

## Regular Article

# Clinical importance of caffeine dependence and abuse

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### Abstract

Caffeine is the most widely consumed psychoactive substance and is a legal stimulant that is readily available to children. Caffeine has occasionally been considered a drug of abuse and the potential for dependence on caffeine has been debated. Presently, due to a paucity of clinical evidence on caffeine dependence or abuse, no such diagnosis is included in the Diagnostic and Statistical Manual of Mental Disorder—fourth edition. The authors present two cases of abuse or dependence on the caffeine contained in ‘eutrophic’ (energy/nutritional) beverages or caffeine preparations, followed by a review of clinical studies demonstrating evidence that some people can manifest a clinical syndrome of caffeine dependence or abuse. The cases suggest that caffeine can produce a clinical dependence syndrome similar to those produced by other psychoactive substances and has a potential for abuse. In a recent study using a structured interview and the Diagnostic and Statistical Manual of Mental Disorder—fourth edition criteria for substance dependence and abuse, a subset of the general population was found to demonstrate caffeine dependence or caffeine abuse. Therefore, the authors propose that companies or businesses manufacturing or marketing caffeine or products containing caffeine must meet the following guidelines: (i) clearly indicate the caffeine content of products containing comparatively higher quantities of caffeine; (ii) warn that such products should be avoided by infants and children wherever possible, and inform adult consumers about the precise quantity of caffeine that is considered safe for consumption; and (iii) clearly state that consuming large quantities of caffeine and the long-term use of caffeine carry health risks.

### Key words

abuse, caffeine consumption, dependence, health risks.

## INTRODUCTION

Caffeine is present in a number of dietary sources and drugs, including coffee, tea, candy bars, soft drinks, and over-the-counter cold remedies and analgesics. Caffeine is the most commonly used psychoactive drug in the world,<sup>1</sup> consumed daily by approximately 80% of the world’s population.<sup>2</sup> The amount of caffeine contained in foods and beverages varies widely. However, as a standard, a typical cup of brewed coffee contains approximately 100 mg of caffeine and a cup of green tea contains 20–30 mg of caffeine.<sup>3</sup> Caffeine consumption from all sources reaches 210–238 mg/person per day in the USA and Canada and more than 400 mg/person per day in Sweden and Finland.<sup>4,5</sup>

Whether individuals can abuse or become dependent on caffeine remains a contentious issue.<sup>6–9</sup> However, due to a paucity of clinical evidence on caffeine dependence and abuse,<sup>6</sup> the Diagnostic and Statistical Manual of Mental Disorders—fourth edition (DSM-IV) of the American Psychiatric Association does not currently include criteria for caffeine dependence or abuse.

Herein, the authors present two cases of caffeine dependence or abuse, followed by a brief review of clinical studies demonstrating evidence that some people can manifest a clinical syndrome of caffeine dependence or abuse similar to the dependence on or abuse of other psychoactive drugs.

## CASE REPORTS

### Case 1

The patient was a man aged 59 years at his first medical consultation. The primary complaints included feelings

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Received 9 August 2006; revised 22 January 2007; accepted 4 February 2007.

of euphoria, talkativeness and hyperactivity, feelings of versatility, anxiety, and sleep disturbance. He had no family history of inherited psychological problems. He had no history of alcohol, coffee, or tobacco consumption. He habitually drank 10 cups of Japanese green tea daily (caffeine content of 200–300 mg/day<sup>3</sup>).

Since the age of 30, the patient had recurrent fatigue for which he started drinking one bottled energy drink per day. At the age of 41 he changed jobs, however, he was unable to adjust to the job and his fatigue worsened. The following year, in order to 'divert his mind from his fatigue', he increased his intake of the energy drink to two bottles per day. From the age of 54 he began carrying energy drinks to work and increased his daily intake of the drink to three bottles per day, which increased to four or five bottles per day at age 58.

