

Mania induced by high content caffeinated energy drinks

Lizardo Cruzado¹
Miguel Sánchez-Fernández²
Carla Cortez-Vergara³
Galia Rojas-Rojas²

¹Médico Psiquiatra. Universidad Peruana Cayetano Heredia
Instituto Nacional de Salud Mental "Honorio Delgado-Hideyo Noguchi"
Lima, Perú

²Médico residente de Psiquiatría. Universidad Peruana Cayetano Heredia
Instituto Nacional de Salud Mental "Honorio Delgado-Hideyo Noguchi"
Lima, Perú

³Médica residente de Psiquiatría. Universidad Nacional Mayor de San Marcos. Instituto
Nacional de Salud Mental "Honorio Delgado-Hideyo Noguchi"
Lima, Perú

Correspondence:
Lizardo Cruzado
Instituto Nacional de Salud Mental "Honorio Delgado - Hideyo Noguchi".
Av. Eloy Espinoza 709. Urbanización Palao. San Martín de Porres. Lima 31. Lima, Perú.
Tel.: (511) 614-9205
E-mail: lizardo_cruzado@yahoo.com

Dear Editor

Caffeine consumption is so common and extended that its pharmacological effects on the human psyche have been underestimated. This is reflected in the popularity of high caffeine level energy drinks that are sold without any warning or restriction. There are few reports on psychosis associated to high doses of caffeine in which the explanatory molecular mechanism would be A1 and A2A adenosine receptor blockage and the consequential strengthening of the dopaminergic transmission. However, in spite of the direct and indirect evidence that links mania with increase in dopaminergic activity, the reports of caffeine-induced mania are very rare. We present the case of a female patient who consumed energy drinks with high caffeine concentration and who developed maniac episodes on two occasions. We propose the need to evaluate meticulously the association between caffeine and affective episodes.

Introduction

Caffeine is the most consumed psychoactive substance in the world. It is calculated that it is consumed by 80% of the world population, either as coffee or as an ingredient of carbonated soft or energy drinks. The popularity of the latter has been exponentially increasing in the last decades, unfortunately without the due regulations. This makes it possible for consumers to have free access to drinks with concentrations as high as 500 mg of caffeine per can.¹

Substance-induced psychosis is a frequent psychiatric diagnosis. However, psychosis specifically induced by caffeine is still a rare phenomenon with few published

reports in the literature. Cases of caffeine-induced mania are even more uncommon.² The North American classification of mental disorders (DSM-5)³ and the International Classification of Diseases (ICD-10)⁴ recognize the existence of caffeine consumption induced disorders, that is, intoxication, abstinence, anxiety disorder and sleep disorder. However, they do not consider the diagnosis of psychoses or mood state disorder induced by caffeine consumption. One case of caffeine consumption induced mania in a patient not previously diagnosed of bipolar disorder has been described in the literature.⁵ Another case has been described in which the patient was already diagnosed of bipolar disorder and relapsed due to consumption of caffeine rich energy drinks.⁶ Furthermore, a case of bipolar schizoaffective disorder has been reported. This case was refractory to the medication but improved after suspension of caffeine consumption.⁷ There are also three cases of dual patients: bipolar and psychoactive substance consumers who relapsed into mania or depression, apparently in association with high doses of caffeine intake.⁸

Although there are no exact figures on the incidence of caffeine consumption associated mania, even a low prevalence would mean a considerable number of affected persons since caffeine consumption is very extended.⁹ In this report, we present the case of a female patient without no previous diagnosis of bipolar disorder or background of depression who developed maniac episodes associated to consumption of high doses of caffeine on two occasions and in which suspension of caffeine consumption was fundamental in its resolution.

A Case Report

A 31-year-old female patient, single, with professional accountant and postgraduate student, who had previously been healthy and who weighed 54 kg. One month prior to coming to our psychiatric emergency department, she was subjected to a greater work load and academic demands so that she increased her consumption of filtered coffee from 2 to 5 cups daily and began to drink 3 to 4 rations of the energy drink Magnus® Omnilife Products daily (each ration contains 81 mg of caffeine, 202 mg of taurine and 151 mg of glycine). After a few days, the patient noticed that her performance improved and that she had less sensation of fatigue while those close to her noticed increased irritability in her social interaction. Our patient progressively reached consumption of up to 10 rations daily of the mentioned energy drink (in addition to the five cups of filtered coffee per day) and began to feel more optimistic and cheerful, with exaggerated ideas about the importance of her performance, predicting that she would go from being a conventional employee rapidly and easily to being the manager of the company. In the last week before receiving medical care, she only needed to sleep four hours,

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experienced auditory hallucinations (voices of her professors that made suggestions to her on "leadership" and then from envious colleagues who criticized her and denigrated her. Finally, she became aggressive towards her relatives when they tried to control her hyperactivity, so that she was brought to the emergency department.

