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EC PHARMACOLOGY AND TOXICOLOGY

Case Report

Unforeseen Consequence of Efavirenz Discontinuation

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Received: April 12, 2021; **Published:** October 29, 2021

Abstract

Background: Efavirenz has been approved in the United States for treatment of human immunodeficiency syndrome since 1998. Since that time, it has been one of the most commonly prescribed anti-retroviral medications. The neuropsychiatric effects of efavirenz have been well documented, and include vivid dreams, fatigue, and mood changes including the risk of suicide. While the depressive nature of efavirenz has been well documented, this case describes an episode of acute mania following the discontinuation of efavirenz.

Case Presentation: A 46-year old man who had over 10 years of psychiatric and human immunodeficiency virus treatment stability had his efavirenz containing regimen due to numerous symptoms consistent with depression. He had not been on any psychiatric medication in over 10 years. Two months after the change in medication the patient had a severe outburst of anger at work. This seemed to be an isolated event leading to a diagnosis of intermittent explosive disorder and the improvement in mood after removal of efavirenz was significant. He described feeling emotions and making friends again. Unfortunately, his symptoms continued to change including increased sexual activity, increased risk seeking behavior, and significant legal trouble. Ultimately, the patient spent more than 9 months in a State Forensic Psychiatric unit being treated with aripiprazole and risperidone. At most recent office visit, the patient describes.

Conclusion: Efavirenz has been and continues to be one of the most commonly prescribed anti-retroviral medications. However, with the release of newer agents with improved safety profiles many patients are being changed from efavirenz containing regimens. Should efavirenz mood stabilizing effects, careful monitoring of patients transitioning off of this medication should be in place.

Keywords: *HIV; Efavirenz; Mood-Stabilizer*

Introduction

Efavirenz was first approved for use in the United States in 1998. In 2006, it was included as a medication in the first single tablet regimen for the treatment of human immunodeficiency syndrome (HIV) under the brand name Atripla. Atripla was the only single tablet regimen available through 2011. During this time period it was consider first line therapy based on the Department of Health and Hu-

man Services (DHHS) treatment guidelines. The neuropsychiatric side effects of efavirenz are well documented throughout the literature. These side effects include vivid dreams, insomnia, and mood changes including risk of suicide. These side effects have been reported to occur in up to 40 - 50% of patients [1-4]. The presence of neuropsychiatric effects have often necessitated a switch from efavirenz containing regimens, the most common of which is co-formulated tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV), to other HIV regimes. Efavirenz is therefore often avoided in patients with baseline neuropsychiatric disorders.

Case Presentation

The patient is a 46 year old male who had over ten years of psychiatric stability without psychiatric medications. His HIV was well controlled with a CD4 count well above 500 cells/mm^3 and a viral load consistently < 40 copies/mm^3 for over 10 years. Although he described stability in terms of HIV, he struggled with a lack of enjoyment in life. He no longer socialized, had not been sexually active in years, and did nothing other than "work, sleep and eat". Due to the known neuropsychiatric effects of efavirenz, he was changed from TDF/FTC/EFV to co-formulated tenofovir alafenamide/emtricitabine/rilpivirine (TAF/FTV/RPV), specifically to alleviate the presumed depressant side effects of the efavirenz.

Two months after the change in medication the patient urgently presented to his Infectious Disease (ID) physician after being suspended from work for an anger outburst. He reported he had "lost control" of his anger and had a strong desire to hurt a co-worker who was wearing what the patient felt to be a t-shirt promoting "radical terrorist propaganda". The patient described trying to address this with management, but his anger persisted constituting his suspension. Of note, the patient had no previous relationship or interactions with this co-worker. During the visit with ID, he was noted to be irritable, yelling at staff, and was difficult to re-direct. His brief psychosocial history was obtained and he indicated that he had recently felt "liberated" to buy new things after living a frugal lifestyle for so long. He also discussed having increased sexual activity after having decreased libido for years prior. Due to this dramatic change in behavior and urgent referral to psychiatry was sent.