In August of the next year at age 59, he received a job promotion, with a resulting increase in overtime hours. He attempted to become comfortable with his new tasks, and continued to work even after returning home late at night. From this period in his life, his daytime fatigue began to worsen, and the intake of the energy drink increased to seven or eight bottles per day. In September of the same year, he became talkative, pompous, and began to have frequent interpersonal problems with his wife as well as with colleagues at work. In addition to these symptoms, in October, he became impulsively extravagant, and showed certain dissociative behaviors, such as removing the rose buds from his neighbor's rose bush. At the end of October, his embarrassed family brought him to the outpatient psychiatry department. During his consultation, he was restless, repeatedly sat down and stood up, and talked euphorically incessantly about random topics. In contrast, he admitted feelings of anxiety and insecurity.

Based on his history and current symptoms, the authors strongly suspected he had a secondary mania resulting from caffeine intoxication due to chronic consumption of an energy drink. Therefore, considering his recurrent interpersonal problems at work, his impulsively extravagant and dissociative behavior, hospital admission and treatment was recommended, as well as a gradual withdrawal from the energy drink. However, because he strongly refused hospital admission and therapy, the authors agreed on the following condition for outpatient treatment: the energy drink should be gradually discontinued and not more than one bottle should be consumed in a 3-day period. To confirm his progress, the patient was asked to consult with the outpatient department every 3 days. In addition, a small dose of haloperidol and lithium carbonate was given during the gradual withdrawal period. After 5 days of decreased intake of the energy drink, the above-

mentioned conditions improved. After 3 weeks, the symptoms completely disappeared.

No significant abnormality was noted in computed tomography or magnetic resonance imaging examination of the head. No mixing of wave signals or epileptiform patterns were observed on electroencephalography.

Although it has been 10 years since his first hospital visit, the patient has had no recurrence of a manic state and no intake of the energy drink.

## Case 2

This patient was a 40-year-old housewife with no family history of inherited psychological problems and no history of alcohol or tobacco consumption. She habitually drank five cups of instant coffee per day (caffeine quantity, 305–360 mg/day<sup>3</sup>) and about three cups of green tea per day (caffeine quantity, 60–90 mg/day<sup>3</sup>). Because her father, who lived in a neighboring prefecture, was hospitalized due to heart disease, she had been taking care of him since 6 weeks before her first medical consultation. Three times per week, she drove her own car to see her father. She began taking a caffeine preparation (12 tablets per box, containing a total of 500 mg of caffeine) while driving, in order to prevent sleepiness. Symptoms of tachycardia, tremors, cold sweats, and feelings that her cheeks were hot and blood was rushing to her head, began to appear approximately 5 weeks before her initial consultation. However, after taking the caffeine preparation, 'her head cleared, her body condition became comfortable, and her powers of concentration increased' temporarily. As a result, she started to take the preparation regularly, at times other than when she was driving.

Since approximately 3 weeks before her initial consultation, she had been taking 24 tablets per day (caffeine quantity, 1000 mg). At that time, in addition to the previously mentioned symptoms, symptoms of strong anxiety, absence of calmness, a feeling of agitation, and sleep disturbance appeared. Therefore, she tried many times to stop taking the caffeine preparation, however, each time she stopped, she experienced a strong headache and her feelings of anxiety noticeably worsened, resulting in each attempt ending unsuccessfully. At 1 week before the initial consultation her feelings of anxiety became stronger and she could not perform household chores, therefore, she visited the outpatient department for medical consultation. Cardiographic examination showed only tachycardia, and no significant findings were observed in a hemobiochemical examination, a cephalic computed tomography, and on an electroencephalogram.

Based on her history and current symptoms, the authors strongly suspected she had caffeine intoxication due to high consumption of a caffeine preparation. Therefore, the authors agreed on the following conditions for outpatient treatment: the caffeine preparation should be gradually discontinued and not more than two tablets should be consumed in a 3-day period. To confirm her progress, the patient was asked to consult with the outpatient department every 3 days. In addition, 1 mg of lorazepam was given for 2 weeks. After 2 weeks, the symptoms completely disappeared.

Although it has been 7 years since her first hospital visit, the patient has had no recurrence of caffeine intoxication and no consumption of the caffeine preparation.

