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Anxiolytics and Antidepressants: Problem or Solution?

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Abstract

Mental disorders are serious neuropsychiatric diseases that affect the development of daily life of the person who suffers and during the last decades the number of affected has increased. In these cases, pharmacological treatment is an essential and necessary therapeutic tool. However, problems associated with these treatments, such as addiction, have been described after their use. Interestingly, these pharmacological treatments against mental disorders could improve other types of pathologies, as occurs in the mental illness of addiction.

The objective of this work is to analyze the most recent scientific literature in relation to the problem of addiction to legal drugs, mainly anxiolytics and antidepressants, as well as the possible therapeutic use of these for the treatment of addictions. For this, an exhaustive search was carried out in the main scientific databases, selecting the most recent articles that use the keywords that interest us and that are published in the last 5 years. The data points to the great problem of consumption of legal drugs but also to a possible similarity in their mechanism of action between addiction to substances of abuse and mental problems, so that some drugs against mental problems could be used as a pharmacological tool in the addiction to substances.

Keywords: Anxiety; Depression; Anxiolytic; Antidepressant; Drug abuse

Introduction

Currently, mental illness affects a large percentage of the population. Mental disorders produce and affect basic psychological processes [1]. They show high prevalence in our society and interfere in the normal life of the individual who suffers. Between 1990 and 2013, cases have increased by almost 50%, from 416 million to 615 million people affected, which means almost 10% of the world's population and amounting to 30% of diseases in the world.

It has been observed that despite a great diversity of treatments and/or methods to counteract them, they continue to rise. In addition, many of the people affected are susceptible to developing other pathologies, being an example of this, the addiction generated after the excessive consumption of these legal drugs, speaking then of dual pathology [2,3]. In recent years, it has been shown that different drugs have shown efficacy in overcoming mental illness [4,5]. However, a continued use of them can cause a loss of self-control, leading to the occurrence of addiction.

Drug addiction is defined as a chronic and recurrent disease that is characterized by the loss of control over the use of substances, the compulsive search for it and the appearance of a negative emotional state when it is not present [6]. On the other hand, it presents with the clinical problem of relapse even after long periods of abstinence without consuming the drug [6], which generates great health, social and legal problems in consumers and in society in general. Epidemiologically, the European Observatory of Drugs and Drug Addiction, 2016 [7] shows very alarming data regarding the consumption of such addictive substances.

Literature Review

Anxiety is one of the disorders that appears in our society with greater prevalence. It can be defined as a state of tension, produced by an anticipation of damage or danger that in the immediate future and sometimes accompanied by a feeling of dysphoria [1]. Anxiety warns us of an imminent danger and allows people to carry out the measures they believe are necessary to combat that danger. That is, it is an adaptive behavior for the individual that allows us to fight or flee from an opponent. Faced with a situation of threat to our survival (for example, seeing a lion running towards us) a whole series of physiological resources are launched in our body to combat this situation.

Our senses are sharpened, our heart beats faster, more glucose reaches our muscles to be able to run, etc. All this is the result of the activation of our sympathetic nervous system that guarantees our survival [8]. However, if this situation of tension and physiological activation is maintained over time, problems begin to appear due to the release of cortisol maintained in our body [8]. Cortisol is a glucocorticoid that can

severely damage our body and even interfere with other biological systems, such as the immune system [9]. It is then when we talk about maladaptive anxiety because it does not allow the person to adapt to the situation and guarantee survival, but otherwise, it hinders the activities of daily life (anxiety before exams, social anxiety ...) (**Table 1**).

Table 1 Distinguishing between pathological and non-pathological anxiety.

Adaptive Anxiety	Pathological Anxiety
Focused attention on the threatening situation	Focus on the response
Increase performance	Performance maintained
Originated by anxiety stimulus	It has no trigger
Adequate adaptive response	Disproportionate response
Concern to certain fields	Massive concern to different fields

The symptomatology is very diverse but can be broadly grouped into sleep problems (insomnia of conciliation, frequent awakenings and feeling of not resting), neurological problems (headaches, vertiginous syndromes and syncope), neurodegenerative (profuse sweating, trembling, tingling, paresthesia, pallor) and urinals (frequent urination, bladder tenesmus) [10]. Although with this, it does not mean that a person with anxiety has to present all the symptoms at the same time or that they manifest themselves equally in all people.

Thus, the dimensions that comprise the concept of anxiety are of various types: physiological dimension (activation of various nerve centers, vascular, respiratory changes ...), cognitive dimension (negative thoughts, risk assessments, low self-esteem ...) and behavioral dimension (defensive behavior, aggressiveness ...).

The origin of anxiety disorders seems to have several causes. On the one hand, personality factors influence (for example, neurotic people are more prone to the appearance of anxious symptoms), but also environmental factors (lifestyle, stressful experiences throughout the life of the individual ...), psychosocial factors (the family environment, the society in which we live ...) or even genetic factors. However, it seems that neurobiological factors (neurotransmission systems and activated anatomical structures) play a fundamental role in the appearance of this disorder.

