"Great responders and recovery". Clozapine associated to granulocyte colony stimulating factor

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Dear Editor,

The "treatment and cure" model emphasises symptoms relief and the prevention of relapses. While this is the objective of recovery-oriented mental health departments, the improvement of symptoms remains important and can play a key role in patient recovery[1].

We present the case of a 28-year-old woman diagnosed with schizophrenic psychosis and showing a poor response to antipsychotics (before the introduction of clozapine for the first time, she had received haloperidol 15-30 mg/day for 8 weeks, olanzapine 20-30 mg/day for 12 weeks, perphenazine 24 mg/day for 8 weeks and risperidone 9 mg/day for 8-10 weeks). The patient had required a significant number of long-term hospital admissions. Positive results were obtained with clozapine, though the drug had to be discontinued due to neutropenia. Different antipsychotic treatments were tested, with a slow evolving clinical course. The decision was therefore made after several months to reintroduce the drug despite reports in the literature of recurrent agranulocytosis (even of greater severity); neutropenia again developed[2]. Different drug combinations were prescribed, without effective therapeutic results (haloperidol 30 mg/day for 4 weeks, olanzapine 30 mg/day for 5 weeks, aripiprazole 30 mg/day for 4 weeks). It should be mentioned that these previous antipsychotics were tested before restarting clozapine for the third time because partial responses to them had occurred at some time during the clinical course. Although these responses were not sustained over time, sufficient clinical remission was achieved to allow hospital discharge.

The Department of Hematology was consulted, and it was decided to reintroduce clozapine more slowly and gradually (dose increments of 25-50 mg/week), with closer hematological monitoring (two urgent weekly blood counts on Mondays and Thursdays, in order to receive the results as soon as possible and be able to intervene quickly and promptly if necessary). A decrease was recorded in the white blood cell and neutrophil counts (2200 leukocytes; 822 neutrophils). At this point and given the null or poor response to the other antipsychotics and the progressive functional impairment of the patient, treatment with granulocyte colony stimulating factor (G-CSF) was decided on a compassionate basis, since this indication was not contemplated in the summary of product characteristics[3-7]. The increased frequency of hematological monitoring was explained and accepted by the patient, who experienced no problems. Most of the intensive management protocol was developed during hospital stay and then continued on an outpatient basis for an additional 6 months, followed by weekly controls and then monthly monitoring after one year. The patient visited the Area Rehabilitation Unit each day to participate in workshops and individual therapies. The blood counts were therefore obtained in that Unit, without the patient having to report to the hospital or primary care center. After the administration of G-CSF, the patient developed a self-limited pseudoinfluenza condition over 2-3 days that was treated with paracetamol.

The successive blood counts showed that the sample collected after breakfast exhibited better leukocyte and neutrophil counts than under fasting conditions. This phenomenon had been reported in the literature and was justified by the peripheral distribution of the white blood cells after food intake[4]. For this reason, the blood counts were obtained in mid-morning, when the leukocyte counts re-

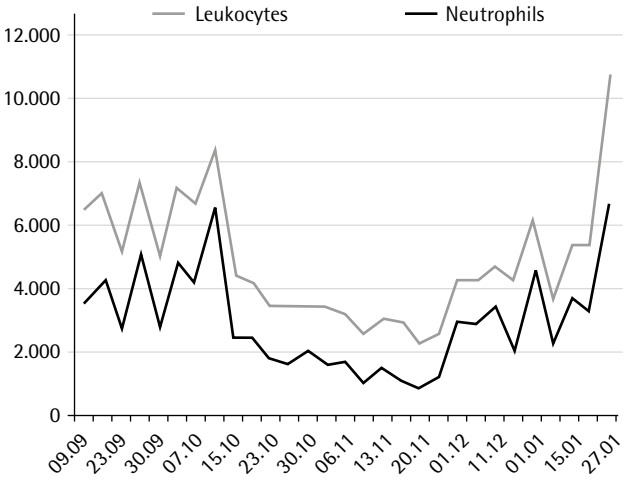

Figure 1 — *Evolution of leukocyte and neutrophil counts during clozapine treatment*

Table 1 Direct pre- and post-treatment scores obtained with the Brief Psychiatric Rating Scale (BPRS), the HONOS functional assessment scale, and Quality of Life Scale for schizophrenia (QLS)

	DS PRE-treatment	DS POST-treatment
BPRS	43	17
QLS	2	61
HONOS	26	8
	Positive symptoms: 15	Positive symptoms: 6
	Negative symptoms: 6	Negative symptoms: 3

mained within normal limits, and no further administration of the colony stimulating factor was required (Figure 1).