### Diagnosis of cases

The Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM-IV)<sup>10</sup> diagnosis of substance dependence requires the fulfillment of three of the following seven criteria: (1) tolerance; (2) withdrawal; (3) intake of a substance in larger amounts or over a longer period of time than intended; (4) persistent desire or unsuccessful efforts to reduce intake or control use; (5) a great deal of time spent on the activities necessary for obtaining, using, or recovering from the effects of the substance; (6) important social, occupational, or recreational activities are stopped or reduced because of substance use; and (7) use is continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Furthermore, the DSM-IV diagnosis of substance abuse requires the fulfillment of one or more of the following four criteria: (i) recurrent use resulting in failure to fulfill obligations; (ii) recurrent use in situations that are hazardous; (iii) recurrent legal problems from use; and (iv) continued use despite persistent social or interpersonal problems from use.

The International Classification of Disorders (ICD-10) of the World Health Organization (WHO)<sup>11</sup> uses generic criteria similar to the DSM-IV for identifying dependence and abuse (the latter termed 'harmful use').

As previously mentioned, there is currently no category in the DSM-IV for substance use disorders (dependence and abuse) involving caffeine.

As for the energy drink which Case 1 consumed, it is advertised frequently in the mass media mainly on television by a production manufacturer as 'effective in nutritional fortification and relieving fatigue.' According to his statement, he first compared several kinds of energy drink. For the following reasons, he came to

take an energy drink of a specific brand in large quantities since the age of 41: (i) the price was low (the energy drink he selected costs approximately US\$1 dollar per bottle. There were also some deluxe energy drinks that cost more than 10 dollars per bottle); (ii) rather than buying different kinds of energy drinks, or buying individual units of the same energy drink, it was more economical to buy in bulk at the drugstore; and (iii) its effect was advertised frequently in the mass media. This energy drink is very popular in Japan, and there are energy drinks with similar ingredients abroad.<sup>12,13</sup>

As for the diagnosis, substance abuse of DSM-IV, when the diagnostic standard of substance dependence was satisfied even at one time in the past, the diagnostic name of substance dependence takes precedence.<sup>10</sup> The intake quantity of the energy drink of Case 1 per day rose from three to four–five, and from seven increasing finally to eight. Then a rise in tolerance could be recognized.

The authors investigated his medical history in detail at his first medical consultation, including whether he had tried to reduce his drink intake till then, or whether there were symptoms of caffeine withdrawal. The result did not show such. His symptoms satisfied (1) and (3) of diagnostic criteria of substance dependence of DSM-IV at the same time. Three or more items of the diagnostic criteria were not satisfied.

However, due to the repeated intake of energy drinks, Case 1 could not carry out his roles and obligations at home and in his workplace. Furthermore, as a result of his manic condition, which was considered to have been caused by the intake of large quantities of the energy drink, he had trouble with interpersonal relationships. Even though his wife suggested numerous times that he stop consuming the drink, he could not stop using it. These conditions meet categories (i) and (iv) of the DSM-IV diagnostic criteria for substance abuse. Therefore, based on these symptoms, the authors can diagnose Case 1 with 'caffeine abuse'.

Case 2 commuted along a highway alone several hundred kilometers by privately owned car to nurse her father. As traveling on the highway was monotonous and caused sleepiness, she had always taken rest at a service area on the way. On those occasions she saw caffeine preparations sold to keep long-distance drivers awake. She started to buy the same preparation after she used it once because the effect was immediate. The experience told her that caffeine could not only raise her concentration but also keep her awake. In addition, when she bought a caffeine preparation, she selected those whose caffeine content was as high as possible even in similar commodities. Because of that, she ended up always buying the same commodity.

In Case 2, the maximum quantity of daily caffeine intake reached 1365–1450 mg/day (1000 mg from a caffeine preparation, and 365–450 mg from coffee and green tea). Her symptoms of tachycardia, palpitation, feeling of heat in the cheeks and of rushing of blood to the head, sleep disorder, absence of calmness, strong feelings of anxiety and fretfulness, satisfy the DSM-IV diagnostic criteria for caffeine intoxication. The obvious worsening of her feelings of anxiety and the appearance of a strong headache after she stopped ingesting the caffeine preparation also satisfies the DSM-IV diagnostic criteria regarding caffeine withdrawal. As her symptoms also meet categories (1), (2) and (4) of the seven DSM-IV diagnostic criteria for substance dependence, the authors can diagnose Case 2 with caffeine dependence.