In the initial evaluation, the patient was alert, oriented and nervous, her mood was anxious and irritable, speech was tachylalic and she admitted feeling mentally "accelerated." She also had delusional ideas of grandeur, reported auditory hallucinations and lacked awareness of disease. No abnormalities were found in her physical examination and her laboratory tests (including metabolites of cocaine, marijuana and amphetamines and CT scan of the brain) were normal. She scored 35 points on the *Young Mania Rating Scale* (YMRS)¹⁰. The diagnosis of manic syndrome was suggested and 2 mg of risperidone and 2 mg of clonazepam every 24 hours were prescribed. At three days of evolution, there was no variation in the intensity of her symptoms and the dose of risperidone was increased to 3 mg daily. However, the patient continued to drink 7 to 8 portions of her energy drink daily. A frank improvement was only observed when the possibility of a caffeine induced maniac episode was suspected and she was urged to stop drinking it. Her symptoms completely disappeared in hardly one month, during the first week of which she experienced some somnolence and mild headache. Since the antipsychotic caused mild Parkinsonism in her and the patient was totally asymptomatic, this medication was progressively withdrawn over a period of four months, without relapses. The patient remained with a normal mood and without medication for four more months.

After this period, the patient began to consume the same energy drink again. At first, she drank two rations daily but when she reached six rations daily, she began to be disinhibited and expansive again. She said she felt full of energy, she easily became irritable, she did not feel the need to sleep and auditory hallucinations similar to what she previously had reappeared: insulting voices of envious persons who denigrated her. She scored 26 points on the YMRS at this time. Three mg of risperidone and 2 mg of clonazepam were reinitiated daily and she was ordered to stop taking her preferred energy drink. With this, the symptoms described completely disappeared within a two-week period.

She is presently asymptomatic after a one-year follow-up. She has continued to take 1 mg of risperidone although she was told to stop taking the antipsychotic 6 months ago and has not suffered a recurrence of the manic symptoms. Her current score on the YMRS is 4, her premorbid personality corresponded to depressive mood, with anancastic traits, although she never had depressive episodes. Among her family background, it stand out that she has a 22-year old

sister diagnosed of bipolar II disorder and her mother clearly has a hyperthymic temperament.

Discussion

It has been indicated that daily doses of caffeine greater than 10–15 mg/kg of body weight are sometimes associated with the development of psychotic pictures – although not specifically with affective psychoses.¹¹ Our patient reached an intake of about 1300 mg daily of caffeine before the onset of her manic episode (equivalent to 24 mg of caffeine per kg of body weight and day). Caffeine poisoning is a syndrome characterized by restlessness, nervousness, insomnia, diuresis, logorrhea and accelerating thinking, tachycardia and sensation of tirelessness. The threshold for its development is not exact since it ranges from low doses such as 250 mg for mild symptoms – in susceptible subjects – up to doses greater than 1 g intake for the more severe symptoms.³ It must be considered that the pharmacokinetics of caffeine is not linear since it saturates at a dose between 250 and 500 mg. Thus, the usual consumers of high doses, as our patient, will have serum levels of caffeine that are cumulative and progressively growing.¹² However, tolerance to the effects of caffeine develops quickly, both to its sleep disturbance effects and to its subjective and psychomotor effects, thus making the subsequent clinical expression to the caffeine doses consumed less predictable.⁹ Caffeine abstinence has recently been incorporated into the North American classification of mental disorders (DSM-5). The following are included among its symptoms: headache, myalgias, nausea or vomiting, fatigue, somnolence, dysphoric or irritable mood and concentration problems. The mixed development of intoxication and abstinence symptoms make up the so-called mixture of "caffeinism" in which combined symptoms from both entities are described.^{9,13} In our case, several of these signs and symptoms were clear before the full-blown emergence of the manic episode. Furthermore, when she stopped drinking the energy drink, there were some symptoms suggestive of caffeine abstinence. Although the somnolence could also be attributed to the benzodiazepine administered and the irritability was a pre-existing symptom, evident headaches were verified.