Significant improvements were observed in the psychotic symptoms, function and quality of life. Clinical improvement was demonstrated using the Brief Psychiatric Rating Scale (BPRS)[8], recovery of function was evidenced by the Honos scale[9], and improvement in quality of life was confirmed with the Quality of Life Scale for schizophrenia (QLS)[10] (Table 1).

Psychopathological stability has been maintained for three years, warranted by other outcome variables such as fewer hospital readmissions and shorter stays.

Discussion

The present case describes a strategy for reintroducing clozapine associated to granulocyte colony stimulating factor (G-CSF)[6,7] following an episode of neutropenia leading to treatment suspension and clinical worsening of the patient. Clozapine is currently the standard treatment for refractory schizophrenia, being effective in dealing with the positive, negative, cognitive and affective symptoms of psychosis, as well as with suicidal behavior, violent or aggressive behavior, substance abuse and extrapyramidal symptoms[11]. Thanks to such management, patients "wake up" and are able to resume their professional or social activities, with a reduction of the number of days in hospital. We refer to such patients as "great responders". As an inconvenience, blood dyscrasias constitute the most feared side effect of this drug. Agranulocytosis is the most severe of these blood dyscrasias (with an incidence of 0.8% in the first year), being associated to death in 5-10% of the cases[12]. This problem caused the drug to be suspended in some countries, and laboratory monitoring is required as a measure of caution, especially during the first 18 weeks of treatment. The causes of this side effect may include immune mechanisms (some studies having found agranulocytosis to be usually preceded by a dose-independent increase in eosinophil count). Hematopoietic cytokines, specifically G-CSF, have also been considered to play a role, as evidenced by the efficacy of treatment with this stimulating factor[13,14].

Conclusions

- Clozapine remains the antipsychotic of choice for refractory schizophrenia. However, it can cause serious blood dyscrasias that require evaluation of the feasibility of such treatment.
- The occurrence of such hematological complications would not require drug discontinuation, since there are effective treatments for them.
- Uncertainty about the probable cause of blood dyscrasia in people taking clozapine, together with a lack of understanding of the mechanism involved, implies that any attempt to reintroduce the treatment must be made as carefully as possible.
- The risks and benefits of re-exposure to clozapine should be assessed, and a balance must be made among the severity of the hematological disorder, the severity of the mental disease, and the clinical course to be expected if the patient were not treated with clozapine. There are cases in which the clinical condition is so severe that these therapeutic measures must be considered, including G-CSF, with the adoption of close monitoring measures.

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Marijuana consumption: autobiographical analysis of a paradigmatic case between a consumer adolescent and a non-consumer

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Dear Editor,

The World Drug Report 2018[1] published by the United Nations Office on Drugs and Crime, suggests that South America is the second region with the highest marijuana consumption, with a rate of 11.57% in 15 to 16-year-olds, preceded by Europe, where the average consumption in this population reaches 13.92%. The same report suggests that Chile is one of the countries of the region with the highest consumption rates in the last 12 months, reaching 34.79% according to the figure reported in 2015, whilst Uruguay, a country where marijuana consumption is legal, reached 29.7% in 2014[2].

