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Did a switch to a generic antidepressant cause relapse?

We think so. Check out these 7 cases and decide for yourself

Jessica Rosenthal, BA, Brian Kong, BA, Leslie Jacobs, and Martin Katzman, MD, FRCPC

From: START Clinic for Mood and Anxiety Disorders (JR, BK, LJ, MK), The Chicago School of Professional Psychology (JR, BK), University of Western Ontario (JR), McMaster University (BK), The University of Toronto (MK), The Northern School of Medicine (MK), Laurentian University (MK), Lakehead University (MK)

mkatzman@startclinic.ca

Practice recommendations

- Bioequivalence between 2 drugs does not mean equal efficacy for a given patient (**A**).
- If a patient on an antidepressant experiences a sudden relapse of symptoms, check to see whether she (or he) has been switched from a brand-name drug to a generic, or from one generic to another (**C**).

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

All of a sudden, they were back—the panic attacks that had long been under control. The feelings of sadness and worthlessness were back, too. But how could that be? For 9 years she'd been taking 30 mg a day of generic paroxetine to help with her panic disorder, social anxiety disorder, and major depressive disorder, and things had been going along just fine. She hadn't stopped taking her medication—but it sure felt like she had. She spoke with her psychiatrist, who recommended that she call her pharmacy. What she learned surprised her: The pharmacy had switched her from one form of generic paroxetine to another without her knowledge, and that change, it would seem, had led to the re-emergence of her symptoms.

An uneventful switch for many, but not all

Patients are switched from brand-name drugs to generics and from one generic to another all the time in an effort to keep healthcare costs down. And that trend will no doubt continue, given the FDA's announcement last year that it was launching an initiative (The Generic Initiative for Value and Efficiency—GIVE) to increase the number and variety of available generic drugs.[1]

Patients, and their healthcare plans, certainly benefit from these approvals—especially when you consider the sheer numbers involved. In 2004, 24.8 million people purchased an antidepressant.[2]

At our tertiary care clinic for mood and anxiety disorders in Toronto, Canada, we regularly see the difference that antidepressants—whether brand-name or generic—can make in the lives of our patients. However, between 2004 and 2006, we noticed that a number of our patients—including the one in the opener—were suddenly experiencing an increase, or relapse, in symptoms after having been stable on their medications for a long period of time. After a bit of digging, we learned that each of these cases had one thing in common.

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Patients unknowingly switched to generics

When we looked into each case further, we learned that each of the 7 patients had been switched from a brand-name antidepressant to a generic, or from their original generic to another generic, without their knowledge. We suspect that any number of factors could have played a role in the switch, including a change in a drug's availability at a particular pharmacy or a change made by a pharmacy benefit management (PBM) company.

The drugs involved in our 7 cases were generic forms of citalopram and paroxetine. The patients subsequently suffered from an increase in symptoms or a relapse in symptoms following a significant amount of time in remission.

As a result, some dosages were altered, and in one case, a medication was added, in an effort to return patients to their original state—prior to the change in medication.

Similar experiences have been reported elsewhere. Quite recently, Van Ameringen and colleagues[3] reported on 20 anxiety patients who were unknowingly switched from Celexa to generic citalopram and experienced new adverse events or a re-emergence of their anxiety symptoms. In addition, patient concerns about the effectiveness of one generic form of Wellbutrin prompted a study by an independent laboratory and an investigation by the FDA.[4] (At press time, the FDA was expected to release the results of its evaluation.) Symptom relapse with other generics, including generic fluoxetine and generic paroxetine, have also been reported.[3]

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In one report, 20 patients had new adverse events or a re-emergence of anxiety when switched from Celexa to generic citalopram

Bioequivalence, yes, but efficacy—maybe not

No evidence of efficacy is required to release a generic form of brand-name medication to the market—only bioequivalence (80% to 125% blood concentrations of the brand medication's active compound).[5,6]

At first glance, this fact may seem to be of minimal significance—that is, until you consider the following.

- **A variety of nonactive ingredients** may affect a drug's pharmacokinetics and, ultimately, its effectiveness and tolerability.[5]
- **Studies that test bioequivalence** are often undertaken in healthy volunteer subjects (usually men of university age), which may not be comparable to other populations (eg, postmenopausal women).

Thus, a switch to a generic form of an antidepressant, antipsychotic, mood stabilizer, or benzodiazepine, maintaining a concentration of only 80% of the original brand, might result in a sudden change in efficacy yielding an increased risk of withdrawal symptoms or even a relapse of a previously well-treated illness.[5] Alternatively, if a patient is switched to a generic drug that maintains a 120% bioequivalence, there could be a sudden increase in adverse events.[7] This could lead to a decrease in compliance and potentially prompt a clinician to misread the specific symptomatic presentation as a worsening of the symptoms.[8]

Considering such risks, it is disconcerting to note that patients and their physicians may not always realize that a switch has been made from a brand-name drug to a generic.[5]

Our 7 cases: How they evolved

Our observations of the 7 patients whose medications were switched from a brand-name medication to a generic (or from one generic to another) were not planned—they simply evolved from the years of treating these patients. Thus, we did not consider, nor control for, other factors in the patients' lives.

