Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Well-controlled on lithium and fluoxetine, Ms. Q has a hypomanic episode while on a cruise. Is it a breakthrough relapse, SSRI-induced switch, or something else?

The patient who got sick at sea

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HISTORY DEPRESSED AND DROPPING OUT

Ms. Q, age 23, presented 6 years ago with a profound anergic depression with suicidal thinking and social withdrawal. This caused her to drop out of high school for approximately 4 months. She also gained 30 lbs across 3 months, further diminishing her low self-image.

At the time, Ms. Q was diagnosed as having unipolar depression. Fluoxetine, 20 mg/d titrated to 40 mg/d, resolved her symptoms before she started college the following year.

Three years later, while continuing on fluoxetine at the same dosage, Ms. Q experienced dysphoric mania, with irritability, grandiosity, and impaired judgment. She was behaving promiscuously during this episode but was not using alcohol or other substances.

After a subsequent manic episode, she was diagnosed with bipolar type I affective disorder. Haloperidol, 10 mg/d for 2 weeks, resolved her mania. She was then maintained on fluoxetine, 50 mg/d, but was not given a mood stabilizer or antipsychotic.

Two years later, I was called in to consult on Ms. Q's case. She was euthymic and stable at that time but 2 months earlier had experienced a euphoric manic episode characterized by 5 days of racing thoughts, lack of sleep, and manic motoric acceleration. She had stopped seeing her psychiatrist near college and admitted that she needed to work with someone more experienced than her primary care physician in addressing psychiatric symptoms.

When Ms. Q was age 4, her maternal aunt committed suicide via gas poisoning. Also, her paternal grandmother committed suicide before she was born, and her mother had been treated for dysthymia. She has no significant medical history.

Addressing Ms. Q's bipolar affective disorder poses a clinical challenge. Controlling her mania is a priority but I also need to continue treating her depression, given her significant family history of affective disturbance.

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How would you manage Ms. Q's bipolar affective disorder?

- **add a mood stabilizer to fluoxetine therapy**
- **start a mood stabilizer and stop fluoxetine**
- **prescribe an atypical antipsychotic as a primary thymoleptic**

Dr. Schneider's observations

To address Ms. Q's mania, I added controlled-release lithium, 900 mg/d, yielding a blood level of 0.9 mEq/L. Ms. Q was not rapid cycling, was taking her fluoxetine as prescribed, and was not abusing alcohol or drugs, so she seemed an appropriate candidate for lithium treatment.

To manage her depression, I cautiously continued fluoxetine, 40 mg/d. The antidepressant had not obviously destabilized her illness, and Ms. Q felt that it allowed her to work and maintain a social life.

TREATMENT CRUISING AND CYCLING

After 8 months of stability, Ms. Q developed a sudden dysphoric hypomanic episode, with depressed mood, increased energy, racing thoughts, and inability to sleep. She had some insight into her condition and sought consultation with me.

Ms. Q's parents reported that she had been taking lithium and fluoxetine as prescribed, was taking no other medications, was not using alcohol or drugs, and experienced no unusual stressors, change in diet, or other lifestyle changes. Having her symptoms re-emerge despite faithful medication adherence made Ms. Q extremely anxious and bewildered her and her parents.

Ms. Q later recalled that her parents had taken her on a coastal cruise to Mexico the week before her cycling episode, and that her symptoms emerged while on ship. She began to experience initial and mid-cycle insomnia and was unusually irritable over minor annoyances.

Having seen Ms. Q immediately after the cruise, I added olanzapine, 5 mg nightly for 5 days, to prevent a full-blown manic episode. About 6 days later, she said she was excessively tired, but her insomnia and irritability had ceased. I stopped olanzapine and returned Ms. Q to her previous regimen.

What caused Ms. Q's manic episode?

- **continuing fluoxetine usage**
- **lithium blood level decrease**
- **a breakthrough relapse**

Dr. Schneider's observations

Ms. Q appeared to have sustained an unexpected relapse into hypomania despite treatment adherence. At this point, I was concerned that:

- fluoxetine might have destabilized her illness
- her lithium level decreased without explanation
- or she had a "breakthrough" relapse while on medication.

Upon returning home, however, Ms. Q's lithium blood level was 0.8 mEq/L, consistent with prior levels. Also, she had remained stable for 8 months while taking fluoxetine.

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How would you have handled this case?

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FOLLOW-UP A 'SICKENING' DISCOVERY

At follow up approximately 1 week later, Ms. Q reported that she had continuously worn scopolamine patches throughout the 8-day cruise to prevent motion sickness. She had forgotten to mention this, however, during our emergency consultation. She had experienced some mydriasis and dry mouth during the cruise but did not remove the patch for fear of seasickness.

On further questioning, Ms. Q said she knew the patch was designed to be used for 2 to 3 days maximum, but added she was responding well to its effects and foresaw no problems with extended use.

