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# A Case Series of Abuse of a New Opioid Combination, Norjizak

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**ABSTRACT.** Cushing's syndrome results from lengthy and inappropriate exposure to excessive concentrations of either endogenous or exogenous glucocorticoids. This study described 30 patients with a novel type of severe exogenous Cushing's syndrome in a group of intravenous drug users due to illicit use and dependence on a new opioid combination, Norjizak. Thirty consecutive patients (2 women and 28 men) who presented with a novel type of severe exogenous Cushing's syndrome and other complications were admitted to the emergency departments of Qom and Isfahan University of Medical Sciences, Isfahan, Iran, between September 2005 and September 2007 were enrolled. All participating patients were intravenous drug users who used a narcotic drug called Norjizak, a combination of different opioids with dexamethason or benzodiazepines. Patients were first evaluated and managed based on the current illness, and then entered into a detoxification program by a medical team. Clinical data were collected by an open interview and the patient's files using a standard form. High-performance liquid chromatography was used to determined glucocorticoid existence in the brand. The major complaints and clinical findings were withdrawal symptoms, severe edema, osteoporotic fracture, impairment in glucose tolerance, decreased libido, and sepsis (including necrotizing pneumonia, cutaneous infection, multivalvular endocarditis, osteomyelitis, and urogenital infection). Most patients had started with 2 or 3 vials per day and then increased the dose compulsively to maximum of approximately 15 to 20 vials per day. The concentration of Dexamethhasone disodium phosphate in each 2 mL vial was 0.4 to 1 mg/mL. Heroin was also found in them. We are witnessing a special exogenous Cushing syndrome due to

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the mixing of opiates and dexamethasone. Norjizak syndrome is the clinical condition of poisoning with a second material when it is combined with opiates due to compulsive dose increment and long duration.

**KEYWORDS.** Addiction, glucocorticoid, Norjizak, opium, substance abuse



## *INTRODUCTION*

Cushing's syndrome results from lengthy and inappropriate exposure to excessive concentrations of either endogenous or exogenous glucocorticoids. It is relatively rare and most commonly affects adults aged 20 to 50 years. Recently, we have observed and managed several cases of severe exogenous Cushing's syndrome and other complications in a group of intravenous drug users due to illicit use of a new opioid combination drug known as Norjizak, a probably handmade drug that borrowed its name from Norgesic (the registered trade name of buprenorphine, Reckitt Benckiser plc., London, UK). It is in the form of 2 mL vials containing yellow fluid (Figure 1), a combination of different opioids plus non-opiate compounds like dexamethasone and benzodiazepine. Dependent on duration and the dose of this drug, patients may present with diverse complications.

Information from other parts of Iran reveals the increasing use of this illicit drug. Unconfirmed reports reveal that the drug may have also been distributed in other regions such as Pakistan and countries beside Caspian basin. Police discoveries in the pathway of Afghanistan and Pakistan borders in the southeast to Turkey borders in the northwest of Iran reveal Norjizak may rapidly be distributed also in Europe by smugglers (personal communication with Iranian police department). Because of extensive distribution and spurious advertisement of the drug as opium cessation remedy and the fact of significant euphoria and sense of well-being (at least at the beginning), many addicts in the region are changing their habits toward Norjizak.

This study aimed to describe 30 patients with a novel type of severe exogenous Cushing's syndrome in a group of intravenous drug users due to illicit use of a new opioid combination known as Norjizak.

