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An Association of Ephedra* Use with Psychosis and Autonomic Hyperactivity

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Ephedra extract is used in a number of dietary supplements taken for a variety of purposes including weight loss. Although recent events have led to calls for Ephedra to be removed from the market and the FDA has had over 18,000 adverse event reports, newspaper reports cite only a few instances of clearly associated adverse events associated with Ephedra use. In this communication, we review the literature and present a case report of Ephedra use associated with the onset of psychosis and autonomic hyperactivity after administration of risperidone. We conclude that the behavioral effects of Ephedra are a public health concern.

Keywords Ephedra; Ephedrine; Serotonin syndrome; Risperidone.

INTRODUCTION

Ephedra (Ephedraceae) is the common name for a family of plants whose extract, mainly ephredrine alkaloids, is used in dietary supplements that promote increased energy and weight loss (1). Over the past several years, a number of events including the death of Baltimore Oriole's pitcher Steve Belcher have led to calls for the removal of products containing Ephedra extracts from over-the-counter preparations. Unfortunately, although the FDA reports over 18,000 adverse event reports, media reviews of these events have cited a dearth of clearly documented connections between Ephedra use and adverse outcomes (2–4). This lack of documentation has lead critics of potential FDA intervention to question whether regulation of Ephedra containing products is warranted.

One area of healthcare in which critics allege relatively few events have been reported is behavioral medicine. In a well publicized comprehensive review of ephedra use in weight loss and athletic performance, Shekelle and colleagues found only 7 sufficiently documented reports of adverse psychiatric events associated with ephedra use (2). This may be an understatement of the true impact as a search of MedLine using the keywords "psychosis" and "ephedra or ephedrine" generated 49 articles. However, it should be noted that many of these 49 studies did not consider the role of concomitant medications or possible surreptitious substance use. In this report we briefly review these articles and further report a case of ephedra use being associated with psychosis and serotonin syndrome.

CASE REPORT

T.N. is a 19 year old female admitted to the University of Iowa for psychosis. Approximately 6 months prior to admission, the subject began taking large, yet unspecified amounts of Metabolife™ and Hydroxycut™ in an attempt to lose weight. Two months prior to admission she began

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military boot camp and discontinued use of Metabolife. Almost immediately, she reported the rapid onset of a 5 day syndrome of sleeplessness and paranoia. She was transferred to a medical unit, treated with olanzapine and did well. Next, she was transferred to a holding company for 10 days where she discontinued olanzapine and was discharged. After discharge and ten days prior to admission, she resumed heavy use of Metabolife and moved home. Over these 10 days, she became increasingly suspicious and guarded. Finally, on the day of admission, she failed to attend an important personal event secondary to a belief that the military had constructed a roadblock to prevent her attendance at the event. She was then admitted to the University of Iowa.

Her prior psychiatric history was remarkable for alcohol abuse. She denied other substance use, affective or psychotic disorders. The patient and parents deny substance use, psychotic or affective disorders in first degree relatives of the patient. However, there was a question of schizophrenia in a great aunt.

Her entry physical exam and laboratory exams, including a urine drug screen, were unremarkable. Initial mental status exam was notable for the presence of paranoia, thought blocking and tangentiality. She was initiated on risperidone 1 mg qhs gradually increasing to 2 mg qhs on day 3, and bupropion 100 mg qd. The symptoms of psychosis rapidly abated and the patient did well. On the night of hospital day 5, the patient did not sleep and developed hyper-religiousness and marked anxiety. In response the riperidone was increased to 3 mg qhs and the patient received a total of 2 mg of lorezapam. On the morning of day 6, the patient's temperature, blood pressure and pulse were noted to be elevated with two separate assessments over a period of an hour resulting in values of T 37.5° C 148/80 p 160 and T 37.7° C 150/82 p 144 (admission vitals 106/78 p 80). An exam of the patient showed that she was paranoid, slightly diaphoretic, unable to give the correct date and grossly disorganized with the patient unable to bathe herself. A tentative diagnosis of Neuroleptic Malignant Syndrome (NMS) was entertained and consultation was sought. A full medical and neurological exam was normal with the exception of mild hyper-reflexia and continued elevated autonomic functions. A full laboratory exam including serum creatinine kinase and white blood cell count were also unremarkable. Nevertheless, the buproprion and risperidone were discontinued; a supportive care plan was initiated with the only medications being given were acetaminophen and lorezapam as needed. Her autonomic signs remained elevated on days 6 and 7, with her pulse, blood pressure and temperature gradually returning to baseline by day 10. Behaviorally, between days 6 and 9, she was guarded, delusional, and hyper-religious. However, she slept well and was lethargic, with slow, occassionally latent speech and was neither impulsive nor hypersexual. On day 9, secondary to continued marked anxiety and paranoia, she was initiated on clonezapam 1 mg BID and a diagnosis of Serotonergic Syndrome was entertained. The anxiety and paranoia improved over the next 3 days with the thought disorder symptoms being the last to clear. On day 12, she was sent on pass with her parents and was noted to be near baseline. On day 13, she was discharged to home on clonezapam 1 mg BID. She and her parents were repeatedly cautioned to avoid compounds containing ephedra.

After discharge, the subject was tapered off the clonezapam and did well. She entered college and after 6 months, recurrent anxiety or psychosis have not been noted.

DISCUSSION

In summary, we present a case of psychosis associated with the heavy use of an ephedra containing dietary supplement exacerbated by mild delirium and autonomic hyperactivity associated with the administration of risperidone and buproprion.

