Urological Science 25 (2014) 22–24

Contents lists available at SciVerse ScienceDirect

Urological Science

journal homepage: www.urol-sci.com

Case report

# Acute manic and psychotic symptoms following subcutaneous leuprolide acetate in a male patient without prior psychiatric history: A case report and literature review

Yuan-Hung Pong [a,b], Yu-Chuan Lu [a], Vinscent F.S. Tsai [b], Pei-Lin Huang [b], Ju-Ton Hsieh [a], Hong-Chiang Chang [a,*]

[a] Department of Urology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan
[b] Department of Urology, Ten Chan Hospital, Zhong-Li, Taiwan

ARTICLE INFO

*Article history:*
Received 29 October 2012
Received in revised form
14 December 2012
Accepted 25 February 2013
Available online 5 July 2013

*Keywords:*
adverse events
leuprolide acetate
manic status
prostate cancer
psychosis

ABSTRACT

Leuprolide acetate is usually used in the treatment of advanced prostate cancer. The adverse events associated with administration of leuprolide acetate include fatigue, hot flashes, loss of libido, impotence, and depression. These side effects can be treated conservatively. Acute manic and psychiatric symptoms following leuprolide acetate injection are very rare. Few case reports have been published documenting these symptoms. Here, we describe the case of a 62-year-old male with metastatic prostate cancer, who developed acute manic and psychiatric symptoms 2 months after subcutaneous leuprolide acetate injection. These symptoms were relieved after administration of neuroleptic drugs, such as risperidone. Administration of leuprolide acetate was eventually stopped. The exact mechanism causing the manic and psychiatric adverse events is unclear. Some experts have theorized that estrogen withdrawal following leuprolide acetate therapy may induce psychiatric symptoms. Manic episodes may arise from a deficit in central serotonergic neurotransmission. Based on these hypotheses, risperidone, lithium, and some anticonvulsants, such as divalproex sodium and carbamazepine, have been used effectively in the treatment and prophylaxis of manic episodes. Although psychiatric adverse events are rare following administration of leuprolide acetate, clinicians should be aware of the possibility.


## 1. Introduction

Leuprolide acetate is a synthetic nonpeptide analog of naturally occurring gonadotropin-releasing hormone. Leuprolide acetate overstimulates the body's own production of human luteinizing hormone-releasing hormone, which then shuts down. Through this process, leuprolide acetate reduces the amount of testosterone in men and estrogen in women.

Leuprolide acetate is usually used in the treatment of advanced prostate cancer in men and symptoms of endometriosis in women. It is also used to treat precocious puberty in both male and female children. Fatigue, hot flashes, loss of libido, and impotence are the most common adverse effects, all of which can be treated conservatively. Adverse events affecting the central nervous system, such as anxiety, blurred vision, lethargy, mood swings, insomnia, and depression have been reported in <5% of patients treated with leuprolide acetate. Acute manic and psychiatric symptoms are rarely reported as a result of leuprolide acetate injection. Only a few case reports have been presented in the medical literature. Here, we report the case of a 62-year-old male with metastatic prostate cancer, in whom acute manic and psychiatric symptoms developed 2 months after subcutaneous leuprolide acetate injection.

## 2. Case report

We describe the case of a 62-year-old man without previous psychiatric history or mood disorder diagnosed in October 2010 with prostate cancer, which metastasized to the bone. Androgen deprivation therapy was administered monthly in the form of leuprolide acetate (3.75 mg) subcutaneous injections. After the second dosage, the patient gradually became increasingly elated, expressive, hyperactive, and increasingly talkative about his work and future plans. A decreased need for sleep also developed. The patient's medical history revealed no drug abuse or alcohol

* Corresponding author. Department of Urology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Number 7, Chung Shan South Road, Zhongzheng District, Taipei City 10002, Taiwan.
*E-mail address:* changhong@ntu.edu.tw (H.-C. Chang).

1879-5226 
http://dx.doi.org/10.1016/j.urols.2013.05.010

consumption until that time. Laboratory examinations showed normal thyroid and adrenal function. A toxicology screen was negative for illegal substances. However, impaired liver function was revealed, and may have been caused by hepatitis C. Brain magnetic resonance imaging demonstrated atrophy, but no obvious brain or skull metastases. Electroencephalography revealed no overt abnormalities; however, hypersomnolent tendencies were noted.

Upon admission, oral neuroleptic drug treatment was started (risperidone and haloperidol) under the diagnosis of substance-induced acute manic episode, according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. Manic symptoms subsided 1 week after administration of this treatment. One month after discharge, the patient's overall good condition allowed discontinuation of leuprolide acetate. Follow-up revealed no psychiatric symptoms requiring hospitalization. Risperidone for controlling symptoms was also discontinued.

## 3. Discussion

Prostate cancer is very prevalent in geriatric populations. Since 1995, approximately 2,600,000 men in the United States have been diagnosed with prostate cancer, and nearly 375,000 men have lost their lives to this disease.[1] However, mortality rates due to prostate cancer appear to be declining; 34,475 men died in 1995 from the disease compared with an estimated 30,350 in 2005. This is due to improvements in prostate cancer treatments. Androgen deprivation therapy, such as leuprolide acetate, goserelin acetate, and triptorelin acetate are commonly used in the treatment of advanced prostate cancer. Adverse events, such as fatigue, hot flashes, depression, and loss of libido are common and can be treated conservatively. However, acute manic and psychiatric symptoms following leuprolide acetate treatment are very rare. Only a few case reports are available in the medical literature; most of these cases were females in whom leuprolide acetate treatment was administered for endometriosis.