## DISCUSSION

Recently, there has been increasing interest in determining the extent to which the generic DSM-IV criteria for drug dependence syndrome can be meaningfully applied to caffeine.<sup>6</sup> In four recent studies using structured interviews and the DSM diagnostic criteria for substance dependence and abuse, a subset of the general adult population was found to demonstrate a dependence on caffeine or caffeine abuse.

The first study was a random telephone survey conducted by Hughes *et al.*<sup>14</sup> The investigators applied the generic DSM-III-revised criteria for substance dependence to 166 current caffeine users, and found that 27% had mild caffeine dependence (three–four criteria), 14% had moderate dependence (five–six criteria), and 3% had severe dependence (seven–nine criteria). The second study was a diagnostic evaluation of people who reported problems with their caffeine use.<sup>15</sup> After telephone screening was performed on 99 subjects, Strain *et al.* found 16 individuals that fulfilled four out of the seven criteria cited above, and were therefore considered to be dependent on caffeine. These individuals met the DSM-IV criteria (1), (2), (4) and (7). Criteria (3), (5) and (6) were excluded because they do not apply to substances widely available and culturally accepted. Seven of the subjects fulfilled criterion (7) and reported a history of physical conditions such as pregnancy, palpitations, and gastrointestinal problems that had led physicians to recommend that they reduce or eliminate caffeine consumption; all seven had failed to comply with the physicians' recommendations. The study by Strain *et al.* described in detail 16 cases and provides clearly documented evidence of clinically significant drug abuse behaviors. For example, one subject regularly was unable to go to work and abandoned childcare responsibilities whenever she was in caffeine

withdrawal. A third study, performed by Hughes *et al.*,<sup>16</sup> applied the generic DSM-IV criteria for substance dependence to 162 randomly selected caffeine users via a structured telephone interview, these individuals' caffeine use in the last year was evaluated. A total of 30% of current users endorsed three or more of the seven criteria for dependence. DSM-IV criteria for substance abuse and the prevalence of endorsement in current users were: recurrent use resulting in failure to fulfill obligations (15%), recurrent use in situations that are hazardous (1%), recurrent legal problems from use and continued use despite persistent social or interpersonal problems from use (2%). A total of 3% endorsed one or more of these symptoms and did not meet criteria for dependence and, therefore, would have met DSM-IV criteria for abuse. The most recent study conducted by Svikis *et al.* showed that more than half (57%) of a group of employed and highly educated caffeine-using pregnant woman fulfilled the DSM-IV criteria for lifetime substance dependence applied to caffeine, with 45% of the group reporting that they had persistent desire or unsuccessful efforts to cut down or control caffeine use, and 43% reporting continued use despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.<sup>17</sup>

Caffeine is a legal stimulant that is readily available to children. Consumption of caffeine by children and adolescents is increasing, and while the effects of caffeine on adults have been studied, little is known about its effects on children and adolescents.<sup>18</sup> In the study conducted by Bernstein *et al.*, 21% of the 19 adolescents who participated in a structured interview about their caffeine use, endorsed three or more of the criteria, therefore, meeting the requirements for a diagnosis of caffeine dependence.<sup>19</sup> In another study conducted by the same investigators, 22% of the adolescent sample of daily caffeine users met criteria for caffeine dependence based on meeting at least three of the four DSM-IV substance dependence criteria used in the study by Strain *et al.*<sup>15,18</sup>

While there were several limitations to these adult and adolescent studies (e.g. telephone survey protocol, small sample size, population of self-identified problematic caffeine users), these results and the current cases suggest that caffeine can produce a clinical dependence syndrome similar to those produced by other psychoactive substances and has a potential for abuse. Therefore, substance abuse syndrome may be more common than is generally recognized.