In addition, we did not identify, nor did we examine, cases in which an unknown switch to a generic medication (or different generic form) was well tolerated.

That said, here are the 7 cases, with details of how they evolved—and resolved.

Each of the patients described here reported that prior to the change in symptoms, she (or he) was unaware of the change to a generic form of the medication.

CASE 1—Ms. A

Age: 55

Dx: Generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder, major depressive disorder, and dysthymia

Initial treatment: 40 mg a day of Celexa

Switched to: Generic citalopram

Subsequent patient complaint: Increased anxiety

Treatment decision: Switched the patient back to Celexa

In May 2005, Ms. A was started on 10 mg a day of Celexa. We increased her dosage until she reached a dose of 40 mg a day by August 2005. She reported to us that she was feeling significantly better and suffering from fewer symptoms from her illnesses.

In October 2005, she was switched to a generic version of citalopram and experienced increased anxiety. As a result, we switched her back to Celexa in November of 2005, and she returned to her previously treated state.

CASE 2—Ms. B

Age: 26

Dx: Generalized anxiety disorder, panic disorder (without agoraphobia), and major depressive disorder

Initial treatment: 30 mg a day of Paxil and cognitive behavioral therapy

Switched to: Generic paroxetine

Subsequent patient complaint: Return of symptoms of generalized anxiety disorder and major depressive disorder

Treatment decision: Increased the dosage of the generic paroxetine to 40 mg and then again to 50 mg

We saw Ms. B in 2001 and treated her with Paxil for generalized anxiety disorder, panic disorder (without agoraphobia), and major depressive disorder. She was stabilized on the Paxil and received cognitive behavioral therapy. She was well until January 2006.

In January, after her father died, her symptoms of major depressive disorder and generalized anxiety disorder returned. We looked into the matter and learned that her pharmacy had switched her Paxil to generic paroxetine.

As a result, we increased the dosage of her generic paroxetine to 40 mg a day, and then to 50 mg a day to restabilize her symptoms. We hypothesized that her worsening symptoms and her need for an increased dosage could have been prompted by her father's death. It may, however, have also been explained by a change to generic paroxetine.

CASE 3—Ms. C

Age: 27

Dx: Post-traumatic stress disorder, social anxiety disorder, generalized anxiety disorder, anorexia nervosa, dysthymia, and major depressive disorder (in partial remission)

Initial treatment: 30 mg a day of Celexa and cognitive behavioral therapy

Switched to: Generic form of citalopram

Subsequent patient complaint: Relapsed into a major depressive episode; experienced worsening symptoms of generalized anxiety disorder and social anxiety disorder

Treatment decision: Increased dosage of generic citalopram to 60 mg a day, and added 50 mg a day of trazodone. Subsequently switched the patient back to 30 mg a day of Celexa and discontinued the trazodone

We saw Ms. C in 2005, and she met the criteria for post-traumatic stress disorder, social anxiety disorder, generalized anxiety disorder, anorexia nervosa, dysthymia, and major depressive disorder that was in partial remission. After 5 months of treatment, which included 30 mg a day of Celexa and cognitive behavioral therapy, she no longer met the criteria for any of the diagnoses.

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None of our patients reported being aware of the medication switch

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Pharmacists should notify patients and physicians when changing from a brand name to a generic

Suddenly, though, she relapsed into a major depressive episode and experienced worsening symptoms of generalized anxiety disorder and social anxiety disorder. We investigated further and discovered that she had been put on a generic form of citalopram. Over the next 6 months, we increased her dose of the generic citalopram from 30 mg a day to 60 mg a day; we also added 50 mg a day of trazodone. Her condition did not improve, so we then switched her back to Celexa at 30 mg a day and discontinued the adjunctive treatment.

CASE 4—Ms. D

Age: 44

Dx: Panic disorder with agoraphobia, social anxiety disorder, and major depressive disorder

Initial treatment: 30 mg a day of generic paroxetine

Switched to: A different generic paroxetine

Subsequent patient complaint: Sudden return of panic attacks and severe worsening of depression

Treatment decision: Returned patient to the original form of generic paroxetine

In 1996, Ms. D was diagnosed with panic disorder with agoraphobia, social anxiety disorder, and major depressive disorder. She was treated with 30 mg a day of a generic paroxetine and stabilized for 9 years.

In September 2005, however, Ms. D noted a severe worsening in her depression and a sudden return of her panic attacks. She spoke with her psychiatrist (MK), who suggested she call the pharmacy.

The pharmacist confirmed the psychiatrist's suspicions: The pharmacy had switched her from her original generic form of paroxetine to another generic. Her psychiatrist switched her back to the original form of generic paroxetine, and there was a complete return to remission within 4 weeks.