To grasp this consumption phenomenon, it is interesting to incorporate the insights of other related measurements that characterize the current scenario and allow evaluating its future development, these are risk perception, accessibility and consumption within the household. The latest National Drug Study in Chile[3] shows that risk perception in adolescents presents a constant and exponential decreasing trend in the last ten years, thus, risk perception associated with *experimental use* has decreased from 42.5% to 28.9%, while the risk perception regarding *frequent consumption* has decreased from 90.3% to 64.9% in the same period, a phenomenon confirmed by other of our studies[4]. Regarding the perception on marijuana accessibility, it increased for second consecutive year, reaching 51.6% in youngsters from 12 to 18 years old, and the proportion of adolescents that confirmed living with at least one consumer of this drug increased to 8.7%. At a population level, this rate suggests a statistically significant increase of 3.8 points, which transforms marijuana into the most consumed illegal drug in Chilean households.

Regarding its damage, some studies suggest that consuming marijuana before the age of 17 would cause major neurobiological changes compared to later consumption[5-8]. There is a general consensus among researchers that marijuana may affect the cognitive processes involved in social and school performance, including impairments in memory, attention, concentration, information organization and processing strategies[4,9,10]. This impairment of cognitive functions may lead to a poor school performance and even early school desertion[11].

In this sense, it is worth emphasizing on the *amotivational syndrome* as a pathognomonic condition of the marijuana consumer, characterized by energy loss, aboulia, and an important decline of regular activities[12]. All these damages may lead to higher failure possibilities in the adoption of roles, goals and purposes that define the adolescence stage[13].

All of this led us to presume a relationship that causes impairment in the ability to project and organize time efficiently according to a specific goal, which we investigated using a qualitative method with a narrative approach[14]. Autobiographical stories related to past and present experiences and future projects were compared in consumer and non-consumer youngsters[13]. For narrative analysis, Linseth and Norberg's hermeneutic phenomenological method was used, which was inspired by Ricoeur's ideas on the possibility of knowing people's private experiences by interpreting the meaning of the narrative, an autobiography in this case[15].

Seeking a clinical view on the phenomenon of identity construction in adolescents, we furthered the narrative analysis of the sample obtained by Dörr, Acevedo and Espi-

noza in 2014[14]. The study is based on two *intense*[16] or paradigmatic cases, understood as cases that "without being extreme, manifest the studied phenomenon with particular intensity or drama" (p.616)[17]. Both are male students with the same school level and type of establishment.

The result of this analysis shows differences in both autobiographies in terms of length and content of the narratives, with the consumer's being notoriously shorter than the non-consumer's. In terms of content, the descriptions of past situations made by the non-consumer are lengthier, mentioning more experiences. Their comments on family were precise and focused on their tastes and interests, without justifying themselves in past conflicts. The narrative emphasized details from specific events of great relevance to his childhood, highlighting the presence of reflections on the significant impact of these traumatic past experiences and the desire to overcome them through concrete actions.

On the other hand, even though consumer youngsters achieved to express their wishes, they did not mention concrete actions consistent with their goals, focusing more on the obstacles than in future solutions. In general, the young consumer narratives were characterized by the reference to past elements with little or no relation to future wishes, with no clear purpose for their present actions.

It is worth mentioning that the search for a place in society is very important in adolescents' lives, which requires a constant role exercise and exploring a more specific definition within society[17]. For this exercise, the ability to anticipate is fundamental, as it requires projecting expectations for the future, which will be more achievable if the adverse elements and difficulties experienced in the past are incorporated as learning[18-21]. In this sense, the young consumer describes vague and contradictory wishes and hopes, without being able to propose concrete goals nor plans to achieve them. We observed an inability to establish relationships among past, present and future, in the sense that they have, apparently, no conscience that future actions depend on present actions, showing a disruption in the ability to anticipate. Thus, it is possible to deduce that the young consumer would experience an underlying sensation of "not being called by the future," being instead "trapped" in the immediacy of the present[22], while the non-consumer experiences an opposite phenomenon: the relation between past and future wishes with present actions as a means to achieve them.

Considering this, we intended to highlight the relevance of the concept of temporality to youngsters' experiences as being fundamental for the comprehension of the effect caused by marijuana consumption on identity construction. In this sense, it is interesting to expand the study to a more diverse population in terms of another drug consumption, in order to provide a more specific comprehension of how temporality is affected according to the type of drug.

