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Case Report

Brexpiprazole-Induced Gynecomastia in a Thirteen-Year Old Male

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ABSTRACT

This case report involves a thirteen-year-old male with a history of anxiety, depression, autism spectrum disorder, and attention deficit hyperactivity disorder (ADHD) who developed significant weight gain and gynecomastia ten months after starting brexpiprazole. He had prior trials of quetiapine and aripiprazole which caused significant weight gain but did not cause gynecomastia. He had been taking sertraline and guanfacine for almost two years prior to starting brexpiprazole. Eight months later he was started on dexmethylphenidate for ADHD symptoms. There were no other recent exposures. After these symptoms developed, brexpiprazole and dexmethylphenidate were discontinued and several weeks later his gynecomastia resolved. Dexmethylphenidate is not known to cause gynecomastia. Although atypical antipsychotics have been known to cause gynecomastia, no case reports have identified brexpiprazole causing gynecomastia. Sertraline, a known cytochrome P450 2D6 inhibitor, is one of the primary metabolizers of brexpiprazole. We hypothesize that sertraline may have delayed the metabolism of brexpiprazole through inhibition of cytochrome P450 2D6 which led to elevated levels of brexpiprazole. This may have contributed to development of gynecomastia. This case report emphasizes the importance of closely monitoring drug-drug interactions as well as uncommon adverse effects of medications.

Keywords: Antipsychotics; Brexpiprazole; Gynecomastia; Depression

INTRODUCTION

Gynecomastia is defined as glandular proliferation in the male breast and most cases are thought to be caused by estrogen and androgen imbalances. Studies of pubertal gynecomastia have been conflicting, with some studies demonstrating gynecomastia with normal estrogen levels and other studies demonstrating gynecomastia with elevated estrogen levels [1]. Other causes of pubertal gynecomastia can include medication-induced, adrenal and testicular neoplasms, and androgen insensitivity.

Although there are case reports of atypical antipsychotics including risperidone causing gynecomastia, to date there are no case reports of brexpiprazole causing gynecomastia. One large scale study assessed the short- and long-term prolactin-related adverse effects associated with brexpiprazole. Out of 882 subjects in the six-week short term study, none of the subjects developed gynecomastia. Out of 1,240 subjects in the 52-week long term study, only one subject developed gynecomastia [2]. Antipsychotics are thought to cause gynecomastia through hyperprolactinemia by blocking D2 dopamine receptors in the hypothalamus-pituitary axis [3]. Within this axis D2 receptor agonism by dopamine acts as an inhibitor of prolactin release. However, with antipsychotics acting antagonistically on D2 receptors prolactin is no longer inhibited, leading to hyperprolactinemia. Brexpiprazole, a partial agonist at 5-HT1A and dopamine D2 receptors and an antagonist at 5-HT2A receptors, is known to have a reduced risk for causing prolactinemia-induced gynecomastia.

CASE REPORT

A thirteen-year old male with a history of major depressive disorder, generalized anxiety disorder, autism spectrum disorder, and attention deficit hyperactivity disorder (ADHD) was started on brexpiprazole for depressive symptoms while in outpatient treatment. For about 20 months prior to starting brexpiprazole, he had been taking sertraline for depression and anxiety as well as guanfacine for attention deficit hyperactivity disorder. In the past, he had trialed aripiprazole and quetiapine with which he

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had significant weight gain. After taking brexpiprazole for about eight months, dexmethylphenidate was started for ADHD symptoms. After taking brexpiprazole for about ten months, the patient had gained thirty-five pounds and started developing what appeared to be gynecomastia. Around this time, he saw his primary care doctor for a further assessment who confirmed that the patient had gynecomastia. The patient had denied previous episodes of gynecomastia. He also denied any substance use or other new exposures. Brexpiprazole was afterwards discontinued. Dexmethylphenidate was also discontinued at this time due to concern for it possibly contributing to gynecomastia and due to the patient having a history of intolerance to stimulant medications. The patient's gynecomastia resolved after several weeks.

DISCUSSION

Gynecomastia may result from imbalances in levels of androgens and estrogens or elevated prolactin levels, and it occurs more commonly in adults compared to adolescents. Adolescent gynecomastia is usually seen in the early stages of puberty likely due to low testosterone levels compared to estradiol [4]. Although gynecomastia is usually a physiological occurrence in adolescents, it is important to be cautious of medications that may cause it. Although the mechanism is not clear, selective serotonin reuptake inhibitors (SSRIs) including sertraline have been associated with gynecomastia [5]. Several theories propose that follicular stimulating hormone, luteinizing hormone, estrogen, testosterone, and prolactin may be involved in this mechanism.

While a definitive mechanism of action has yet to be elucidated on SSRIs affecting release of prolactin, it is known that serotonin is an indirect modulator of prolactin release. One proposed mechanism involves modulation of postsynaptic serotonin 5-HT1A, 5-HT2, 5-HT2C, and possibly 5-HT3 receptors within the paraventricular nucleus (PVN) of the hypothalamus [6]. The PVN plays a role in regulation of corticotropin-releasing hormone, vasopressin, and thyrotropin-releasing hormone, with thyrotropin-releasing hormone functioning to regulate thyroid-stimulating hormone and prolactin [7]. Another possible mechanism involving serotonin on prolactin release is by stimulation of local GABAergic neurons by tuberoinfundibular dopamine cells. 5-HT1A receptors are located on these cells and serotonergic stimulation of them would inhibit dopamine [6]. Inhibition of dopamine would then lead to dis-inhibition of prolactin release contributing to hyperprolactinemia and effects associated with it. However, it must be noted that many studies evaluating SSRI-induced hyperprolactinemia have a small sample size and relatively short monitoring duration to observe hyperprolactinemia. Further research into the precise mechanism by which SSRIs can contribute to hyperprolactinemia is warranted.

Gynecomastia is not a known side effect of guanfacine and dexmethylphenidate. The patient had tolerated sertraline and guanfacine well for almost two years without developing gynecomastia or other side effects. However, there is a drug-drug interaction between sertraline and brexpiprazole that results in increased brexpiprazole levels. Sertraline, a cytochrome P450 2D6 inhibitor, increases brexpiprazole levels due to brexpiprazole being a major substrate for cytochrome P450 2D6 [8,9]. Thus, the patient's use of sertraline may have increased his levels of brexpiprazole which may have contributed to the development of gynecomastia.

CONCLUSION

Although the patient had been taking four medications simultaneously, it can be hypothesized that brexpiprazole played a role in the development of gynecomastia in this patient given gynecomastia being a potential adverse effect of the medication. Furthermore, increased levels of brexpiprazole resulting from concurrent use of sertraline and brexpiprazole may have increased the risk of adverse effects including gynecomastia in this patient. This case emphasizes the importance of closely monitoring adverse effects of brexpiprazole including less common ones such as gynecomastia as well as potential interactions with other medications.

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