Our patient increased her usual consumption of caffeine more than five times her normal consumption in just a few days. This is a significant aspect prior to the onset of her symptoms and suggestive of a possible causality relationship. However, one aspect to consider is that similar doses of caffeine may trigger different clinical effects in the consumers due to genetic differences in the pharmacokinetic and pharmacodynamic tolerance to caffeine.⁹

The action of caffeine on the central nervous system consists in competitive antagonism at adenosine receptors (A1 and A2A), intracellular phosphodiesterase inhibition,

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GABA-A receptor blockers and also intracellular calcium release, although the principal effects of the caffeine are attributed to adenosine receptor blockage even at very high doses.⁹ In regards to this action mechanism, the adenosinic A2A receptor blockage produces an increase in dopaminergic neurotransmission (specifically through the D2 dopamine receptor) with the consequent stimulating properties while the A1 adenosinic receptor blockage acts through the D1 dopaminergic receptors that regulate neurotransmitter release such as acetylcholine, glutamate and dopamine per se.¹²

Up to now, the hypothesis of a hyperdopaminergic state has been useful for the neurobiological explanation of psychosis and mania. Based on the available animal models, it has been demonstrated that a picture comparable to mania can be produced when a single high dose of a psychostimulant is administered to an animal that has never had such substance while for the psychosis model, repeated administration of the same stimulating substance for a relatively prolonged time is necessary. Similar behavior effects are observed in humans, where acute administration of a psychostimulant may generate a transitory elevation of the mood and increased pleasure-seeking behavior while the repeated administration of said psychostimulant may trigger psychotic pictures with persecutory and referential delusions.¹⁴

Heuristically, it is interesting to note that the caffeinism picture, with its cohort of dysphoria, uneasiness, excitation, tachylalia, insomnia and restlessness, has several symptoms in common with a mixed type affective episode while on the contrary, caffeine abstinence causes symptoms that may be allocated to that of depression, among them fatigue, headaches, depression and dysphoric mood.¹² The complexity on the molecular level of the interactions of the caffeine in the central nervous system is not only based on the different molecular effects it has. It is also based on the fact that adenosine is located and has receptors in almost all the brain cells, having a fine modulation role in the synchronization of brain activity and homeostasis.^{2,9}

Different evidence has associated the increase of dopaminergic neurotransmission to the development of mania pictures.¹⁵ In fact, recent reviews support the role of the dopaminergic pathways in the different symptomatic components of the bipolar disorder, that is, not only mania but also depression and psychosis.¹⁶ This is based on the primary clinical symptoms or substance-induced symptoms, the neurobiology underlying the swings and the pharmacological interventions capable of reverting the mentioned psychopathological syndromes.

When further studying the association between caffeine and affective pictures, there are cumulative data on the ability of caffeine to induce mood changes when taken in high doses (either anxious or manic, according to the

individual idiosyncrasy) and to protect the mood swings at moderate doses (reducing anxiety or favoring a mild mood elevation).⁹ Some data even point to a reduction of the incidence of suicide based on the caffeine intake.⁹ On the other hand, an association has been found between the bipolar spectrum (measured with the *Hypomania Checklist-32*) and greater intake of social drugs such as tobacco and caffeine.¹⁷ The bidirectionality of this relationship has still not been adequately studied.

Another glimpse into the action mechanisms of caffeine on the development of psychotic symptoms comes from the study of healthy individuals subjected to stress in whom greater caffeine intake was correlated with proclivity to experience hallucinations. The increase of the cortisolic response secondary to caffeine consumption could be involved in this.^{18,19} Our patient also had stress situations prior to the onset of her symptoms, along with her excessive caffeine intake.

