Psychotic Exacerbation Following Subcutaneous Leuprolide in a Male Patient With Previous History of Schizophrenia

To the Editor: Leuprolide acetate is a synthetic analog of naturally occurring gonadotropin-releasing hormone (GnRH) and, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis.[1] Leuprolide acetate is indicated for the palliative treatment of advanced prostate cancer and is available as a 1-month, 3-month, 4-month, and 6-month subcutaneous injection. In males, administration of leuprolide acetate results in testosterone levels below castrate threshold (< 50 ng/dL), with this decrease occurring within 2 to 4 weeks after initiation of treatment.[1,2]

Although there have been reports[2–4] in the literature demonstrating patients experiencing emotional lability, depression, mania, and psychotic symptoms with GnRH agonist use, these reports have mainly been in patients with no prior history of psychiatric illness (Table 1). There is only 1 case[5] that we identified in the literature of a patient with a previous psychiatric illness who received leuprolide acetate and experienced worsening psychiatric symptoms (Table 1). The leuprolide acetate subcutaneous injection package insert[1] lists insomnia and anxiety as occurring in < 2% of patients. Here, we present the case of a man with prior psychiatric history of paranoid schizophrenia who experienced an acute exacerbation of his psychotic symptoms after receiving a 6-month subcutaneous injection of leuprolide acetate.

Case report. A 67-year-old black man presented to the emergency department in March 2016 because of continued acute psychiatric decompensation with homicidal ideations toward his immediate relatives. The patient was discharged from the inpatient psychiatry unit 2 days prior with a similar presentation. The patient exhibited increased irritability, screaming, and frequent episodes of paranoia. Relevant past medical history included a 20-year history of paranoid schizophrenia (*DSM-IV* criteria), prostate cancer, type 2 diabetes mellitus, and coronary artery disease. The patient was diagnosed with prostate cancer with no metastases in July 2012, and he was able to complete 6 treatments of radiation therapy that ended in February 2013. Due to his continued rise in prostate-specific antigen levels postradiation, leuprolide acetate 45 mg subcutaneously every 6 months was initiated in February 2016.

Presently, all relevant laboratory data were within normal limits. The patient reported no drug allergies, smoked a half pack of cigarettes per day with limited alcohol consumption, and denied current illicit drug use. His current psychotropic medication regimen included haloperidol 15 mg by mouth twice daily and benztropine 1 mg twice a day, which the patient had been stable on for 3 years. The attending psychiatrist decided to increase the patient's haloperidol dose to 20 mg twice daily. Despite the dose increase of the haloperidol, the patient continued to be irritable, paranoid, and uncooperative with medical staff. Olanzapine 2.5 mg was eventually initiated and titrated to 5 mg daily. With the addition of olanzapine, the patient reported improved sleep and mood and a decrease in paranoia. At discharge, the patient was displaying no paranoia or aggression, denied homicidal ideation, and displayed fair insight into his disease management.

To our knowledge, this is the first case report describing a patient with a previous psychotic illness who received leuprolide therapy and subsequently experienced worsening psychosis after being psychiatrically stable for an extended period of time. Previous research has shown that a decrease in testosterone levels can alter the dopamine system in the prefrontal cortex, which is one of the mechanisms proposed to be associated with psychotic behavior.[4,6–8] With this knowledge, it is imperative for health care providers to screen patients for preexisting psychiatric illnesses before initiating GnRH agonist therapy. Screening patients for preexisting mental illness prior to treatment will allow clinicians to choose a shorter-acting formulation to prevent persistent psychiatric exacerbations from occurring throughout therapy while also limiting psychotropic polypharmacy.

Table 1. Other Published Cases in Prostate Cancer of GnRH Agonist-Induced Psychiatric Episodes

Case Study	Age (y/sex)	Reason for Treatment	GnRH Dosing	Psychiatric Side Effects	Treatment/Outcomes
Chavez and Reilly[2]	65/male	Prostate cancer with no metastases	Leuprolide 45 mg intramuscularly every 6 mo	Two weeks after initiation, the patient developed agitation, progressive sleep loss, excessive outbursts, delusions, irritability, and impulsive behaviors	Required hospitalization; treated with olanzapine 20 mg daily with improvement in symptoms; patient discontinued with no recurrence of symptoms; did not receive additional leuprolide therapy
Pong et al[3]	62/male	Prostate cancer with metastases to the bone	Leuprolide acetate 3.75 mg intramuscularly monthly	After the second dose, the patient developed elation and expressive, hyperactive, and sleep disturbances	Was hospitalized; treated with risperidone and haloperidol, leuprolide and risperidone discontinued after follow-up
Bernad et al[4]	62/male	Prostate adenocarcinoma with no metastases	Triptorelin 11.25 mg intramuscularly every 3 mo	Four weeks after initiation, the patient developed insomnia, irritability, and anhedonia followed by delusions and impulsive behaviors	Required hospitalization; treated with citalopram 20 mg daily and olanzapine 20 mg daily; switched to goserelin with relapse at 8 months and the addition of aripiprazole 2 mg daily for additional treatment with no further relapses
Kao et al[5]	60/male	Prostate adenocarcinoma	Leuprorelin acetate 3.75 mg intramuscularly monthly	Two days after initiation, the patient developed mood fluctuations, depressed mood, irritability, anxiety, aggravated anhedonia, and sleep disturbances	Was hospitalized during initiation of leuprorelin acetate; treated with escitalopram 10 mg daily with improvement in symptoms to disappearance by week 3

Abbreviation: GnRH = gonadotropin-releasing hormone

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