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Hilary P. Stevenson MD, PhD
St. Mary Mercy Hospital, Livonia, Michigan, hstevens@med.wayne.edu

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INFORMED CONSENT:
Do atypical antipsychotics trigger manic switching in patients with bipolar I disorder?

HILARY P. STEVENSON, MD, PhD, St. Mary Mercy Hospital, Livonia, MI, hstevens@med.wayne.edu>

ABSTRACT A 22-year-old newly diagnosed patient with bipolar is discussing with her doctor the safety of starting an atypical antipsychotic as part of her treatment plan for depression. The patient was recently diagnosed with bipolar disorder after years of ups and downs making school and her relationship especially difficult. After seeking out a university student health psychiatrist for a severe depressive episode she was prescribed an antidepressant, which within a few weeks triggered a manic episode that required hospitalization. Since that time she has been compliant with her medications but has fallen into another depressive episode. Her psychiatrist encourages her to begin taking the atypical antipsychotic quetiapine because it may help with her current mood. Given her experience with antidepressants she is apprehensive. She asks, is it possible that a medication like quetiapine could trigger another manic episode?

Keywords: *psychiatry, antipsychotic, mania, depression*

Clinical Context

Clarisse Taylor, a 22-year-old patient with newly diagnosed bipolar I disorder is asking her doctor about the safety of starting an atypical antipsychotic as part of her treatment plan for depression. The patient was recently diagnosed with bipolar disorder after years of ups and downs related to her mood, making school and her interpersonal relationships especially difficult. After seeking out a university student health psychiatrist for a severe depressive episode she was prescribed an antidepressant, which within a few weeks triggered a manic episode that required hospitalization. These experiences were disruptive to her life and affected trust in the doctors she needed to help manage her disorder. Since hospitalization, she has been adherent with her medications but has experienced another depressive episode. Her psychiatrist encourages her to begin taking the atypical antipsychotic quetiapine because it may help with her current mood. Given her experience with an antidepressants she is apprehensive. She asks:

Clinical Question

Is it possible that a medication like quetiapine could trigger a manic episode in people diagnosed with bipolar I disorder?

Related Literature

In order to address the patient's concerns, an investigation of the ability of antipsychotics to induce mania in bipolar patients was performed in the literature. To answer this question a systematic search strategy was employed using PubMed. These included

HILARY P. STEVENSON, MD, PhD, *is a resident at St. Mary Mercy Hospital in Livonia, Michigan.*

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searching with terms including antipsychotic, atypical antipsychotic, antipsychotic + mania, antipsychotic + switching, antipsychotic bipolar depression, antipsychotic mood stabilization.

There are a variety of medications used to treat bipolar mania, which include anti-manic, anti-epileptics and antipsychotics. The primary medications used for bipolar depression are antipsychotics[1] and have also been shown to have some mood stabilization effects.[2] Antidepressants cannot be used until the patient has been on a mood stabilizer for some time and is fully stabilized.[3]

This author's search resulted in many case reports that indicated that clinically used antipsychotics can in fact cause switching into hypomania/mania. A review of the literature performed by Benyamina & Samalin revealed that since 2004 there have been "36 cases of olanzapine induced switch into mania, 44 cases by risperidone, 27 cases by ziprasidone, and 15 cases by quetiapine.[4] In that paper the authors method was first to review the literature using search terms with databases such as PubMed, Scirus, EMBASE, Cochrane Library, Science Direct. They also used other sources including medical professional meeting abstracts. Their results showed that they found no papers directly focused on manic switching as the primary goal of the report. However, the above mentioned study, covering a wide array of antipsychotics did indeed report manic switching as secondary outcomes.

Considering all of these reports in the literature, why would medications that are supposed to help with mood stabilization also able to cause manic switching in some patients?[5-11] The atypical antipsychotic, risperidone, mechanism of manic switching depends on the dosage the patient receives and on the subsequently brain receptor occupancy of these drugs at different doses.[12,13] Risperidone has high 5HT-2A receptor affinity at low dosages of the drug.[12] These are the same receptors involved with the mechanism of action of antidepressants.[14] However, at higher, "maintenance" dosage of the drug the dopamine D2 receptor occupancy overcomes the 5HT-2A activity.[13] Second generation antipsychotic quetiapine also has the same affinity for 5HT-2A receptors at lower dosages (below 300 mg low dose, bipolar maintenance 600-900 mg).[15,16] This drug is one of the three antipsychotics FDA approved for bipolar depression specifically, which includes two others, lurasidone and olanzapine/fluoxetine.

Since the publication of Benyamina & Samalin 2012 article there have been additional reports that the third generation antipsychotic lurasidone could cause a switch to mania in bipolar patients. This drug has a strong affinity for D2 and 5HT2A and 5HT1A receptors.[17] It has been hypothesized that lurasidone is an effective medication for bipolar depression due to 5HT1A partial agonism. By this mechanism it may enhance DA and norepinephrine in the prefrontal cortex.[18] Case reports suggest that increasing dosages of lurasidone increase risk of mania and its resolution as opposed to lower dosages increasing risk of mania second generation drugs.[18]

Since there is a clear risk for second and third generation antipsychotics inducing a paradoxical effect of manic switching, can these drugs safely be used for patients with bipolar depression? Both risks and protective factors have been identified when performing medication management for these patients.[19] Risk factors include a previous switching event, young age, and not presently on a mood stabilizer.[20,21] Patients with rapid cycling are also at risk.[22-24] Protective factors including taking lithium at appropriate blood levels for more than one month.[25] Additionally, a switching event that responded rapidly to treatment decreases the likelihood of switching once on a mood stabilizer.[26] A stable home and social environment have also been identified as protective against manic events induced by antidepressants and antipsychotics.[19]

Specifically which atypical antipsychotics are safest to prescribe in this instance? Second generation quetiapine switching risk is at lower dosages and does not generally occur at higher ones. This means that if someone is at risk, the dosage can go in either direction and mania risk should decrease rapidly. However, in the case of lurasidone, case reports indicate that there is risk at all dosages and that lowering the blood levels is the only way to reduce risk.[18,27,28] Quetiapine may be the safer of the two.

SORT Grade of Recommendation C.

Informed Consent

Flesch-Kincaid Grade Level for the following passage is 6.6; Flesch Reading Ease = 68.

"Let's discuss your options for managing your bipolar illness. The last time we talked, I mentioned a medicine called quetiapine. You worried it may trigger a manic episode like the last antidepressant. I did some research. I want to share with you the harms and benefits of taking this medication.

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"Quetiapine is approved to treat bipolar depression. My research surprised me. I didn't know this medication can rarely be associated with a manic event. So, your concerns are real. Even though I've treated many patients with this medicine, I've never seen that type of reaction. We don't really know if it was the medicine or the disease that caused these events. But you have reasons that would prevent this from happening again. Being on lithium for over one month, keeping a schedule and having stable friends and family supports make the risk less.

"An important research paper looked at people with your current condition.[29] This paper did show that the medicine helps with depression. Additionally, they specifically looked at the risk of mania. The authors found that the rate was the same as for placebo. For you now, the risk is quite low.

"Because your depression getting worse, I would say that this medication is still the best medicine for you. I think it is safer than last time because you have been on lithium. Lithium prevents mania. I'm hopeful because you are actively involved in finding what is best for you. That makes me think you will do well in the years to come."

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