Two days after seeing his ID physician he presented for psychiatric evaluation. The patient continued to display episodes of anger lasting less than an hour. He indicated that in the past he had problems with anger outbursts, including an episode where he had broken glass after an argument with his roommate. A thorough review of manic symptoms was completed and outside of the anger outbursts he denied all other symptoms of mania. He indicated that he had been sleeping well, denied other impulsive behaviors, and did not present as having excessive energy, pressured speech or expressing grandiosity. He did indicate a positive emotional change after switching from efavirenz to rilpivirine, telling the psychiatrist "I can actually feel emotions…I am making friends…I feel like my old self."

Past psychiatric history revealed one prior inpatient psychiatric hospitalization after a similar episode of anger at which time the patient believed he might have been diagnosed with bipolar disorder, but was uncertain of the specific diagnosis. At that time, he was started on unknown doses of risperidone and valproic acid which he indicated were not helpful. He therefore discontinued them and has not been on these medications for over 10 years. The patient denied having manic or hypomanic symptoms for the 10 years while he was off psychiatric medications. In reviewing his family history, the patient believed that his mother had bipolar disorder, but could not confirm a formal diagnosis.

Given the relatively short time periods of his prior history of anger outbursts, lack of criterion for mania and his insight into the inappropriateness of his actions including expressing remorse, the diagnosis of Intermittent Explosive Disorder (IED) was reviewed with patient. After reviewing the criteria for IED the patient felt this was consistent with his symptoms and diagnosis of IED was made. The patient was started on sertraline 25 mg daily and told to follow up in 2 weeks. On follow up patient indicated improvement with sertraline stating it had "taken off the edge" and helped with anger, but he still had concerns for anger. Criteria for mania and hypomania were thoroughly reviewed and again patient denied these symptoms. Sertraline was therefore increased to 50mg daily with a follow-up appointment.

After being lost to care for 3 months, the patient was contacted by an HIV case manager. It was determined the patient had been arrested and charged with home invasion and stealing a car 3 months prior. Patient indicated to case manager that he had had a "manic episode". During a provider visit the patient revealed he had been released from prison based on a psychiatric diagnosis and was awaiting admission to the State of Michigan forensic psychiatric facility for evaluation. Patient indicated during his "manic episode" he had increased sexual activity, something that the patient did not experience when he was on TDF/FTC/EFV.

The patient was in the State Forensic Psychiatric Unit for 9 months and on re-presentation to the HIV clinic he was on risperidone 2 mg nightly and aripiprazole 15 mg daily. During his forensic psychiatry stay patient had been continued on TAF/FTC/RPV. Patient presented as stable and indicated he had not been having any manic symptoms.

Discussion

To our knowledge there are no other case reports of induction of mania after a switch from an efavirenz containing regimen. Two prior case reports have reported induction of mania with efavirenz use [5-7], but in our case we highlight the possible induction of mania with the removal of efavirenz.

Our patient's initial presentation to the HIV clinic showed symptoms consistent with mania or hypomania, but on referral to psychiatry and after thorough review of psychiatric history this event appeared to be time limited. Also, patient showed insight into anger as well as remorse for anger outbursts at work. Details of prior concern for bipolar disorder were limited and treatment at that time was ineffective, per patient. Reviewing criteria for Intermittent Explosive Disorder revealed multiple consistencies and thus decision to treat with selective serotonin re-uptake inhibitor, sertraline, was made [8].

There is obviously the concern of anti-depressant induced mania but studies show the rate of Sertraline induced mania to be, 0.4% [9]. Our hypothesis is that TDF/FTC/EFV, more specifically efavirenz, had a mood stabilizing effect on the patient and when switched to TAF/FTC/RPV this mood stabilizing effect was removed. Removal of the mood stabilizing effect could have triggered initial presentation to Infectious Disease physician, and continued absence of efavirenz could have led to a formal manic episode. It is also important to note that efavirenz has an extremely long half-life of approximately 3 days leading to slow removal of the drug from his system thereby prolonging the potential mood stabilizing effects.

Conclusion

With efavirenz being moved to an alternative treatment in the DHHS HIV Treatment Guidelines more patients are likely to be transitioned away from efavirenz. If efavirenz does possess mood stabilizing properties, careful monitoring should be given to those patients transitioning off of this anti-retroviral treatment. This is particularly true in those with a history of psychiatric illness.

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Volume 9 Issue 11 November 2021