Thus, changes in neurotransmission and the activation of reciprocal connections between the amygdala and CFO (frontal orbital cortex) appear to be fundamental [11]. In addition, anxious symptoms usually show comorbidity with other types of mental disorders such as psychosomatic disorders or, more commonly, depression. Anxiety and depression with two types of mental disorders that almost always appear together [12].

Thus, the most predominant mental disorder along with anxiety is depression, a mental disorder frequent mainly in industrialized and advanced societies, which is characterized by the absence of positive affectivity, presence of sadness, loss of interest or pleasure (anhedonia) and feeling tired [1].

Every person throughout their life, passes through different times, some will be happy and in other cases we will be invaded by feelings of sadness, negative, which are usually of a temporary nature and vanish throughout the days. However, this does not mean that we have depression, since this pathology goes further, affecting our daily life and becoming necessary the help of specialists and treatment to overcome it.

As in the case of anxiety, depressive symptomatology is very variable, and not all people coincide in the symptoms, nor in the intensity itself and even the duration varies from one individual to another.

The symptoms presented by the patients who suffer from it are both emotional (feelings of guilt, uselessness, lack of expectations and also a low state of mind) as well as physical symptoms (muscular pains, digestive problems, cramps, changes in appetite, sleep disturbances, general discomfort, restlessness, lack of energy) and behavioral (not wanting to leave home, from bed, not wanting to talk, not eating or overeating ...). Likewise, cognitive symptoms may appear, attention loss, negative thoughts, pessimism or lack of memory, persistent feeling of tiredness, difficulty in making decisions.

As we have previously commented, it is a multidimensional disorder and it seems that in its appearance neurotransmission systems also play a very decisive role [13]. Hence, we can distinguish between exogenous depressions (due to an external cause such as the death of a relative or depressions associated with other diseases, such as cancer) and endogenous depressions (without apparent external cause).

At the biological level, the neurochemical hypothesis of depression postulates on the one hand a deficiency of monoaminergic neurotransmitters, mainly (noradrenaline and serotonin) NA and 5-HT, and also (dopamine) DA. On the other hand, it is postulated that there is an alteration of receptors in the neuron that has to capture these neurotransmitters. Among all the neurotransmitters involved, 5-HT mainly stands out, involved in motivation and it seems that people with depression do not have enough synthesis, release or re-absorption of it, so their motivation is lower than the rest of people.

Hence, the most well-known antidepressants are called selective serotonin reuptake inhibitors (SSRIs) because they act by blocking the reuptake of this neurotransmitter and, therefore, serotonin acts longer in the synaptic space [14]. Among the most well-known SSRIs in the market, fluoxetine with its name is more commonly known commercially as Prozac [15]. The problem with antidepressants is that they are

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drugs with many side effects in consumers as well as producing dependence.

Table 2 Differential diagnosis anxiety vs. depression.

Anxiety	Depression
Originated by a response of our body and mind to anticipated situations	Originated by our body in front of traumatic situations
Interpretation of a threat	Interpretation of a failure or loss
Most prominent feeling is fear	The most outstanding feeling is sadness
There is no loss of pleasure	You find loss of pleasure

Neurobiological relationship between addiction and mental disorders (Anxiety and depression)

Currently, thousands of people are addicted to different substances [7]. Given that drug use has been a topic of great interest, the psychosocial relationship found in drug use has been studied and what factors increase and decrease it. The presence of anxiety and depression has been one of the factors that increase this consumption of substances, given that they contribute a simple and quick way to alleviate the symptoms produced by these diseases, and produce gratifying sensations for people [16]. However, different studies have shown that these anxiolytic and antidepressant drugs could also show efficacy in the treatment of addiction to different substances, probably due to the similar mechanism of neurobiological action between mental disorders and substance addiction (**Table 2**).

For this, we show below a compilation of the most recent articles that explain this relationship.

Anxiolytics and relationship with addiction

As we have already commented throughout the chapter, it is known that anxiolytics cause dependence [17]. However, the relationship between the use of anxiolytics together with other types of illegal substances or the role of these types of drugs in the treatment of addiction to substances of abuse can be studied in more depth. That is why, below, we present the main and most recent scientific articles found in relation to these variables showing the main results found.

Scientific papers have shown that a long-term treatment with BZD can be a critical problem [18]. If we look at the epidemiological characteristics of this consumption, the data suggest that women are more likely to consume BZD in the long term and that among the most consumed BZDs are lorazepam, alprazolam and lormetazepam, although the consumption of similar BZD is also very popular. Thus, Shukla et al. [19] conducted a study between 2007-2014 to assess the dependence of patients in South India. They reviewed a sample in 170 admitted patients who reported benzodiazepine (BZD) use. The results showed that alprazolam (50.6%), nitrazepam (23.5%), and zolpidem (11.2%) were the drugs of greatest abuse. Among these, alcohol dependence was present in 37 subjects, and opioid consumption in 41. In contrast, only 28 patients showed sedative dependence without any other disorder. However, the psychiatric illness was only diagnosed in 67 patients.

