

**MANIA INDUCED BY STEROID-ADULTERATED HERBAL MEDICINE: A CASE REPORT**LYDIA LAY YEN GAN<sup>1</sup>, LUKE SY-CHERNG WOON<sup>2</sup>, MARIA ULFAAHMAD ZAWAWI<sup>2</sup>, MARHANI MIDIN<sup>2\*</sup><sup>1</sup>Department of Pharmacy, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. <sup>2</sup>Department of Psychiatry, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. Email: marhani@ppukm.ukm.edu.my*Received: 5 March 2018, Revised and Accepted: 06 April 2018***ABSTRACT**

Traditional herbal medicines are generally perceived as natural and safe. Nonetheless, adulteration of such complementary products, including Chinese Proprietary Medicines with undeclared drugs, notably steroids, is a recognized problem. While there are many accounts of Cushing's syndrome due to steroid content in traditional medicines, psychiatric complications caused by the similar insults are not reported throughout the literature. We report a case of acute mania after the short-term use of steroid-adulterated herbal product in a previously healthy young male. It shows that psychiatric complications can occur in such a scenario without the physical and metabolic features of Cushing's syndrome, and pharmacodynamic interaction between the herbal ingredient and adulterant is a possible factor. The case also highlights the need for awareness of culturally influenced health product consumption and its potential effects on clinical conditions, as well as the important role of a robust surveillance system for such products.

**Keywords:** Adulteration, Chinese Proprietary Medicine, Dexamethasone, Herbal medicine, Mania, Steroid

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**INTRODUCTION**

Steroid therapy, widely used to treat inflammatory and autoimmune disorders, is known to cause psychiatric disturbances such as major depression, mania, and psychosis. Mental disorders can occur in up to 60% of patients who take corticosteroids regularly [1]. On the other hand, conventional herbal medicines are believed by many to be natural and void of side effects [2]. The consumption of traditional Chinese's medicine as a form of complementary medicine is, especially, prevalent in Chinese and other East Asian societies [3].

Unfortunately, there are many cases of Chinese herbal medicines, particularly Chinese Proprietary Medicine being adulterated with corticosteroids to enhance their efficacy, leading to serious adverse effects such as iatrogenic Cushing's syndrome [4]. Certain medicinal herbs have also been associated with significant neuropsychiatric unfavorable effects [5]. However, reports of psychiatric adverse events due to traditional herbal products adulterated with steroids are wanting in the literature.

We report a case of acute mania after the short-term use of steroid-adulterated herbal product in a healthy young man. Possible mechanisms involved and clinical implications are discussed.

**CASE REPORT**

A 36-year-old ethnic Chinese gentleman was brought to a Malaysian university hospital by his relatives for markedly changed behavior for the past 2 weeks. In the emergency department, the patient boisterously proclaimed that he was about to get married on that day, inviting everyone present to attend his wedding, of which his relatives were totally unaware. He also announced that he was about to book a plane and travel around the world with his bride.

Further interview with the patient and collaborative history from his relatives revealed florid manic symptoms. For the past 2 weeks, the patient experienced elevated mood with frequent mood swings and irritability. He felt very energetic most of the time and required noticeably little sleep. He believed that he possessed special "mind power" that would allow him to lift Malaysia and other countries out of poverty miraculously. He also became very enthusiastic about a

Chinese Proprietary Medicinal product, which he used for his joint pain, spending more than 5,000 Malaysian ringgit to purchase it. He disclosed an unrealistic plan of buying up the Taiwanese company that produced the medicine and expanding the business in Malaysia, Hong Kong, and China, believing that he would become exceedingly wealthy through this venture. His many symptoms rendered him unable to return to his job and led to heated arguments with his family members.

The patient worked as a butcher and had twice divorced in the past. He did not have prior history of medical or psychiatric illness. Family history of mental disorders was absent. The patient also had no prior illicit substance use. Mental state examination revealed a thin young man with medium height, who was over-friendly and displayed excessive familiarity toward the doctor. He was very jovial; his affect was congruent with his thoughts. He talked in a loud voice at an increased rate. Throughout the interview, the patient was brimming with confidence and expressed grandiose ideas. There was no perceptual disturbance. The patient was fully orientated to time, place, and person.

Physical examination did not show signs of Cushing's syndrome or other endocrine disorders. Vital signs were normal. Baseline investigations, which included full blood count, renal profile, liver function test, and thyroid function test, returned normal results. Urine drug tests were negative. Computed tomography of the brain did not show intracranial hemorrhage or space occupying lesion. The initial provisional diagnosis of bipolar I disorder in manic episode was made. The patient was given a stat dose of tablet olanzapine 5mg and was admitted to psychiatric ward for observation.

As the consumption of traditional medicine featured prominently in the patient's presentation, more detailed relevant history was obtained from his relatives. It was noted that 3 weeks earlier, prompted by severe pain at his right big toe, the patient purchased a Chinese Proprietary Medicinal product called "Niao Suan Wan," purportedly for gouty arthritis, from a local Chinese medicine shop. He took two pills of the product in the morning and one pill at night every day, right up to his hospitalization. Within the 1<sup>st</sup> day, his pain resolved and the patient was very happy with the results. He continued to consume the product and attributed to it additional beneficial effects on blood circulation and urination. About a week later, psychiatric symptoms emerged suddenly.

The herbal product was further scrutinized. The patient's relatives were asked to bring the packaging of the herbal supplement for inspection. The listed herbal ingredients were *Panax ginseng* and *Ginkgo biloba*. On checking with the National Pharmaceutical Regulatory Authorities (NPRA) of Malaysia, it was known that "Niao Suan Wan" had previously been investigated for adverse drug reactions (ADRs). The NPRA database contained a documented report of a patient who developed Cushing's syndrome after consuming the same product within 2 years. An illicit drug analysis discovered that the product was adulterated with dexamethasone.