Dr. Schneider's observations

This case illustrates the potentially destabilizing effects of a seemingly innocuous concomitant medication in patients with bipolar disorder.

Scopolamine, indicated for preventing nausea and vomiting associated with motion sickness, is a centrally acting belladonna alkaloid with primary anticholinergic activity. The agent is thought to block transmission from the vestibular nuclei to higher brain centers and from the reticular formation to the brain's so-called "vomiting centers."

The transdermal agent can cause drowsiness, dryness of secretory areas, and impaired motor function. It has no known direct pharmacokinetic interaction with lithium. Use for >5 consecutive days can cause anticholinergic delirium-like states, especially in older patients.

For Ms. Q, scopolamine's direct anticholinergic action may have destabilized an affective disorder in remission. The putative mechanism of anticholinergic-induced psychosis, delirium, mania, and depression has not been well explained and may differ among these states. The serotonergic and cholinergic systems, however, are assumed to be in a type of balance. Cholinergic deficiencies—as seen in dementia or with medications that have anticholinergic potential—may increase sensitivity to serotonergic tone, thus contributing to Ms. Q's switch to mania.[1]

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Table

Mood destabilization, other effects reported after herbal supplement use

Herbal supplement	Common use(s)	Adverse effects in psychiatric patients
Dehydroepiandrosterone (DHEA)	Alzheimer's dementia treatment, body muscle-fat ratio enhancement, stress relief, sexual enhancer	Acute mania when taken with other psychotropics;[2] patients with history of affective disorder can exhibit mania when taking DHEA[3]
Gingko biloba	Cognitive/memory enhancement	Nausea, diarrhea, bleeding in patients taking psychotropics[4,5] Massive purpura after concomitant gingko plus citalopram or venlafaxine (clinical experience)
Ginseng	Stimulant, also purportedly an aphrodisiac	Ginseng-induced mania in two patients with depressive disorders[6,7]
Horny goat weed	Purported sexual enhancer for men	New-onset hypomania in 66-year-old man after ingesting compound for 2 weeks[8]
St. John's wort	Primary or secondary antidepressant	Multiple cases of mania induction, affective destabilization attributed to presumed cytotoxic effects[9]

Psychiatrists should ask patients whether they are taking another medication:
- **at initial presentation**
- **at every visit**
- **every 3 months**

Dr. Schneider's observations

Ask the patient at each office visit if he or she is concomitantly using an over-the-counter (OTC) medication or a prescription agent from another physician. As with scopolamine, diet pills and oral contraceptives can also destabilize mood or cause depression. Often patients neglect to tell their psychiatrists they started taking an antibiotic, antihypertensive, or other medication since their last visit.

Undetected use of herbal supplements also is a burgeoning clinical problem. Most physicians do not routinely ask patients whether they are using a nonprescription medication, and some clinicians know little about these products' side effects or interactions with other drugs. Adverse events associated with herbal agents *(Table)* are difficult to interpret because the purity and amounts of active compounds vary widely.

Diet pills. Use of prescription and OTC anorectics is common among weight-conscious Americans.

Appetite suppressants have been reported to cause depression during use or withdrawal,[10] but large epidemiologic studies have not determined which diet pills are most associated with depressive symptoms.

Oral contraceptives. Mood changes are an ongoing, noticeable side effect of oral contraceptives[11] regardless of whether the patient is taking a psychotropic. Depression is a frequently cited reason for oral contraceptive discontinuation.[12]

The literature is mixed on how oral contraceptives stabilize or destabilize mood and affect. Hormone-induced mood changes may be caused by:

- estrogen-induced B6 deficiency and subsequent decrease in serotonin and gamma-aminobutyric acid (GABA) because of lower affinity for pyridoxal phosphatate[13]
- progesterone or estrogen-mediated augmentation of GABA-induced glutamate suppression
- progesterone-mediated increase in monoamine oxidase activity, leading to lower serotonin concentrations.[14]

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Related resources

- Physicians' Desk Reference supplements for over-the-counter medications and nutraceuticals. www.pdr.net/pdrnet/librarian (click on "PDR bookstore").
- Farley D. How to get the most benefits with the fewest risks. *Web MD*. http://my.webmd.com/content/article/6/1680_51630.htm.

DRUG BRAND NAMES

Fluoxetine • Prozac
Haloperdiol • Haldol
Lithium • Eskalith, others
Olanzapine • Zyprexa
Scopolamine • Transderm Scop

DISCLOSURE

Dr. Schneider is a consultant to and speaker for Bristol-Myers Squibb Co., Forest Pharmaceuticals, and Wyeth Pharmaceuticals. He holds research grants from the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD), the Stanley Medical Research Institute, and the Alzheimer's Association (Ronald Reagan Research Award).

Bottom Line

Patients often neglect to tell the psychiatrist they have started taking another prescription or over-the-counter medication. Ask patients at each visit about concomitant medication use, as some OTC and prescription drugs can destabilize a pre-existing or latent psychiatric disorder.