For their part, Stein et al. [20] conducted a study with 438 people on opioid detoxification treatment, of which 176 were positive in the use of benzodiazepines during the last month, showing that anxiety was the main reason common for which patients consumed the BZD. In this case, the results showed that the most used BZD was alprazolam (52%). Similar results were shown by Babakhanian et al. [21] in a study of 114 male and female opioid users with an average age of 36.5 years. The study showed that the use of BZD in opioid dependent patients is very common, being the most used alprazolam (100%), chlordiazepoxide (96.5%), clonazepam (94.7%) and diazepam (86.8%). Among the main reasons for the consumption of these substances were depression (77%), anxiety (72.8%), followed by problems in the control of anger (44.7%). In conclusion, the authors stated that the non-medical abuse of the BZD is a very common problem in patients addicted to opiates.

In relation, with the power of certain benzodiazepines to reverse some of the effects caused by the consumption of certain substances of abuse, Spence et al. [22] conducted a study in rodents on aprazolam and oxazepam, showing the effects of the discriminative stimulus of methamphetamine and cocaine. The result was that aprazolam at high doses increases the subjective effects of lower doses of methamphetamine, but has no effect on cocaine discrimination, showing that alprazolam differentially affects the effects of discriminative stimulation of methamphetamine and cocaine.

Antidepressants and relationship with addiction

There are serious medical, psychiatric and socioeconomic consequences that are occurring worldwide due to the consumption of stimulants [23,24]. So far, no effective pharmacological treatment has been established, but it seems that mirtazapine (antidepressant) has proven to be a promising drug to treat addiction to stimulants [25]. In relation to this idea, Salazar-Juárez et al. [26] demonstrated that mirtazapine modifies various alterations induced by drug abuse. The results obtained in his study show that a daily dose of mirtazapine for 30 days induces the attenuation of cocaine-

dependent locomotor activity as well as induction, arguing that this antidepressant could be used as an effective therapy for cocaine abuse.

In addition, mirtazapine seems to be effective also in the treatment of alcohol dependence, due to its action in the serotoninergic system [27]. One study treated adult men who regularly consumed alcohol with placebo while another group was treated with mirtazapine, both during the same time period, demonstrating that men treated with mirtazapine benefited from the treatment compared to others.

On the other hand, it has been shown that chronic treatment with Fluoxetine causes alterations in 5HT2A receptors and although it may not be useful for the treatment of continuous abuse of cocaine, it may be effective in the prevention of relapses [28].

However, despite the fact that certain antidepressants can show effective results for the treatment of certain substances of abuse, at present there is a high prescription rate of antidepressants within the population, an alarming fact being the prescribing of these drugs among young people, with a nervous system still immature [29]. In this sense, Iñiguez et al. [30] studied the possible long-term causes of this consumption by performing work on male rats during the adolescent and adult stages. The results showed that treatment with Fluoxetine for 15 consecutive days makes rodents treated during adolescence with this drug more sensitive to the gratifying properties of cocaine in later stages, so the premature treatment of this antidepressant would have a negative effect of health for consumers.

Conclusion

Addictions pose a challenge in daily clinical practice, so more studies are needed to allow us to know new aspects of this pathology, to be able to carry out an effective and adequate treatment. The problem is the difficulty both in identifying patients and in exercising control over them. It is true that withdrawal syndrome of many substances causes symptoms of anxiety and depression and treatments of this type could be effective in many cases, but we must not forget that these drugs belong to a group of risk drugs that can also cause a high degree of dependency. However, anxiolytic and antidepressant drugs can both prevent addiction to other substances of abuse although some results are confusing.

Thus, a single study shows that treatment with alprazolam is convenient in amphetamine-consuming patients, whereas in cocaine-using patients it is ineffective, contrary to what most proposes with fluoxetine [26]. On the other hand, fluoxetine has been studied for the treatment of a possible addiction to both stimulating substances of the CNS (the case of cocaine), and depressant substances although in smaller quantities (the case of alcohol).

While some studies support the treatment of fluoxetine to cope with cocaine dependence, others are positioned in a totally opposite position and it is argued that currently there is no clinical evidence that fluoxetine can be considered an effective treatment for cocaine addiction.

In any case, the objective of this paper is to give visibility to the serious problem of both the addiction to legal drugs in industrialized societies and the addiction to substances of abuse, showing that perhaps some anxiolytic and antidepressant drugs can be effective to reverse some of the effects produced by drugs. The final objective pursued with the exposure of these data is to be able to advance in the knowledge of mental illnesses such as anxiety, depression and addiction in order to find possible effective pharmacological therapies and to know the neurobiological mechanisms involved in them.

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