The association of ephedra with the onset of psychosis is not surprising. The main psychoactive Ephedra alkaloid, ephedrine, is well-described α and β adrenergic agonist (5) with over 40 publications on MedLine alleging a connection between it and psychosis. Stimulant abuse is thought to act synergistically with underlying biological diatheses to increase the likelihood of the expression of psychosis (6). Interestingly in this light, a prior publication has also linked Metabolife use to the onset of psychosis followed by a full blown syndrome of schizophrenia (7). As of yet in the present case, we have not noted this progression. Still, the patient is very young and the suggestion of schizophrenia in a distant relative indicates that the subject may be at minimally elevated genetic risk.

The timing of her acute exacerbations is interesting. Though our patient was clearly psychotic while using the extract, acute worsening of her condition occurred twice after cessation of the product. The first exacerbation occurred upon entering boot camp while the second occurred after initiating bupropion and risperidone. Acute aggravation of psychosis following induction into boot camp is a commonly observed reaction to the stress of military life (8). Hence, the timing of the first episode of acute psychosis is understandable. However, the timing of the second and the association of autonomic hyperactivity is puzzling. A possible explanation for the exacerbation of psychosis and the addition of mild delirium and autonomic hyperactivity is Serotonin Syndrome (9). Serotonin Syndrome is a cluster of symptoms that include mental status changes, autonomic instability, gastrointestinal distress, and increased motor tone. It is distinguished from the more well known Neuroleptic Malignant Syndrome by milder hyperthermia and less rigidity, but with greater amounts of hyper-reflexia and myoclonus (10). The current case meets the updated diagnostic criteria for Serotonergic Syndrome

suggested by Radomski and colleagues (11). However, the lack of many other features of Serotonin Syndrome such as rigidity, myoclonus and tremor are troubling.

The pharmocological interaction through which this Serotonin-like Syndrome may have occurred is also not certain. Risperidone has been implicated in several cases of possible Serotonin Syndrome (12–14). However, these cases have always been in association with another drug such as a Selective Serotonin Reuptake Inhibitor (SSRI) and this patient was only on low dose bupropion, which has only weak serotonergic properties. One intriguing possibility through which increased serotonergic activity may have occurred is through the use of ephedra. Ephedra extracts contain a variety of sympathomimetic alkaloids whose prototypal compound, ephedrine, itself is a reversible Monoamine Oxidase A inhibitor (15) with an elimination half life of approximately 6 hours. However, variable clearance of ephedrine has been noted (15) and it is possible that lingering activity of ephedrine alkaloid or surreptitious use of extracts on the ward by the patient could have potentiated the effects of the risperidone. Alternatively, an interaction with bupropion is possible and increases in serotonergic neuronal firing does occur in response to bupropion administration (16). However, an association of bupropion and Serotonin Syndrome has not been reported.

In summary, we report another case of psychosis associated with ephedra use and the occurrence of a syndrome of autonomic instability and mental status changes associated with risperidone treatment of the psychotic syndrome. We note prior associations of ephedra with psychosis and suggest that the use of ephedra in dietary supplements may need increased scrutiny and that systematic studies of the role of ephedra in psychosis are warranted.

REFERENCES

1. Walton, R and Manos, GH: Psychosis related to ephedra-containing herbal supplement use. *South Med J* 2003; 96(7):718–20.
2. Shekelle, PG, Hardy, ML, Morton, SC, Maglione, M, Mojica, WA, Suttorp, MJ, Rhodes, SL, Jungvig, L and Gagne, J: Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: A meta-analysis. *Jama* 2003; 289(12):1537–45.
3. Knight, J: Safety concerns prompt US ban on dietary supplement. *Nature* 2004; 427(6970):90.
4. Nelson, R: FDA issues alert on ephedra supplements in the USA. *Lancet* 2004; 363(9403):135.
5. Weiner BT: Norepinephrine, epinephrine, and the sympathomimetic amines. In: Gilman AG, Goodman LS, Gilman A, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: MacMillan; 1980: 138–175.
6. Yui, K, Goto, K, Ikemoto, S, Ishiguro, T, Angrist, B, Duncan, GE, Sheitman, BB, Lieberman, JA, Bracha, SH and Ali, SF: Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: The role of sensitization. *Mol Psychiatry* 1999; 4(6): 512–23.
7. Verduin, ML and Labbate, LA: Psychosis and delirium following metabolife use. *Psychopharmacol Bull* 2002; 36(3):42–5.
8. Tan, H-Y and Ang, Y-G: First-episode psychosis in the military: A comparative study of prodromal symptoms. *Aust N Z J Psychiatry* 2001; 35(4):512–519.
9. Sternbach, H: The serotonin syndrome. *Am J Psychiatry* 1991; 148(6):705–13.
10. Carbone, JR: The neuroleptic malignant and serotonin syndromes. *Emerg Med Clin North Am* 2000; 18(2): 317–25.
11. Radomski, JW, Dursun, SM, Reveley, MA and Kutcher, SP: An exploratory approach to the serotonin syndrome: An update of clinical phenomenology and revised diagnostic criteria. *Med Hypotheses* 2000; 55(3):218–24.
12. Hamilton, S and Malone, K: Serotonin syndrome during treatment with paroxetine and risperidone. *J Clin Psychopharmacol* 2000; 20(1):103–5.
13. Reeves, RR, Mack, JE and Beddingfield, JJ: Neurotoxic syndrome associated with risperidone and fluvoxamine. *Ann Pharmacother* 2002; 36(3):440–3.
14. Karki, SD and Masood, GR: Combination risperidone and SSRI-induced serotonin syndrome. *Ann Pharmacother* 2003; 37(3):388–91.
15. Ulus, IH, Maher, TJ and Wurtman, RJ: Characterization of phentermine and related compounds as monoamine oxidase (MAO) inhibitors. *Biochem Pharmacol* 2000; 59(12):1611–21.
16. Dong, J and Blier, P: Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment. *Psychopharmacology (Berl)* 2001; 155(1): 52–7.