Certainly, there is an important distinction to be made between legal, socially domesticated drugs (such as caffeine and nicotine) and illegal drugs (such as cocaine and heroin). The authors find particular

similarities between nicotine and caffeine. The problem of caffeine dependence has been compared with that of nicotine and has been widely discussed.<sup>6,15</sup> Caffeine and nicotine are both substances that can be purchased legally and their consumption is socially acceptable in many countries and is less toxic when taken in standard quantities. Nonetheless, the health effects associated with the long-term use of nicotine, as well as the issue of dependence, are known by many people including consumers. Smoking is well established as a recognized cause of cancer, lung disease, coronary heart disease, and stroke; it is considered the single most important avoidable cause of premature morbidity and mortality in the world. Additionally, nicotine dependence causes more death and disability than all the other drug disorders combined.<sup>20</sup>

However, the fact that this is not the case for caffeine poses a problem. In other words, it is widely known that 'tobacco is hazardous to health' and smokers are fully aware of this health risk. Also, smokers wishing to quit can do so through specific treatment programs and many therapeutic drugs are available. Moreover, in many countries, it is against the law for children and adolescents to smoke. Although it is widely known that consuming small doses of caffeine 'increases alertness and makes one less drowsy', knowledge about caffeine dependence or the risks associated with consumption of sudden large doses or the occurrence of withdrawal symptoms is primarily limited to researchers. In short, when compared to tobacco or alcohol, very little information is available regarding caffeine use. Therefore, because consumers receive insufficient information on caffeine, there is a tendency (especially among children and teenagers) to consume large quantities,<sup>18,19</sup> or indulge in long-term consumption of caffeine since they are unaware of the actual caffeine content in foods and beverages they consume. Moreover, only a limited proportion of people are aware of the health hazards associated with caffeine.

It is widely accepted that the main mechanism of action of caffeine in the central nervous system is antagonism at the level of adenosine receptors. In addition, important secondary effects also occur on many classes of neurotransmitters, including dopamine.<sup>21</sup> Therefore, caffeine may produce its behavioral effects by removing the negative modulatory effects of adenosine from dopamine receptors and stimulating dopaminergic activity.<sup>22</sup> Due to its widespread use and low abuse potential, caffeine has been considered an atypical drug of abuse.<sup>23</sup> According to the results of recent review studies that were performed to focus on the effects of caffeine mediated by adenosine receptors and on the influence that pre-exposure to caffeine may exert on the effects of classical drugs of abuse.<sup>24</sup>

As mentioned above, while some investigators state that although it can be argued that caffeine fulfills regulatory criteria as a dependence-producing drug, it has a low dependence potential and the extensive use of caffeine-containing beverages poses little apparent risk to the consumer or society, the current cases suggest that caffeine can produce a clinical dependence syndrome similar to those produced by other psychoactive substances and has a potential for abuse.

## CONCLUSIONS

While not including caffeine dependence or abuse as a diagnosis in the DSM-IV because of insufficient clinical evidence of caffeine dependence and abuse<sup>6</sup> is medically correct, this approach may be disappointing for primary care physicians and psychiatrists because it may deprive consumers of the awareness of the issues associated with caffeine use, particularly for individuals who consume large quantities. It is valuable for psychiatrists and primary care physicians to recognize caffeine dependence or abuse as a clinical syndrome, since some people are distressed by their caffeine use and feel they can not control or stop their problematic use. Broderick and Benjamin recommend the following prevention model of caffeine-induced psychiatric disorders. The first step is recognition of patients with caffeine-induced symptoms. Enquiries about caffeine consumption should be routine for all patients, especially those with psychiatric complaints. The second step is patient education. This includes discussion about the possible sources of caffeine as well as how caffeine might contribute to several symptoms, including withdrawal.<sup>25</sup>

Therefore, the authors propose that companies or businesses manufacturing or marketing caffeine or products containing high quantities of caffeine (e.g. coffee, caffeinated-soda drinks, over-the-counter analgesics and cold remedies, caffeinated-tablets, energy drinks) must meet the following guidelines: (i) clearly indicate the caffeine content of products containing comparatively higher quantities of caffeine; (ii) warn that such products should be avoided by infants and children wherever possible, and inform adult consumers about the precise quantity of caffeine that is considered safe for consumption; and (iii) clearly state that consuming large quantities of caffeine and the long-term use of caffeine carry health risks.

## REFERENCES

1. Barone JJ, Roberts HR. Human consumption of caffeine. In: Dews PB (ed.). *Caffeine: Perspectives from Recent Research*. Springer-Verlag, New York, 1984; 59–73.