## *PATIENTS AND METHODS*

Thirty consecutive patients admitted to the emergency, toxicology, or endocrinology clinics of Isfahan and Qom University of Medical Sciences, Isfahan, Iran, between September 2005 and September 2007 with a history of Norjizak use and clinical findings of a novel type of severe exogenous Cushing-like symptoms were enrolled in this study. They were evaluated and managed based on their current illness. After clinical stability, patients were invited to enroll in this study. After obtaining informed consent, those who agreed to enroll were included in the data analysis. Pictures were taken and patients then were put in a drug cessation program by a medical team of a toxicologist, a psychiatrist, an endocrinologist, and other experts if indicated. Norjizak vials were analyzed for presence of glucocorticoids by high-performance liquid chromatography at three independent centers belonging to the same universities and by liquid chromatography mass spectroscopy in another center. Dexamethasone, hydrocortisone, prednisone, beclomethasone, triamcinolone, and prednisolone were the main glucocorticoids analyzed in the vials. From each vial, 2 $\mu$L were analyzed after mixing 200 $\mu$L sample with 200 $\mu$L Formate buffer (2 mM; pH = 2.4). In the liquid chromatography (LC) assay, the Mobile phase was Acetonitrile: Ammonium (25:75) Formate buffer (2 mM, pH = 2.4); Flow rate: 0.35 mL/min, oven temperature 55°C; MSD were Negative Ion polarity, electrospray ionization–mass spectrometry (ESI-MS) Ion source, dry temperature 350°C, nebulizer 30 psi, dry gas 12 L/min, acquisition method and scanning was from 50 to 550 m/z capillary voltage 30,000 V. Other parameters were as suggested by the manufacturer. To detect opioid content of the vials, gas chromatography–mass spectrometry (GC/MS) (varian1200, CA, USA) was used. In

FIGURE 1. Norjizak vials.

the GC/MS analysis the column was HPI, 30 meter length, and the mobile phase was helium 1 mL/min. Tenets of the current version of the Declaration of Helsinki were followed, institutional ethical committee approval was granted, and the nature of the study was explained to the patient. After a detailed discussion with the physician, patients made a final decision and each patient signed an informed consent form.

A pre-designed questionnaire including clinical data was completed for each patient. These include physical examination, measurement of blood pressure, fasting blood glucose, glycosylated hemoglobin ($HbA_{1c}$), urine protein, triglyceride, cholesterol, and serum creatinine.

## *RESULTS*

During a 2-year study period, 30 patients (2 women and 28 men) with clinical findings of a novel type of severe exogenous Cushing-like symptoms were admitted to the emergency, toxicology, or endocrinology clinics of Isfahan and Qom University of Medical Sciences. All patients had mean (standard deviation [SD]) duration of Norjizak use for 9.4 (7.3) months, with ages ranging from 19 to 45 years (mean age (SD) = 31.5 (7.1) years). The self-reported mean (SD) number of vials used was 7.5 (4.3) (range = 2 to 20). The mean (SD) body mass index score was 27.5 (5.8) kg/m$^2$. Eleven (36.7%) patients were single and 19 (63.3%) were married. The most frequent reason of referral, observed in 12 (40.0%) patients, was either cessation or withdrawal symptoms. Other complaints are presented in Table 1.

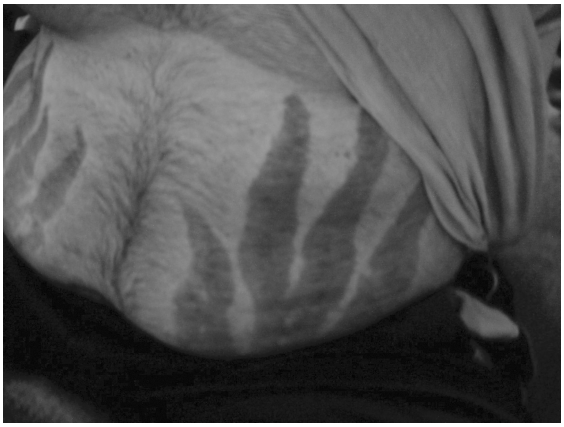
TABLE 1. Frequency of Clinical Findings in the Participants

