

CASES THAT TEST YOUR SKILLS

A teenager with longstanding ADHD and schizoaffective disorder lapses quickly into a deep depression with manic and suicidal features. Her doctors desperately seek the cause of this sudden downturn.

The search for the hidden depressant

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History Initial symptoms

Ms. G, 17, has battled attention-deficit/hyperactivity disorder (ADHD) since age 6, and within the past 2 years was also diagnosed as having schizoaffective disorder, bipolar type. An outpatient child psychiatrist and a therapist have helped keep her symptoms in control through much of her life.

During one recent visit to her psychiatrist, however, she complained of decreased energy, increased crying spells, broken sleep, and a depressed mood. She reported that these symptoms began approximately 2 months before the visit, and neither she nor her parents could identify a clear-cut cause.

Throughout her life she has complied with her drug regimens. For 2 years she has been taking divalproex sodium, 500 mg twice daily to manage her manic and depressive episodes, dextroamphetamine sulfate, 30 mg in the morning for her ADHD; risperidone, 2 mg at bedtime for her psychotic symptoms; and mestranol, 60 mcg/d, plus

norethindrone, 1 mg/d, for contraception. A recent valproic acid reading of 62 µg/ml is consistent with levels over the last 2 years.

During previous psychotic episodes, Ms. G often became delusional and paranoid with command-type hallucinations. She destroyed her room during her most recent episode.

Ms. G's adoptive mother accompanied her during this visit. She is concerned for her daughter, especially with the start of school about 1 month away.

Which would you address first: the depression or the psychosis? Would you change Ms. G's medication and if so, how?



Figure 1

DEPRESSION IN SCHIZOPHRENIA: IMPROVING OUTCOMES

Ensuring compliance

- Encourage family involvement¹¹
- Use atypical antipsychotics to minimize side effects and polypharmacy¹²

Preserving social and vocational functioning

- Consider psychotherapy, which may delay relapse into psychosis for some patients¹³
- Employ major role therapy—including social casework and vocational rehabilitation counseling—and drug therapy¹⁴

Promoting reintegration

- Utilize cognitive rehabilitation programs¹⁵
- Establish a strong support group, especially with family if possible¹¹

Preventing suicide

- Treat underlying mood disorders as well as psychosis¹⁶
- Use atypical antipsychotics—which may address mood symptoms¹⁷—as monotherapy

Drs. Yu's and Maguire's observations

Complaints of depression in a patient with schizoaffective disorder are especially concerning because multiple domains could be affected (Figure 1). For patients with schizophrenia, the 60% lifetime incidence of major depressive disorder substantially exceeds the 8 to 26% risk in the general population. Ms. G's comorbid depression also may predispose her to an increased rate of relapse into schizoaffective psychosis, poor treatment response, and a longer duration of psychotic illness that could require hospitalization.¹

Although Ms. G's divalproex level was therapeutic (between 50 and 100 µg/ml), some data indicate that valproic acid may be less effective in schizoaffective disorder than in bipolar I disorder. Still, treatment of schizoaffective disorder often follows antimanic and antidepressant protocols.²

Treatment An agent is added

The outpatient psychiatrist adds fluoxetine, 20 mg each morning, to address Ms. G's depressive symptoms. She reports no improvement after 1 month, and her fluoxetine is increased to 30 mg/d.

Three weeks later, Ms. G's parents bring her to the psychiatrist for an emergency visit. She reports suicidal ideation over the previous month. Rolling up both sleeves, she reveals several superficial cuts on her forearms and wrists that she inflicted after breaking up with her boyfriend.

Her mother, appearing anxious and overwhelmed, reports that her daughter pushed her because she had refused to give Ms. G her calling card. She had told her mother that she wanted to call a boy in Utah that she had met over the Internet.

Ms. G's speech is noticeably pressured and she is extremely distractible. Her mother notes that her daughter is sleeping only 2 to 3 hours a night, yet exhibits no decrease in energy. Still depressed, her affect is markedly labile, crying at one moment when discussing her suicidality, then railing at her mother when she tries to explain Ms. G's aggressiveness. When the psychiatrist recommends hospitalization to stabilize her symptoms, she vehemently demands to be let out so that she can run in front of a moving car. The police are called, and she is restrained and brought into the hospital.

What caused Ms. G's sudden decline? How would you address it?

▶

Drs. Yu's and Maguire's observations

Although antidepressants can effectively treat depression in schizoaffective disorder, many of these medications can trigger a manic episode,³ which can include mania, mixed mania with depression, or rapid cycling every few days or hours. In Ms. G's case, an increase in serotonin due to the fluoxetine may have caused her mania.

We would stop the fluoxetine and see if her manic symp-

toms resolve. Fluoxetine's long half-life (4 to 16 days) cuts down the odds of a serotonin-discontinuation syndrome, making immediate discontinuation feasible.

Still, the cause of Ms. G's depressive symptoms remains unknown. At this stage, observation in the adolescent inpatient ward holds our best hope of reaching a definitive diagnosis.