2. James JE. *Understanding Caffeine: a Biobehavioral Analysis*. Sage Publications, Thousand Oaks, CA, 1997.
3. Paluska SA. Caffeine and exercise. *Curr. Sports Med. Rep.* 2003; **4**: 213–219.
4. Barone JJ, Roberts HR. Caffeine consumption. *Food Chem. Toxicol.* 1996; **34**: 119–129.
5. Debry G. *Coffee and Health*. John Libbey, Paris, 1994.
6. Hughes JR, Oliveto AH, Helzer JE *et al.* Should caffeine abuse, dependence, or withdrawal be added to DSM-IV and ICD-10? *Am. J. Psychiatry* 1992; **149**: 33–40.
7. Heishman SJ, Henningfield JE. Is caffeine a drug of dependence? Criteria and comparisons. *Pharmacopsychologia* 1994; **7**: 127–135.
8. Griffiths RR, Munford GK. Caffeine – a drug of abuse? **In**: Bloom FE, Kupfer DJ (eds). *Psychopharmacology: the Fourth Generation of Progress*. Raven Press, New York, 1995; 1699–1713.
9. Nehlig A. Are we dependent upon coffee and caffeine? A review on human and animal data. *Neurosci. Biobehav. Rev.* 1999; **23**: 563–576.
10. *The American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington, DC, 1994.
11. *World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders*. World Health Organization, Geneva, 1992.
12. Reyner LA, Horne JA. Efficacy of a ‘functional energy drink’ in counteracting driver sleepiness. *Physiol. Behav.* 2002; **75**: 331–335.
13. Seidl R, Peyrl A, Nicham R, Hauser E. A taurine and caffeine-containing drink stimulates cognitive performance and well-being. *Amino Acids* 2000; **19**: 635–642.
14. Hughes JR, Oliveto AH, Helzer JE, Bickel WK, Higgins ST. Indications of caffeine dependence in a population-based sample. **In**: Harris L (ed.). *NIDA Research Monograph Series*. US Department of Health and Human Services, National Institute on Drug Abuse, Bethesda, 1993; 194.
15. Strain EC, Mumford GK, Silverman K, Griffiths RR. Caffeine dependence syndrome: Evidence from case histories and experimental evaluation. *JAMA* 1994; **272**: 1043–1048.
16. Hughes JR, Oliveto AH, Liguori A, Carpenter J, Howard T. Endorsement of DSM-IV dependence criteria among caffeine users. *Drug Alcohol Depend.* 1998; **52**: 99–107.
17. Svikis DS, Berger N, Haug NA, Griffiths RR. Caffeine dependence in combination with a family history of alcoholism as a predictor of continued use of caffeine during pregnancy. *Am. J. Psychiatry* 2005; **162**: 2344–2351.
18. Bernstein GA, Carroll ME, Thuras RD, Cosgrove KP, Roth ME. Caffeine dependence in teenagers. *Drug Alcohol Depend.* 1998; **52**: 99–107.
19. Bernstein GA, Carroll ME, Dean NW, Crosby RD, Perwien AR, Benowitz NL. Caffeine withdrawal in normal school-age children. *J. Am. Acad. Child. Adolesc. Psychiatry* 1998; **33**: 856–865.
20. Scmitz N, Kruse J, Kugler J. Disabilities, quality of life, and mental disorders associate with smoking and nicotine dependence. *Am. J. Psychiatry* 2003; **160**: 1670–1676.
21. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Action of caffeine in the Brain with special reference to factors that contribute to its widespread use. *Pharmacol. Rev.* 1999; **51**: 83–133.
22. Garrett BE, Griffiths RR. The role of dopamine in the behavioral effects of caffeine in animals and humans. *Pharmacol. Biochem. Behav.* 1997; **57**: 533–541.
23. Nehlig A. Are we dependent upon coffee and caffeine? A review on human and animal data. *Neurosci. Biobehav. Rev.* 1999; **23**: 563–576.
24. Cauli O, Morelli M. Caffeine and the dopaminergic system. *Behav. Pharmacol.* 2005; **16**: 63–77.
25. Broderick P, Benjamin AB. Caffeine and psychiatric symptoms: A review. *J. Okla. State Med. Assoc.* 2004; **97**: 538–542.

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