal spotting and galactorrhea accompanied by prolactin elevation. It is not likely that bupropion extended release caused these problems in our patient, since symptoms and prolactin levels changed with the dose adjustment of venlafaxine and duloxetine while holding the bupropion dose steady. Although there did not appear to be any interaction of bupropion with venlafaxine and duloxetine by way of inhibition of cytochrome p450 2D6, it is unfortunate that drug levels were not obtained. Potential mechanisms for the patient's side effects were a direct effect of serotonin on prolactin or an indirect effect through serotonin agonism producing dopamine antagonism, possibly by way of 5-HT2c inhibition of mesocortical/mesolimbic dopamine (2). There are reports of older serotonin enhancing antidepressants that have caused elevations of prolactin and galactorrhea (3). Surprisingly, our patient's prior selective serotonin reuptake inhibitor courses did not cause similar side effects, but perhaps this was because they were dosed too low.

Although these findings are unusual, physicians should be aware that patients taking SNRIs could experience hyperprolactinemia, galactorrhea, and nonmenstrual vaginal spotting. Heightened surveillance might increase reporting and a clearer risk could be delineated.

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Gender Identity Disorders and Bipolar Disorder Associated With the Ring Y Chromosome

TO THE EDITOR: Gender identity disorder is a rare condition of atypical gender development in which there is a subjective perception of self in opposition to an individual's gender. The lifetime prevalence of mood disorders comorbidity with gender identity disorder is approximately 45% (1). We report the case of a patient carrying a Y chromosomal abnormality associated with gender identity disorder and comorbid bipolar II disorder.

"Mr. G" was a 31-year-old, single, bank manager who was first referred in May 2000 for depressive symptoms and suicidal thoughts precipitated by the accidental death of his sister and the failure of a heterosexual relationship. His personal history was marked by delayed language acquisition and virtually no social or familial interactions during his school years and after, except for a symbiotic relationship with his sister. His limited social abilities contrasted with his remarkable skills in mathematics and an early inclination for electronics. During the interview, Mr. G revealed his desire since childhood to be a woman, and he asked for a sex change operation. Gender identity disorder was diagnosed. After a few months, Mr G experienced a hypomanic episode with mood lability and began wearing eccentric women's clothing in public and insisted on receiving female sex steroid hormones and sex change surgery.

At admission, the patient met criteria for bipolar II disorder. His physical examination did not reveal any abnormality: his genitalia were normal, and he did not have gynecomastia. A biological examination revealed a disturbed hormonal profile with an elevated follicle stimulating hormone level; a normal testosterone level; and an abnormal karyotype with a mosaicism (45, X[2]/ 46, X, r(Y)[23]), which showed one cell line presenting the ring Y chromosome. This chromosomal formula provided to the patient an argument to claim his sex change. During a 6-year follow-up, the patient was admitted eight times and developed impulsive behavior such as suicidal and self-injurious attempts. A broad range of antidepressants, mood stabilizers, and antipsychotic treatments were unsuccessful until clozapine (75 mg daily) and lithium carbonate (1000 mg daily) permitted a sustained remission. Subsequently, the patient relinquished his demands for a sex change.

Our case shows a possible interaction between transsexualism and bipolar disorder, where both depression and mania exacerbate the demands for sex change, as reported and discussed in the literature (2).

The ring Y chromosome is usually associated with deletions in telomeric regions. It often provokes the loss of the ring chromosome during mitosis, resulting in a mosaic. Several genes on the Y chromosome could account for this complex developmental phenotype that associates gender identity disorder and bipolar disorders with schizoid-like personality and speech delay. The SRY gene (Yp11.3), which is involved in gender determination, is located close to the telomeric region. Its accessibility and regulation could be disturbed by the ring conformation. The SYBL1 and NLGN4Y genes both map to the Yq pseudoautosomal region and encode proteins that are essential for functional synapses. Variants of those genes have been found to be associated with bipolar (3) and autism spectrum disorders (4), respectively.