Based on the available information, the patient was treated as medication-induced bipolar disorder. In the ward, he was prescribed tablet olanzapine 10 mg ON and tablet clonazepam 1mg BID. After 3 days, olanzapine was escalated to 15 mg ON. Due to persistent manic symptoms, it was further titrated up to 20 mg ON after a week. By the day 11 of admission, symptoms had fully resolved and the patient was discharged home. He remained in remission when he was seen in the outpatient clinic 2 weeks after discharge.

## DISCUSSION

The diagnosis of medication-induced bipolar disorder was based on several considerations. The patient presented with acute manic symptoms causing significant clinical impairment, which developed after the consumption of a traditional medicinal product. The identified adulterant in the product as recorded in national database, namely, dexamethasone [1] and one of the active ingredients, *Panax ginseng* [5], is capable of producing manic symptoms. The association between the implicated product and psychiatric unfavorable effect in this patient was also substantiated by a score of 4 on the Naranjo ADR probability scale [6], which is classified as "possible." Furthermore, there was no personal and family history of mood disorders. Finally, the manic symptoms swiftly resolved after the cessation of the offending product and further confirmed the diagnosis of medication-induced bipolar disorder.

The steroid content in the offending product is deemed to be important in triggering the manic episode. A study by Fardet *et al.* showed that the adjusted hazard ratio of individuals taking oral glucocorticoids developing mania comparing to unexposed adult population is 4.35 [7]. 26% of patients developed mania and 10% developed depression during therapy with 80 mg/day of prednisolone for a span of 5 days [8]. Psychiatric adverse effects could also occur in patients receiving lower doses of corticosteroids for variable duration (40 mg/day or less of prednisolone and 10 mg/day or less of dexamethasone) [9,10]. Our patient consumed an herbal preparation adulterated with dexamethasone, but the amount consumed was uncertain as the NPRA did not perform the quantification tests on adulterated herbal products. Nonetheless, the severity of steroid-induced psychiatric disorders is not closely associated with steroid dosage [11]. This contrasts with iatrogenic Cushing's syndrome caused by corticosteroids, which is dependent on dose and duration of treatment [12]. Hence, it is important to remember that steroid-induced mood disturbance can occur before the appearance of any Cushingoid features in an individual and at variable steroid doses.

Manic symptoms can be the result of steroid actions in the brain, which are mediated by two intracellular receptor subtypes, namely, glucocorticoid receptor and mineralocorticoid receptor. Both receptors are widely distributed throughout the brain, with highest levels found in the hypothalamus, pituitary gland, and the hippocampus [13]. One vital neurotransmitter system in the brain, the serotonergic system, which is responsible in mood, cognition, and behavior, is affected by corticosteroids [14-16]. Steroid receptor-mediated modulation of the brain serotonergic system can thus be an important mechanism that causes emotional dysregulation and emergence of manic symptoms [17].

*Panax ginseng* was one of the ingredients in the herbal product consumed by the patient and might have synergistically contributed to the occurrence of mania together with dexamethasone. Ginseng is a popular

"tonic" herb with cumulative strengthening effects when consumed regularly [18] and is widely taken to alleviate stress and fatigue and to improve endurance [19]. Nevertheless, consumption at high doses and/or long duration can lead to side effects such as insomnia, nervousness, diarrhea, and hypertonicity [20]. Most importantly, there are several reports of ginseng-induced mania consumption in patients with [21,22] and without depression [23]. While the precise mechanisms are not known, ginseng can have an effect on the hypothalamic-pituitary-adrenal axis, resulting in changes of corticotropin and corticosteroid levels [19, 24] and thereby potentiating mood instability.

The diagnostic challenge in this case was that the possibility of steroid-induced mania was not immediately apparent, as the presence of steroid use could not be recognized right away. Factors facilitating accurate diagnosis include the clinicians' high index of suspicion owing to the awareness of the problem of adulterated traditional medicines, as well as the availability of established reporting mechanism and database, which allowed rapid retrieval of information on the implicated product. Consequently, the relationship between the patient's use of traditional medicine and manic presentation could be correctly understood and appropriately managed.

A few points can be derived from this case. Information on the intake of any medicinal product including traditional medicines and health supplements is essential in history taking, especially when such practice is part of local cultural norms. It should be noted that adulteration of herbal medicines can also occur in many other countries with vastly different cultural backgrounds, such as India [25] and Brazil [26]. High level of vigilance and close cooperation between clinicians and pharmacists is also crucial. Programs need to be in place for patient education and counseling on the use of such products to alert patients on potential adverse effects. Moreover, proper regulatory mechanisms, at the national or even international level, are required for traditional herbal products [27]. These would include registration of all products with authorities, regulation of relevant parties, such as importers or manufacturers of herbal products, and clinical practitioners, to ensure safe use of such products. Finally, reporting of ADRs due to traditional herbal medicines should be further strengthened to expand the existing databases.

## CONCLUSION

Steroid-adulterated herbal products can be a cause of acute severe affective disorder and require more clinical attention, especially in social contexts where traditional medicine is popular. Current data on adulterated herbal products are still largely anecdotal, and hence, more large-scale surveillance studies on traditional herbal supplements and their psychiatric implications would be necessary.

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## AUTHOR'S CONTRIBUTIONS

Lydia Lay Yen Gan is the main author which conceptualized and wrote the manuscript. Luke Sy-Cherng Woon contributed significantly in organizing the manuscript and providing ideas for discussion. Maria Ulfa Ahmad Zawawi assisted in the provision of clinical data of the case. Marhani Midin supervised the writing project and reviewed the manuscript.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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