Pharmacological blockage of D2 dopaminergic receptors has commonly been one of the resources used most for the treatment of acute mania pictures: and such has been the benefit of the administration of both first and second generation antipsychotics in such contingency. Other interesting evidence on the possibility that caffeine may affect the development of mania comes from the fact that therapy with adenosine receptor modulators such as allopurinol, pentoxifylline or dipyridamole have demonstrated, although this is not totally conclusive, that they are superior to the placebo in the global treatment of the psychopathology, above all positive, in schizophrenia and also in the pharmacological tackling of mania pictures.²⁰

In addition to caffeine, in most energy drinks there are substances such as inositol, glucuronolactone, taurine or glycine, that are attributed certain psychoactive. The drink that our patient took only contained the latter two. Although both are naturally synthesized in our body, the daily intake indicated as safe for taurine is 1000 mg per kg of body weight and the daily global intake of glycine is 2000 mg although doses of up to 60 g daily have been used without harm. Our patient never reached this amount, not even at the time of her maximum consumption.^{21,22} In addition, the scientific evidence only records secondary neuromodulator roles^{22,23} for both substances. The most recent bibliography on taurine defines its role in the central nervous system as protector of neuronal excitotoxicity and osmoregulator while glycine, due to its NMDA type glutamate receptor agonist role, has been used as coadjuvant in the treatment of negative symptoms of schizophrenia: nevertheless, it is the glutamatergic antagonists that have the opposite effect, that is, that are potentially and inductor of psychosis. Therefore, everything directly indicates caffeine as the principal substance to which the inductor effect of mania in our patient can be attributed.

Kraepelin had already mentioned personal temperaments (he called them "basic states")²⁴ as a frequent history in proclivity to bipolar pictures (37% of the Kraepelinian casuistics) but he not only considered them as risk factors but also as constitutive forms of manic-depressive psychosis, although in an attenuated form. It has been observed that depressive temperament, as hyperthymic, cyclothymic, irritable and anxious, are general fertile grounds for emergence of depressive, manic or hypomanic episodes.²⁵ Our patient's temperament was consistent with the depressive type, and although the follow-up time she had was relatively short, she never fulfilled bipolar disorder criteria nor had she presented previous depressive pictures. Recently, the predominance of manic episodes over depressive ones was postulated. The former were assumed as global states or behaviors of excitation and the latter as reactive consequences to them.²⁶ Thus, the triggering of the manic episodes may represent a pathway of great interest for the study of the bipolar spectrum.

It is likely that many manic episodes secondary to caffeine go unnoticed as such, sometimes because they are classified as characteristic of bipolar disorders and others as psychotic disorders or because the history of caffeine consumption is not explicitly gathered, assuming this habit to be totally inoffensive.⁵ Thus, it is recommendable to introduce warnings on the products that contain caffeine on the risk of intake of elevated doses and the possible complications of its overuse.^{2,5} Because consumers receive little information on the risks of excess use of caffeine, there is a tendency to consume large amounts of it, deeming them harmless. Equally, it has been suggested that the collection of data on caffeine intake should be introduced in the usual form of the medical anamnesis, above all the psychiatric one.¹³

In conclusion, special care must be taken with the use of drinks with high caffeine concentration due to their possible association with mood disorders through their dopaminergic action and which in susceptible cases may, as in the case reports, become episodes with frank manic symptoms.

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Relationship between smoking and psychotic symptoms in a patient treated with oral olanzapine. A case report

Antonio Leal-Micharet¹
Francisco J. Vaz-Leal^{1,2}
María J. Méndez-Salguero¹
Fabiola Méndez-Sánchez¹
Itziar Baltasar-Tello¹
Belén Gómez-Tovar¹
Virginia Gajardo-Galán¹

¹Complejo Hospitalario Universitario de Badajoz
Hospital Infanta Cristina

²Universidad de Extremadura. Facultad de Medicina
Departamento de Patología Médico Quirúrgica
Área de Psiquiatría

Correspondence:
Antonio Leal Micharet
Servicio de Psiquiatría
Hospital Infanta Cristina
Avda. Elvas s/n
06011 Badajoz (Spain)
E-mail: antoniolm_10@hotmail.com

Dear Editor

Smoking is strongly related with severe mental health conditions. Tobacco is as significant a psychoactive substance for patient functionality as the medication we use. That is why we must always be aware of the influence it is going to have on the life of the patient, not only socially and functionally, but also when addressing possible pharmacological interactions that may affect the efficacy and tolerability of the medication and therefore the course of the condition. In this case report, we present these interactions from a clinical perspective, stressing the need for monitoring smoking habits in order to achieve efficient treatment adapted to individual patient circumstances.

Introduction

There are a number of factors that can alter the metabolism and efficacy of the drugs used in daily clinical practice, such as food, natural remedies, alcohol or smoking.

The effect of smoking on the pharmacokinetics and pharmacodynamics of some drugs, such as olanzapine, clozapine or theophylline, is well known. It is therefore important to be familiar with the patient's habits when correctly establishing doses, in order to ensure the drug has the desired effect.