In turn, the sense of temporal continuity, understood as the ability to stay true to one's self despite of changes through time, provides people with some biographical fluency, accessing different moments in life without attaching identity to a particular stage and with enough flexibility to incorporate changes (Akthar and Samuel)[23]. Therefore, the temporal dimension becomes fundamental and decisive in the process of identity construction.

From a psychology standpoint, the temporality phenomenon has been underdeveloped; it is thanks to the constructivist approach that it is possible to study temporality, particularly when a relationship between formal thinking and the incorporation of future experience as a conduct determinant is established[24]. Arciero[25] suggests that adolescents can think about a life project only when they achieve abstract thinking, analyzing real future possibilities, to be able to rearrange and resignify their past life in connection with their present and future goals. Thus, as a consequence of the acquisition of formal thinking, the subject incorporates the future dimension through the life project[26-28].

The investigations we have carried out, along with the previously mentioned scientific evidence, show that either from a quantitative or qualitative paradigm, the damage caused by marijuana consumption in adolescents is severe, affecting cognitive aspects that lead to poor school performance caused by an impairment in fundamental executive capabilities such as memory, attention and concentration. Additionally, marijuana interferes with the development of basic abilities in youngsters that enable them to insert themselves as adults in society, by affecting the construction of a life project that provides meaning and purpose.

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The paradox of iboga: intoxication by a natural detoxification remedy

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Dear Editor,

Ibogaine is a psychoactive alkaloid extracted from the Tabernanthe iboga bush. It has been used for the treatment of addictive disorders, particularly opiate addiction[1-3], since the 1950s.

Despite the existence of preclinical studies and case reports supporting its therapeutic use, there is still a need for further research in order for it to be considered a therapeutic agent. Its decades long clandestine use has led to the development of an alternative current of thought that supports its use for the treatment of several addictions[3-5].

We present the case report of a patient who was admitted to the hospital after the consumption of Iboga, along with a review of the existing literature.

Clinical case report

A 31 year old male was admitted to the psychiatric ward after being evaluated for confusional symptoms and severe behavioral alterations. For the last two years the patient had presented symptoms of moderate anxiety as a response to several stress factors and had undergone treatment with fluoxetine and alprazolam. The patient was also suffering from unspecified muscular pain which he managed through automedication with codeine. The progressively incremental dosage of codeine and alprazolam resulted in an abuse of both substances. There was no other medical, surgical or psychiatric background of interest.

In this context, and after learning of its existence and alleged effectiveness, the patient starts detoxification therapy through the use of a medicinal plant: Iboga. We determined the nature of the substance through the analysis of a sample provided by the patient's father, who was his companion during the hospital stay. The test was outsourced to an external laboratory. The patient denies any consumption of the substance and we were unable to determine the exact dose used during the "treatment" which lasted four days and took place in a private home under the supervision of a family member. During this process the patient underwent a complete solid and liquid fast, ingesting only several doses of Iboga and other "natural remedies". The complete treatment sequence and its repercussion on the patient's mental state are detailed below:

- **1st day:** Abrupt cease of both alprazolam and codeine treatment and beginning of an absolute solid and liquid fast.
- **2nd day:** First Iboga dose (we ignore the dose and purity of the active principle). A few minutes after intake the patient experiments a feeling of unsteadiness and unspecified fear that onset a panic attack. Hours later the patient develops a delusion of damage and passive influence against the "therapeutic group" with fluctuating periods of conscience alternated with periods of stupor and hypervigilance with associated psicomotor unrest. Two more doses of Iboga were administered, followed by a cease of behavioural alterations and a drop in the level of consciousness. It is important to consider that, during the different phases the process consisted of, the patient was passively mobilized with pendular movements and was administered unknown substances in the form of vapour inhalations and intake of brews.
- **3rd day:** No further doses of Iboga or other substances. A tendency to sleep is observed along with vivid dreams and soliloquies.
- **4th day:** An unsuccessful attempt at oral intake takes place. Drowsiness and psychomotor inhibition prevail, due to which the family member decides to take him to the hospital ER.