| Clinical Finding | Chief Complaints N (%) | Additional Findings N (%) |
|---|---|---|
| Edema | 5 (16.7) | 22 (73.3) |
| Osteoporosis/fracture | 1 (3.3) | 6 (20.0) |
| Hepatitis | 0 (0.0) | 7 (23.3) |
| Drug cessation/withdrawal symptoms | 12 (40.0) | 15 (50.0) |
| Amenorrhea (% of women) | 1 (50.0) | 1 (50.0) |
| Muscle weakness | 4 (13.3) | 18 (60.0) |
| Sepsis[a] | 2 (6.7) | 9 (30.0) |
| Infective ulcer | 1 (3.3) | 16 (53.3) |
| MI | 1 (3.3) | 0 (0.0) |
| Deep vein thrombosis | 1 (3.3) | 5 (16.7) |
| Coma[b] | 1 (3.3) | 0 (0.0) |
| Severe obesity | 1 (3.3) | 5 (16.7) |
| Decreased libido | 0 (0.0) | 18 (60.0) |
| Diabetes mellitus | 0 (0.0) | 10 (33.3) |

[a]The patient with sepsis complained also from infective ulcer.
[b]The cause of coma was hyperosmolar hyperglycemia.
MI = Myocardial infarction.

Eight patients (26.7%) had used Norjizak because they thought it was a detoxifying medication. In the others, it has been used for its more euphoria compared with their previous substance. Twenty-one patients (70.0%) had striae, which in 15 (71.4%) patients was severe (Figure 2). One patient presented with osteoporotic fracture, five others had osteoporosis on bone densitometry, and one was affected by avascular necrosis of femoral head, but the state of bone health in others was undetermined. Six patients (20.0%) were not cushingoid, but the others had moderate to severe cushingoid features including truncal obesity, rounded face, and supraclavicular fullness. Dorsocervical fat pad, edema, and skin atrophy were frequent findings. Ten patients (33.3%) had impairment in glucose tolerance or diabetes mellitus, which was very severe in two patients (one diabetic ketoacidosis (DKA) and one hyperosmolar state). Eighteen patients (60.0%) had decreased libido. Nine patients (30.0%) had variable forms of sepsis (including necrotizing pneumonia, multivalvular endocarditis, cutaneous infection, osteomyellitis, urinary tract infection, and urogenital infection). Almost all patients had multiple clinical problems (Table 1). Most patients had

FIGURE 2. Severe striae, due to Norjizak use.



started with two or three vials of Norjizak per day, and then had increased the dose compulsively to a maximum of approximately 15 to 20 vials per day.

The most important factor assured Norjizak cessation was adequate opium replacement by methadone. Once patients discontinued Norjizak, they were prescribed a supplemental dose of corticosteroid (Prednisolone 5 mg/day) and advised to increase its dose accordingly in stressful conditions. In adrenal crisis due to either severe infection or Norjizak discontinuation, dexamethasone was initially administered intravenously in stress dose and gradually tapered down to usual maintenance dose of prednisolone after the acute stress was resolved. Interestingly, most patients, despite severe Cushing-like symptoms and expected profound adrenal suppression, tolerated rapid discontinuation of replacement glucocorticoids well.

Biochemical analysis of the Norjizak vials by high-performance liquid chromatography or liquid chromatography mass spectroscopy and GC/MS revealed variable combinations of buprenorphine, Diacetylmorphine (heroin), acetyl codeine, pheniramin, dexamethasone, and benzodiazepine. The concentration of dexamethasone in each 2 mL vial was 0.4 to 1 mg/mL.

## *DISCUSSION*

In this case series study, most patients have started with a relatively low dose of Norjizak but, like other opiate addicts, have increased its use progressively to high doses. Due to high doses and long duration of use, the toxic effects of the other materials mixed with the opium have clinically affected the patients. These are the key points of this syndrome and the basis that makes Norjizak syndrome a distinct entity. To our knowledge, there is no report of Cushing's syndrome induced by the use of Norjizak in the current literature.

Receptor down regulation predisposes opiate addicts to progressive dose increments. In such situation, any material combined with the opiate may reach toxic levels. This material may be a chemical drug, a particle, a microorganism, or a plant poison. Because this dose increment is compulsive, the rational underlying this combination may be used by illegal substance producers. Keeping in mind that Norjizak is produced in Afghanistan and, probably its neighbor countries, the danger seem more significant.