The prevalence of smoking in patients with schizophrenia is higher than in the general population. It is believed that approximately 60% of patients diagnosed with schizophrenia are smokers.^{1,2} These high rates among schizophrenic patients have been described in different cultures, and we

should therefore consider a possible significant biological connection to support this.³ A range of theories have been suggested to explain this high prevalence. The most widely accepted is the theory that smoking is an attempt at self-medication, especially as a means of reducing the undesirable side effects of treatment.⁴ This is particularly important in the case of patients treated with olanzapine or clozapine, as a drop in plasma levels with these drugs in patients who smoke has been documented.^{5,6}

Case Report

A 37-year old male, under long-term treatment with olanzapine, attended due to decompensation of his psychotic condition, with symptoms of hallucination and microdelusional episodes.

Personal background

Admission to a Hospital Psychiatric Unit ten years ago because of a psychotic episode, probably related with consumption of psychoactive substances (cannabis). Initial treatment consisted of oral risperidone (6 mg/day), subsequently replaced with oral olanzapine (10 mg/day), from which time the patient has remained relatively stable.

The patient has had reading-writing and dyslexia problems since childhood. Morbid obesity. Smoking. Low functioning level. He performs simple shopping tasks and lives with a brother who is physically disabled. Poor interpersonal relationships. The patient has an official disability of 66%.

Background of current condition

At the first visit, the patient's brother attended the Psychiatry Unit. He reported that his brother had episodes of aggressiveness and significant alcohol consumption and smoking, worsening over the previous 7-8 months. The patient was also reported to be a compulsive shopper, particularly of food, for binge eating. The patient's brother reported good behavior between episodes, and good adherence to medication. These crises appear to be related with episodes of compulsive smoking (up to 40 cigarettes in 2 hours).

At the second appointment, attended by the patient and his brother, both agreed that the episodes of aggressiveness and compulsive smoking were related, and the patient admitted to having auditory pseudo-hallucinations. He described hearing voices insulting his late parents, telling him that he was going to die. These hallucinations were accompanied by tremors, nervousness and aggressiveness.

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When this occurred, the patient tended to take 30-40 mg of olanzapine, until the symptoms subsided and a state of drowsiness appeared.

Psychopathological examination

During the mental assessment, the patient appeared alert, oriented and cooperative. Psychotic contact. Unkempt appearance. Poor, specific language. Appropriate and correct during the interview. He gave the impression of having low borderline intellectual capacity. Increased latency of responses and continuous need for approval from his brother. Suspicious. Withdrawal. Bradypsychia. He denied regular sensory-perception alterations, although he did describe these on an episodic basis and in relation to heavy smoking, in the form of auditory pseudohallucinations of insults and threats to the patient. He was partially critical of these hallucinations yet experienced them with a significant affective component of anxiety, tremors and intense fear. Occasional irritability and impulsivity, unrelated to smoking habits. No other related emotional alterations. He denied having thoughts about death, suicide or causing harm to others. Compulsive eating. Sleep-maintenance insomnia directly related to the patient's obesity (Obstructive sleep apnea). Partial awareness of his condition; the patient seems to understand the existence of a disorder and the need to comply with treatment, although not its nature. Dependent on care-giver.

Additional tests

- SCL 90
 - Obsessive-compulsive: 23 pts (2.3)
 - Anxiety: 22 pts (2.2)
 - Interpersonal sensitivity: 9 pts (1)
 - Depression: 25 pts (1.92)
 - Hostility: 7 pts (1.16)
 - Phobic anxiety: 16 pts (2.28)
 - Somatizations: 19 pts (1.58)
 - Paranoid ideation: 10 pts (1.66)
 - Psychoticism: 15 pts (1.5)
 - Global Severity Index: 1.77
 - Positive Symptoms Total: 71
 - Positive Distress Index: 2.25

The scores obtained on the SCL-90 are above the mean for all the parameters. The dimensions furthest from the mean were: Obsessive-compulsive symptoms that assess thoughts, actions and impulses that are experienced as impossible to avoid or unwanted. Anxiety assessing the presence of general signs of anxiety such as nervousness, tension, panic attacks and fears. Phobic anxiety, referring to a persistent response of irrational and disproportionate fear. Psychoticism, including symptoms relating to loneliness, schizoid lifestyle, hallucinations and thought control. The paranoid ideation dimension assesses paranoid behaviors, fundamentally regarding thought disorders: projective thought, suspiciousness, fear of loss of autonomy.⁷

The SCL-90 report was compiled with the patient accompanied by his brother, and at a time when he was denying the presence of psychotic symptoms.