Upon arrival to the ER staff notice a fluctuating level of conscience, severe psychic anguish, space-time disorientation and acute distractibility. The patience concisely answers some questions and engages in soliloquies. A delusion of damage is observed along with sensoperceptive alterations in the form of visual (moving plastics) and auditory hallucinations (dialogating auditory pseudohallucinations), accompanied by a listening attitude. A 10mg olanzapine tablet is administered, after which a partial improvement in symptoms is observed.

After disregarding urgent organic pathology, the patient is admitted to the psychiatric hospitalisation unit so as to assess his clinical evolution and better observe the symptoms.

As the patient's stay goes by, confusion and hallucinatory symptoms progressively disappear, leaving predominant delusions of damage and passive influence. Subsequently, delusional cognitions disappear and dissociative symptomatology with derealization and depersonalization phenomena emerges, accompanied by the reliving of past events. Finally, all clinical signs and symptoms cease except for a partial amnesia of the experience and the patient is discharged.

During the patient's stay several tests are carried out so as to identify any organic alterations that could be related to the clinical signs (cranial CT scans, ECG, torax x ray, blood tests, urine sediment examination, drug urine testing and EEG) with no relevant findings. The treatment during the episode is limited to rehydration and forced diuresis through fluidotherapy.

The clinical case is compatible with a secondary confusional syndrome caused both by Ibogaine intoxication and abstinence from benzodiazepines and opiates, along with the possible additional effects caused by dehydration, fasting for several days and the consumption of other substances.

Discussion

We believed it would be of interest to perform a review of the available literature on the subject of Ibogaine and highlight the inconvenients of medicinal plant use. These are popularly referred to as "alternative medicines" or "set of procedures with scarce support from the scientific community" and, far from being safe, may pose a risk to unknowing individuals due to their associated harmful effects[2,5,6].

The therapeutic and spiritual use of this substance predates the XIX century, when it was used by south african tribes as part of their rituals[4].

Between 1940 and 1970, Ibogaine was made available to the public in France as a psychostimulant under the commercial name of "Lambarene"[7].

In the 1950s, chilean psychiatrist Claudio Naranjo and several american psychotherapists characterized the pharmaceutical as a useful treatment for patients suffering from "traumatic experience related psychologic blockades"[2,8].

In 1962 Howard Lotsof, a regular heroin user, accidentally stumbled upon its potential use for the detoxification of opioids when he noticed a lack of abstinence syndrome after a recreational use of the substance. After his experience he promoted the therapeutic agent for the treatment of addictions[3,9].

Considered a substance of abuse, the possession of Ibogaine was made illegal in the USA in 1967. In 1970, the FDA classified it as a Class I substance, along with other psychoactive substances such as LSD[3,9].

After 1980 several preclinical studies were developed such as that of Rotterdam, in which a decrease of abstinence from opiates was observed in animals[10]. In the New York study, a reduction of self administered morphine was measured in rats that had previously been treated with Ibogaine[11].

In 1993, the FDA authorised the University of Miami to carry out Phase I of a study of Ibogaine's pharmacokinetic properties and other safety aspects. Meanwhile, in Rotterdam, clinical trials with heroin and cocaine users were started. Both trials were finally interrupted, the first due to lack of funding and the second after the death of one of the participants[9,12].

After the confirmation of several Ibogaine related deaths more retrospective and rodent studies were carried out. These showed the possibility of serious neurological adverse effects such as cerebellar Purkinje cell degeneration or cardiac effects such as arrhythmias[3,13,14]. According to Schep et al. there are case studies which describe the presence of ataxia, ventricular arrhythmia and sudden death in patients undergoing addiction treatment with Iboga[15].

Ibogaine's neurotoxic mechanisms have been provedin rodents. These effects seem to be unrelated to the previously described "anti-addictive" properties and can probably be explained by the stimulation of the inferior olivary nucleus through neurotoxic effects on Purkinje cells in the cerebellum. The implication of potassium channels in this substance's cardiologic toxicity has been described[1].