CASE 5—Ms. E

Age: 28

Dx: Post-traumatic stress disorder, social anxiety disorder, and major depressive disorder

Initial treatment: 40 mg a day of Paxil and cognitive behavioral therapy

Switched to: Generic paroxetine

Subsequent patient complaint: Significant increase in symptoms of social anxiety disorder and post-traumatic stress disorder, as well as sudden onset of depressive symptoms

Treatment decision: Increased dose of generic paroxetine from 40 mg a day to 60 mg a day

We first saw Ms. E in 2002 and diagnosed her with post-traumatic stress disorder, social anxiety disorder, and major depressive disorder. We put her on 40 mg a day of Paxil, and she received cognitive behavioral therapy. She remained in remission for 2 years.

In the latter part of 2004, however, she noticed a significant increase in her symptoms of social anxiety disorder and post-traumatic stress disorder, as well as a sudden onset of depressive symptoms. Her psychiatrist suspected that she had been put on a generic form of paroxetine. Subsequently, she confirmed with her pharmacist that she had been switched. We raised her dose of the generic paroxetine from 40 mg a day to 60 mg a day, and her symptoms improved.

CASE 6—Mr. F

Age: 54

Dx: Generalized anxiety disorder, major depressive disorder, and panic disorder

Initial treatment: 50 mg a day of Celexa and 100 mg of Seroquel nightly

Switched to: Generic form of citalopram

Subsequent patient complaint: Worsening of depressive symptoms

Treatment decision: Increased the dose of generic citalopram to 80 mg a day, then switched the patient to 10 mg a day of Cipralex (sold as Lexapro in the US)

Mr. F was diagnosed with severe generalized anxiety disorder, major depressive disorder, and panic disorder in 1998. We stabilized him on 50 mg a day of Celexa and 100 mg every night of Seroquel. However, in December 2005 he experienced a worsening of his depressive symptoms, which coincided with a switch to a generic form of citalopram.

At first, we increased his dose to 80 mg a day of the generic citalopram. When that failed to adequately address his symptoms, we switched him to 10 mg a day of Cipralex, which is sold as Lexapro in the US. (The patient did not want to resume taking Celexa.) The patient's symptoms improved.

CASE 7—Ms. G

Age: 43

Dx: Generalized anxiety disorder, major depressive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, alcohol abuse, and bulimia nervosa

Initial treatment: 40 mg a day of Celexa and 150 mg a day of topiramate

Switched to: Generic form of citalopram

Subsequent patient complaint: Significant increase in anxiety

Treatment decision: Increased the dosage of the generic citalopram to 60 mg a day, but there was no improvement. Switched the patient to 10 mg a day of Cipralex

In 2005, we diagnosed Ms. G with generalized anxiety disorder, major depressive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, alcohol abuse, and bulimia nervosa. We then stabilized her on 40 mg a day of Celexa and 150 mg a day of topiramate.

Subsequent to being stabilized, Ms. G experienced a significant increase in anxiety, which corresponded to a switch to a generic form of citalopram. We increased her dosage of the generic citalopram to 60 mg a day, but there was no improvement. We then switched her to 10 mg a day of Cipralex (since the patient did not want to resume taking Celexa), and she returned to her previous level of functioning.

The upside and the downside of generics

Although generics are cheaper for the patient, there can be a downside to switching to—or between—generics, especially if the patient and the physician are not notified of the switch.[9] We believe that the 7 cases detailed here illustrate the negative effects that a switch can have on a patient's well being.

Nevertheless, a number of concerns could be raised about our conclusions. For one, many people who are switched to a generic form of the medication do not lose efficacy or suffer withdrawal. As well, given the lower costs of the generic form of a medication, one could imagine people who are able to remain well, only because they can afford to stay on the medication.

In each of the cases we've presented, there was a switch to another form of the medication (a generic or a different generic). While the appearance of the medications may have been different (and as such may have initiated a change in outcome, purely because patients believed they were on a different medication), none of the patients in these cases reported being aware that they were on a new form of their medication.

Patient notification and efficacy studies needed

Given the fact that mental illness is a prevalent and increasingly common occurrence, it is critical that we do everything we can to control for the costs, both economic and emotional, of the patients and families affected by these disorders. In addition, pharmacists should notify patients and their physicians when making a change from a brand-name medication to generic, or from one generic to another. Doing so

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Given the lower cost of generics, one could imagine people who are able to remain well only because they can afford to keep taking their medication

would allow physicians to monitor a patient's progress effectively and make appropriate changes necessary to ensure the greatest quality of life with the lowest costs.

Further studies are needed to test the efficacy of generic forms of medications to ensure that they are sufficient to use as a replacement for the original medications. In addition, we need researchers to examine whether there is a correlation between relapse rates and the release of generic forms of medications, using a large population. ■

Correspondence

Martin A. Katzman, MD, FRCPC, START Clinic for Mood and Anxiety Disorders, 790 Bay Street, Toronto, Ontario M5G 1N8; mkatzman@startclinic.ca

Disclosure

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