Clinical Opinion

- AXIS I: Paranoid schizophrenia
- AXIS II: Intellectual disability
- AXIS II: Obesity. Obstructive sleep apnea
- AXIS IV: Problems relating to primary support group
- AXIS V: GAF: 51-60

Comments

Olanzapine is fundamentally metabolized by CYP1A2. There are certain factors that affect the functionality of this enzyme group, thus having a significant effect on how olanzapine is metabolized and its efficacy in the target area.

As we have already mentioned, it is very important to establish which of these factors may be present and how the treatment can be adjusted during the patient's interview in order to allow the drug to have the desired effect.

Drugs metabolized by CYP1A2 are listed in Table 1 below.

Despite being a cytochrome that metabolizes a large number of drugs, it acquires special importance in the metabolism of psychoactive drugs, which generally have a narrow therapeutic margin.⁸ This enzyme is also particularly important as it is highly influenced by smoking, physical exercise, grilled meat and some vegetables.⁸

Some studies have demonstrated the appearance of severe adverse effects in the combination of clozapine and caffeine.⁹ A reduced efficacy of olanzapine, caused by a drop in plasma levels associated with smoking, due to the inductor

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Table 1	CYP 1A2
SUBSTRATE	INHIBITORS
Antidepressants: Amitriptyline, clomipramine, fluvoxamine, imipramine, mianserin, mirtazapine	Amiodarone Cimetidine Fluorquinolones
Antipsychotics: Clozapine, haloperidol, olanzapine, thioridazine	Fluvoxamine Furafylline Methoxsalen
Methylanthines: Caffeine, theophylline	Mibefradil Ticlopidine
Miscellaneous Phenacetin, paracetamol, propanolol	

Adapted from Gervasini et al. (2009)⁸

Table 2	CYP Isoenzymes most commonly involved in the metabolism of different antipsychotic drugs	
CYP450	Antipsychotic	Interactions
1A2	Clozapine Olanzapine	Inductor: Smoking Inhibitors: Fluvoxamine
2D6	Clozapine Olanzapine Risperidone Chlorpromazine	Inductor: Fluoxetine, paroxetine, sertraline
3A4	Clozapine Quetiapine Ziprasidone Haloperidol	Inductor: Carbamacepine Inhibitors: Ketoconazole, Erythromycin, fluvoxamine, fluoxetine

effect of tobacco on the enzyme activity in the CYP1A2 complex, has also been observed.¹⁰

There are some published studies that deal with the connection between smoking and antipsychotic treatment. Two hypotheses can be drawn from these. High rates of smokers have been reported among patients under treatment with typical antipsychotic drugs, a fact that is justifiable as the extrapyramidal effects in these than in atypical drugs, and nicotine can help to reduce these.¹¹ Furthermore, in patients treated with olanzapine or clozapine, an increase in smoking can reduce the side effects of treatment as metabolism is accelerated.

Conclusions

Olanzapine is an effective treatment for patients diagnosed with schizophrenia or other psychotic disorders, and for bipolar patients suffering manic episodes.

It is a relatively safe and easy to use drug, however, given the profile of the patients in whom it is used, it is advisable not to lose sight of certain factors. Given the nature of the metabolism of the drug, there are certain details that must be considered, such as concomitant treatment or exposure to certain factors that alter the drug function, such as smoking. In the case presented, smoking resulted in the reappearance of psychotic symptoms that had previously been controlled with a normal dose of olanzapine. This is significant, as normal doses may be insufficient in patients who are heavy smokers. Additionally, changes in smoking habits during evolution must be properly documented, as patients whose symptoms are controlled under a specific dose of the drug may suffer alterations due to an increase in tobacco use, or conversely, they may suffer adverse effects caused by an excess dose if they reduce the habit significantly or give up smoking. This is of such importance that it must be taken into consideration when opting for a particular drug.

In the specific case presented, and given the characteristics of the patient, who was considered unlikely to give up smoking, the use of a different antipsychotic drug should be considered, with the good tolerability that olanzapine has but without the metabolism issues presented by this drug (Table 2).

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