Warnock and Bundren [2] published the first two cases of leuprolide acetate-induced mania. The first case was a 37-year-old female with a history of endometriosis in whom leuprolide acetate was injected for treatment of endometriosis. After the second injection, she presented with decreased motivation, distractibility, passive suicidal ideation, and extreme irritability. These symptoms improved after discontinuation of the injections and without additional medication for manic symptoms. The other case was a 22-year-old female with a history of endometriosis and fallopian tube occlusion, in whom leuprolide acetate was administered. Two weeks after injection, crying spells, decreased sleep, and irritability developed. These symptoms markedly improved after 6 weeks of administration of the antipsychotic drug sertraline.

Rachman et al[3] reported a 28-year-old female with a 6-year history of endometriosis in whom a series of leuprolide acetate injections was administered. After the fifth leuprolide acetate injection, she presented with irritability, argumentativeness, distractibility, and a decreased need for sleep. She was diagnosed with bipolar disorder (manic status). Treatment with lithium carbonate induced calmness and reduced impulsiveness.

Although female cases have been reported since 1997, the first male patient with these symptoms was only reported in 2010 by Chavez and Reilly.[4] Leuprolide acetate injection treatment was administered in a 65-year-old male with a history of metastatic prostate cancer. Two months after the first injection, the patient showed the following peculiarities: extreme agitation, shouting of profanities, decreased sleep, an increasingly talkative nature, and pressured speech. A review of past medical and family history showed no psychiatric illnesses. The behavior deviated markedly from the norm. Symptoms improved on the 9$^{th}$ day after initiation of olanzapine treatment. After discharge, olanzapine was discontinued; 1 month later, the patient was doing well, with no psychiatric symptoms.

The exact mechanism underlying the development of psychiatric symptoms after administration of leuprolide acetate remains unclear. One hypothesis is related to the mood stabilizing effects of estrogen. Abrupt pharmacological castration and subsequent decreased serum estrogen levels may be related to the development of the acute psychosis associated with leuprolide acetate injection in the cases described here. Rachman et al[3] performed animal experiments in female rats that had received an ovariectomy. Significant behavioral changes and hyperactivity were observed postoperatively. Another estrogen protection hypothesis was put forward by Riecher-Rossler in 2002, in which estrogen exerted a protective effect on psychotic symptoms in susceptible patients.[5] Huber et al also found lower levels of total testosterone, free testosterone, and estradiol in men with acute psychosis compared with those in the control group.[6] Another hypothesis regarding the manic episodes, postulated that a deficit in central serotonergic neurotransmission permits the expression of substances that cause manic episodes.[7]

Based on the results of these studies, measurement of testosterone and estradiol levels should be performed in cases like the one reported here. Unfortunately, these measurements were not performed in our case. Clinicians should be aware of the benefit of these tests. Future studies may reveal the exact mechanism underlying manic episodes associated with administration of leuprolide acetate.

The management of leuprolide acetate-induced psychosis cases is not identical. In the case reported here, administration of leuprolide acetate was discontinued, after which the patient was observed until recovery. If symptoms persist or progress, neuroleptic drugs such as risperidone and haloperidol may be considered. Some clinicians and studies have claimed that lithium, anticonvulsants such as divalproex sodium and carbamazepine are effective in the treatment and prophylaxis of manic episodes, because they are involved in enhancement of 5-HT function in the central nervous system.[8]

In the case reported here, no prior psychiatric history or relevant endocrine problems were evident. Thus, the manic behavior and anxiety symptoms were considered to be manifestations of a leuprolide acetate-induced psychiatric disorder. According to a study created by eHealthMe based on 5886 reports from the Food and Drug Administration and the user community, goserelin acetate-induced manic episodes are also possible; these are still, however, very rare.[9]

To our knowledge, this is only the second case report of a male patient, with no prior psychiatric history, in whom acute manic and psychiatric symptoms developed after leuprolide acetate injection. We report this rare case of adverse events occurring following leuprolide acetate administration for fellow clinicians, who should be aware of this rare psychiatric side effect.

## Conflicts of interest statement

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

## Sources of funding

None.

## References


1. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hargino ED, Cookson MS, et al. Guidelines for the management of clinically localized prostate cancer: 2007 update. *J Urol* 2007;**177**:2106–31.
2. Warnock JK, Bundren JC. Anxiety and mood disorders associated with gonadotropin-releasing hormone agonist therapy. *Psychopharmacol Bull* 1997;**33**:311–6.
3. Rachman M, Garfield DA, Rachman I, Cohen R. Lupron-induced mania. *Biol Psychiatry* 1999;**45**:243–4.
4. Chavez B, Reilly T. Manic and psychotic symptoms following subcutaneous leuprolide in a male patient with no prior psychiatric history. *J Clin Psychiatry* 2010;**71**:1696–8.
5. Riecher-Rossler A. Oestrogen effects in schizophrenia and their potential therapeutic implications–review. *Arch Womens Ment Health* 2002;**5**:111–8.
6. Huber TJ, Tettenborna C, Leifkeb E, Emrich HM. Sex hormones in psychotic men. *Psychoneuroendocrinology* 2005;**30**:111–4.
7. Shiah IS, Yatham LN. Serotonin in mania and in the mechanism of action of mood stabilizers: a review of clinical studies. *Bipolar Disorders* 2000;**2**:77–92.
8. McElroy SL, Keck PE, Pope HG, Hudson JI. Valproate in the treatment of bipolar disorder: literature review and clinical guidelines. *J Clin Psychopharmacol* 1992;**12**:42S–52S.
9. eHealthMe website from Food and Drug Administration and the user communityhttp://www.ehealthme.com/drug_interactions_side_effects/Goserelin-Acetate-2792968 [accessed 4.12.12].