Factitious or exogenous Cushing's syndrome is a well-known clinical entity. Glucocorticoid therapy in various forms is extremely common for a wide range of inflammatory, autoimmune, and neoplastic disorders. It is therefore important for the physician to be aware of the possibility of both iatrogenic and factitious Cushing's syndrome. This can be dependent on dose, potency, duration, and route of administration of the glucocorticoids and co-administered medications.[1–4] All forms of glucocorticoids have the potential to cause Cushing's syndrome. Withdrawal from chronic glucocorticoid therapy presents the possibility of adrenal insufficiency and the possibility of steroid withdrawal symptoms.[5] However, whenever facing a cushingoid appearance in addicts, the possibility of using black market drugs with corticosteroids should be kept in mind.

As stated, nearly all patients had evidence of moderate to severe factitious Cushing's syndrome and many patients have presented with its complications. Six patients who were not cushingoid had either short duration or lower dose compared to others. Some clinical manifestations may be different from usual cases of iatrogenic Cushing's syndrome; for example, sever lower extremity edema in most patients is unusual because synthetic glucocorticoids do not have significant mineralocorticoid potency.

Hypogonadism is also an unusual manifestation of Cushing's syndrome. In Norjizak patients, it can be due to high opioid content or a suppressive effect of glucocorticoids on all pituitary axes.

Many patients receiving sustained-action narcotics during therapy for heroin addiction have symptoms of fatigue, depression, diminished libido, and impaired sexual function. Studies on narcotic-induced hypogonadism and sex-hormone levels confirm frequent, sometimes profound, deficiencies in many men and women treated with narcotics.[6–9] Severe obesity may be another mechanism of hypogonadism. Massively obese men often show symptoms of hypogonadism. Increased endogenous opioid inhibition of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator resulting in insufficient stimulation of the pituitary gonadotrophs has been proposed as a possible mechanism.[10–12]

Osteoporosis in the patients may be due to combined effects of both glucocorticoids and opiates. Parameters of mineral consistency of the bone tissue has been shown to decrease both in patients with heroin and buprenorphine addiction.[13] Hypogonadism may also be a contributing factor in osteoporosis. Hypertension was an uncommon and important finding in the patients. Excess glucocorticoids could lead to hypertension and cardiovascular disease. The exact mechanism by which glucocorticoids elevate blood pressure is not completely understood, but it appears to be a complex pathology that involves mineralocorticoid effects, increased responsiveness to vasoconstrictors, and decreased vasodilator production.[14] Glucocorticoids with more mineralocorticoid potency are more probable to cause hypertension. Therefore, hypertension is more prevalent in endogenous Cushing's syndrome. Significant euphoria experienced by the patients may be a consequence of opioid, glucocorticoid,[15,16] and pheniramin[17] components.

High-performance liquid chromatography analysis of vials for detection of synthetic glucocorticoids is the most sensitive test.[18] A liquid chromatography-tandem mass spectrometry has recently been suggested for simultaneous precise and quantitative detection and measuring various synthetic steroids in serum, plasma, urine, and tablets.[19] Unfortunately, we had no access to such valuable utilities but we prove the presence of dexamethasone in the vials and ascertained the diagnosis of exogenous source for their problems by using high-performance liquid chromatography.

This cases series study could draw criticism because this was not a pre-designed team work study; we had no definite and planned protocol for our evaluation. Another limitation was that some of the cases were found and initially managed out of our centers and these reasons led to our inability to document more details of the patients. We did not measured serum or urine concentration of dexmethasone in this report due to resources limitations. Finally, due to poor compliance of the patients and psychiatric and behavioral problems of addicted patients, we were unable to follow many for sufficient period; hence, at the moment, we have no definite conclusion about the time course of the hypothalamic-pituitary-adrenal axis (HPA) returning to normal in this case series.

We are witnessing a special exogenous Cushing syndrome due to the mixing of opiates and dexamethasone for the first time. Norjizak syndrome is the clinical condition of poisoning with a second material, when it is combined with opiates, due to compulsive dose increment and long duration.

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