



## Rare Case of Hypomania Induced by Testosterone Replacement in a Hypogonadal Patient

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### Abstract

Hypogonadism is a dysfunction characterized by the insufficiency and absence of puberty and infertility due to a deficiency of the Gonadotropin-Releasing Hormone (GnRH), which is necessary for regulating the reproductive axis. Treatment typically involves administering testosterone and GnRH or gonadotropin injections, but testosterone administration may result in mood disorders and aggression in some patients. In this article, we present the case of a 27-year-old patient who was stable on Aripiprazole 20 mg/day for bipolar disorder but experienced a manic attack two days after increasing their testosterone dose. Patients with bipolar disorder who receive testosterone replacement therapy should be closely monitored for any behavioral or mood changes. It is crucial to recognize that administering testosterone replacement therapy to patients with bipolar disorder may lead to mood changes or even trigger the onset of bipolar disorder.

### Introduction

Hypogonadotropic hypogonadism is a dysfunction that manifests itself in the insufficiency and absence of puberty and infertility, caused by Gonadotropin-Releasing Hormone deficiency (GnRH) [1]. This hormone is essential for regulating the reproductive axis. Although this endocrine disorder is rare, the most frequent form is congenital hypogonadotropic hypogonadism, which is five times more common in men [2]. Treatment involves injections of testosterone and GnRH or gonadotropin [3], but testosterone administration can cause side effects such as mood disorders and aggression in some patients [4,5]. However, rare cases of patients developing manic episodes after receiving testosterone or androgenic anabolic steroid treatments have been reported in the literature [6-8]. Epidemiological studies that have evaluated the relationship between testosterone levels and mood disorders are rare with contradictory results [5,9-11]. In a randomized controlled study conducted by Pope et al. on healthy men, administration of supraphysiological doses of testosterone induced hypomania in 16% of participants [9]. Although the physical effects of testosterone therapy are well documented [12]. The psychiatric effects and the circumstances that precipitate them are still the subject of studies. In this article, we present a case of a patient who developed a hypomanic episode following testosterone replacement therapy.

### Case Presentation

A 30-year-old single Moroccan patient who has been followed for osteoporosis since the age of 21. He is treated with Risedronate 35 mg weekly. As part of the etiological research for osteoporosis, he was diagnosed with hypogonadotropic hypogonadism. The patient also has psoriasis and his brother is being followed up for intermittent explosive disorder.

In terms of his psychiatric history, he has been under treatment since the age of 22 for depressive episodes and a substance use disorder, notably alcohol and tobacco, with occasional use of ecstasy. He has received several antidepressants since the beginning of his illness and has been hospitalized only once for the management of depression with anxious features and suicidal ideation. During this hospitalization, he was treated with escitalopram 20 mg/day and alprazolam 3 mg/day with gradual decrease. The evolution was marked by occurrence of hypomanic episode that was likely induced by ecstasy use; therefore, a bipolar disorder type II was diagnosed, and this hypomania episode was treated ambulatory with aripiprazole 20 mg/day and carbamazepine 800 mg/day, which led to a rapid resolution of symptoms. However, after a few months, the patient stopped taking carbamazepine due to a decrease in his libido that he attributed to the treatment, and continued taking aripiprazole at a dose of 20 mg/day.

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He presented with his mother to the psychiatric emergency department for psychomotor agitation and insomnia. The psychiatric examination revealed that the patient was agitated in terms of motor activity with increased energy and logorrhea, he had an irritable mood, disinhibited, he presents a flight of ideas, increased self-esteem and insomnia. His mother indicated that he had been unusually unstable over the past few days, presenting multiple violent anger outbursts at the slightest frustration. After completing the ANGST hypomania questionnaire, this episode was diagnosed as hypomania.

His mother noticed that these symptoms began after 2 days of receiving the Andotardyl 250 mg/1 ml injection for his hypogonadotropic hypogonadism, which his treating physician had increased to one ampoule per month, instead of half ampoule as an initial dose. The patient was hospitalized and treated with aripiprazole 20 mg/day and chlorpromazine 200 mg/day, which resulted in gradual improvement during the second week of his hospitalization.

## Discussion

Hypogonadism is an endocrine disorder characterized by insufficient production of testosterone. Symptoms of hypogonadism include low libido, difficulty achieving or maintaining a satisfactory erection, difficulty ejaculating, testicular atrophy, infertility, reduced hair growth, gynecomastia, asthenia, sleep disorders, loss of muscle mass, muscle pain, signs of bone fragility, weight gain, poor concentration, memory impairment, decreased motivation, and mood changes [13]. Several studies have established a correlation between low testosterone levels and depressive symptoms [14]. The results of Woodson et al. study revealed a significant decrease in testosterone levels in men with bipolar depression compared to control men [15]. Similarly, a cross-sectional study of 856 men aged 50 to 89 years, which measured free testosterone levels and evaluated major depressive disorders using the Beck Depression Inventory, revealed a correlation between low testosterone levels and depressive symptoms [16]. This suggests that chronically low testosterone levels in our patient may be an etiological factor in the initial depressive episodes.

Our patient presented signs of hypomania shortly after receiving an injection of 250 mg/1 ml of Androtardyl, which his treating physician had increased to one ampoule per month. Although we cannot definitively exclude spontaneous decompensation of bipolar disorder. This case suggests that testosterone administration can induce hypomania or manic episodes in vulnerable individuals, particularly in patients with personal or family histories suggesting a predisposition to mania or psychosis. Given that our patient had bipolar disorder, it seems that he was particularly sensitive to the increase in testosterone substitution dose, which probably contributed to his hypomanic episode. Similar cases have been reported in the literature. Elboga et al. described the case of a 25-year-old patient with hypogonadotropic hypogonadism and a history of Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD), who experienced a manic episode after testosterone replacement therapy [17]. Weiss et al. reported the case of a 28-year-old man with bipolar disorder who developed mania one month after starting testosterone patch therapy [6]. Papazisis et al. also described the case of a 25-year-old man with a history of depression who presented a manic episode with psychotic features shortly after increasing his daily dose of Androgenic Anabolic Steroids (AAS) to over 2 g per day [7]. However, Franey et al. reported the case of a 30-year-old man with no personal or family history of bipolar

disorder who developed a manic episode after starting AAS use [18]. Similarly, Barbenel et al. also described a case of mania in a bilateral orchiectomy patient taking testosterone replacement therapy [8]. Overall, these observations suggest a possible relationship between blood testosterone levels and mania.

Studies have examined the effects of testosterone on healthy men and have shown that some subjects developed manic symptoms [19,20]. In a randomized controlled study conducted by Pope et al. on healthy men aged 20 to 50 years, the administration of supraphysiological doses of testosterone induced hypomania in 16% of participants [9]. In addition, a study by Sher et al. of 67 patients with bipolar disorder showed a positive correlation between testosterone levels and the number of manic episodes and the number of suicide attempts [21]. In contrast, a case-control study found no significant difference in salivary testosterone levels between the euthymic, depressed, and manic phases in patients with bipolar disorder type I and a healthy control group [10]. In addition, the study by Bhasin et al., which examined the physical effects of a weekly 600 mg dose of testosterone for 10 weeks, found no significant changes in mood or behavior [11].

## Conclusion

It is important to note that patients receiving testosterone substitution therapy may develop manic or hypomanic symptoms. Therefore, careful monitoring for behavioral and mood changes is warranted, especially in patients with bipolar disorder.

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