Since 1990 two Ibogaine derivates have been studied in animal studies: Noribogaine, an active Ibogaine metabolite, and 18-MC, a synthetic derivative produced by the pharmaceutical industry for addiction treatment which lacks most of the unwanted effects of Ibogaine[16,17].

In 2016, Forsyth et al. carried out a study in which 21 healthy volunteers received a single dose of 20 mg of Ibogaine after undergoing a six day treatment with a 20 mg dose of paroxetine or placebo. Subjective mood variations were assessed through the comparison of the answers to a set of psychometric test questions before and two hours after the Ibogaine dose was given. The study found no significant variation in the study variables, regardless of previous treatment with paroxetine or placebo[4]. Thomas Kingsley Brown et al. conducted an observational study of 30 patients diagnosed with opioid dependency according to DSM-IV criteria in which subjects were administered a single dose of 1520 $\pm$ 920 mg of Ibogaine hydrochloride. Reexamination of the patients 1, 2, 6, 9 and 12 months after the Ibogaine dose was given showed an improvement in abstinence symptoms and a lower risk of relapse in patients in which other treatments had not proven effective[18].

On a pharmacokinetic level, Ibogaine is metabolized by the P450 2D6 cytocrome and is stored in adipose tissue. These facts determine an important risk of interaction with other drugs, particularly psychopharmaceuticals[19]. Noribogaine, an active metabolite of Ibogaine, is present in relevant concentrations in blood plasma for several days after exposure to Ibogaine[1].

Its pharmacodynamics are complex. Researchers have focused on the interaction of Ibogaine with the dopaminergic system for its implication in reward circuits of the mesolimbic pathway, including the frontal cortex and the amygdala[1,18-21]. Some studies conclude that its effect on the dopaminergic system is mediated through its interaction with serotonergic receptors 5-HT 1b and 5HT 3[18,22,23]. Other research has linked its effect with other transmission systems such as the glutamatergic, nicotinic, gabaergic, cholinergic and muscarinic systems. It is thus considered that Ibogaine's effect depends on the interaction of all these systems, although this is not without controversy; a polish study suggests that the NMDA receptors have a crucial role in Ibogaine's anti-addictive properties[9,15,17,19].

According to some psychodynamic theory authors, the usefulness of Ibogaine lies on the creation of an intense oniric experience that activates long term memory, forcing a deep introspection that aids comprehension and resolution of conflicts related to the addiction[24].

Generally, its therapeutic use implies the use of Ibogaine hydrochloride in an oral morning dose of 15-20 mg/kg. These treatments are carried out outside of the health-

Table 1 Phases of Ibogaine intoxication

	ACUTE PHASE	PHASE OF EVALUATION	RESIDUAL PHASE
Stard	1-2 hours	5-10 hours	24-36 hours
Duration	4-8 hours	15-20 hours	72 hours
Symptoms	- Emotional lability - Visual hallucinations/ illusions (most intense to keep your eyes closed, even disappear when opened)* - Memory of traumatic experiences	- Fluctuation of attention and level of conscience - Apragmatism	- Decreased sleep needs - Progressive recovery
Objective	Memory of traumatic experiences	Reflection period	Recovery period

* As opposed to classic hallucinogens

care context[25]. Schep LJ et al. suggest an initial therapeutic dose for detoxification purposes of 0.87mg per kg of body weight, substantially lower than other proposals, warning that its adverse effects and related mortality will continue to occur unless the professionals using this substance reconsider the doses at which they are administering it to their patients[15].

According to some clinical reports and existing descriptions in the literature, the effects of Ibogaine consumption can be differentiated into three phases[5,25] (Table 1) parallel to those described in our case study.

As for the legal implications, Ibogaine use remains unregulated in most countries, Spain among them, and is illegal in Australia, Belgium, Denmark, France, Sweden, Switzerland and the U.S.A.[3,5]

Lastly, it is worth highlighting the need for further research so as to clear out any controversies the available literature may create. However, and as our case study clearly shows, we can state that the use of this substance outside of the field of healthcare poses serious risks for users. All in all, it is imperative to establish legal and professional control over therapies like these which usually remain outside of the official circuits, with a subsequent underestimation of their harmful potential[6].

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