Treatment A diagnostic clue surfaces

Blood tests on admission (including a negative drug screen for narcotics or other depressogenic substances) are normal, and her valproic acid level is 61 µg/ml. Her divalproex is increased to 500 mg in the morning and 750 mg at bedtime, and she is tapered off fluoxetine. Her symptoms gradually improve with the change in the medications and her attendance in milieu and group therapy on the ward. A second valproic acid reading on day three of hospitalization is 67 µg/ml.

That day, a nurse informs the inpatient child/adolescent psychiatrist that Ms. G has requested extra hospital gowns. Ms. G later reveals that for about 4 months she has been producing a milky discharge from both breasts, and that the flow has been increasing in frequency and quantity. She adds that she has not menstruated for almost 5 months and complains of breast tenderness.

**What do Ms. G's latest symptoms suggest?
How will your response to these symptoms affect treatment?**

Drs. Yu's and Maguire's observations

Complaints of menstrual irregularities, breast tenderness, and galactorrhea should arouse suspicions of hyperprolactinemia. Because tumors that raise prolactin levels are rare, medications are the most likely culprit in Ms. G's case. Dopamine blockade within the tuberoinfundibular tract is the mechanism of action behind prolactin elevation.⁴

Prolactin levels in patients with schizophrenia are generally normal (1 to 25 mg/L) prior to treatment,⁵ but have

Figure 2

POSSIBLE ADVERSE EFFECTS OF HYPERPROLACTINEMIA⁸

Women

Short-term

- Menstrual disturbances
- Galactorrhea
- Breast engorgement
- Sexual dysfunction
- Infertility

Long-term

- Decreased bone density
- Relative or absolute estrogen deficiency
- Cardiovascular disease
- Cancer (breast, endometrial)
- Depression

Men

Short-term

- Loss of libido
- Erectile dysfunction
- Ejaculatory dysfunction
- Reduced spermatogenesis
- Gynecomastia

Long-term

- Decreased bone density
- Relative or absolute estrogen deficiency
- Cardiovascular disease
- Depression

been known to increase with use of typical antipsychotics. The atypical antipsychotic risperidone has been associated with dose-related increases in plasma prolactin concentration, although Kleinberg et al found no correlation between risperidone-induced plasma prolactin concentrations and adverse events.⁶

Prolactin-sparing atypical antipsychotics such as olanzapine, quetiapine, ziprasidone, and aripiprazole may cause a transient prolactin increase in the first few weeks of use. These levels tend to remain within the normal range before decreasing to baseline levels or lower.^{7,8}

Prolactin elevation in women may lead to an estrogen deficiency, causing changes in mood and cognition and psychopathology⁹ that can manifest as increased depression,

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anxiety, and hostility.¹⁰ Hyperprolactinemia can also cause depression in men, though the mechanism of action is unknown.

Prolactin elevation can lead to numerous other health disturbances (Figure 2). When screening women who are taking antipsychotics, ask about menstrual irregularities, sexual dysfunction, breast tenderness, and galactorrhea. Ask male patients about a loss of libido, erectile dysfunction, ejaculatory dysfunction, and gynecomastia.

When hyperprolactinemia becomes apparent, we suggest discontinuing the offending drug and, if necessary:

- switching to a prolactin-sparing atypical antipsychotic
- or trying another agent, such as bromocriptine or pergolide, if switching to another antipsychotic is infeasible.^{10,11}

Baseline prolactin levels should be measured before starting any prolactin-elevating antipsychotic. Because prolactin levels may not correlate with severity of clinical symptoms, the net change in these levels may be a better indicator.⁴ If prolactin levels exceed 100 mg/L, consider an MRI with fine cuts through the sellae to check for a primary adenoma.⁴

Conclusion A cause is found

An MRI of Ms. G's head is normal, but her serum prolactin level is 125 µg/L. Her risperidone is tapered off, and olanzapine, 10 mg at bedtime, is started with her mother's consent. Two days later, her prolactin level drops to 85 µg/L. Notable improvement is reported on day seven of hospitalization; she is sleeping and eating well with no suicidal or homicidal ideations and notes no psychotic symptoms. She is discharged that day.

Two weeks later, Ms. G's improvement continues. Lab tests reveal normal prolactin levels. Over the next few months, she remains stable, attends school, and takes her medications with no adverse effects.

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Related resources

- Maguire GA. Prolactin elevation with antipsychotic medications: mechanisms of action and clinical consequences. *J Clin Psychiatry* 2002; 63(suppl 4):56-62. Available at: www.psychiatrist.com/supplenet/v63s04/v63s0408.pdf. Accessed March 11, 2003.

DRUG BRAND NAMES

Aripiprazole • Abilify	Pergolide • Permax
Dextroamphetamine sulfate • Dexadrine	Olanzapine • Zyprexa
Divalproex sodium • Depakote	Quetiapine • Seroquel
Fluoxetine • Prozac	Risperidone • Risperdal
Mestranol • Necon 1/50	Ziprasidone • Geodon
Norethindrone • Activella	

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Though multiple agents are often used to manage comorbid mental disorders, adverse drug interactions are a constant threat. Careful exploration of the patient's current stressors, functioning, and medications can uncover causes of unexpected and unfavorable symptoms.

Bottom Line