

Review Article

Neurochemical Aspects in Dual Pathology

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Abstract: There are a lot of brain circuits, neurotransmitters and substances involved in the etiopathogenesis of Dual Disorders. In the last ten years many researchers have tried to explain which of the brain mechanism could play a role in this disorder. In this revision, we make a review of the most robust and conclusive papers about the neurochemical mechanism with the objective to understand the disease and help to discriminate the best psychopharmacological treatment.

Keywords: Brain System, Neurotransmitters, Etiopathogenesis

1. Introduction

The comorbidity between psychosis and disorders due to substance abuse (TUS) is one of the most relevant disorder in the dual pathology spectrum. The reason is due to its clinical severity and its negative social and health implications. Individuals with serious mental illnesses are more likely to have substance-related problems than the people without mental health problems. They also face more difficult recovery trajectories as they cope with dual disorders. Nevertheless, it is almost known about individuals' perspectives regarding their dual recovery experiences.

Dual diagnosis is not an official term recognized in the DSM. However, the term has become synonymous with a specific type of co-morbidity diagnosis. This causes greater difficulty in treatment and difficulties in the maintenance of disease.

This disease is composed on one side by the mental disorder and the problem of drug addiction on the other side. It represents a cross association, where the deteriorating psychiatric condition endangers the situation of consumer protection. It produces a progressive erosion of the patient's psychological stability.

The substance abuse disorders are among the most common psychiatric problems that the clinician must face. It causes a greater number of psychiatric hospitalizations, it increases

violent and suicidal behavior, and it produces higher costs and poorer outcomes in treatment (Hoff & Rosenheck, 1999).

The prevalence of this disease is high; In Mental Health Services is estimated that 44% have alcohol use disorders or dual drug. In Care Centers specialized in drug addicts over 75% have dual mental disorders (Weaver et al, 2003).

It is important to describe that there are high percentages of undetected episodes (Weaver et al, 2003). Other authors (Rodríguez-Jiménez et al, 2008) noted that in acute psychiatric units, up to 25% can be considered dual patients, predominantly consumption of alcohol, cannabis and cocaine.

People of all ages suffer the harmful consequences of drug abuse and addiction.

- Babies exposed to drugs in the womb may be born premature and underweight. This exposure can slow the child's intellectual development and affect behavior later in his life.
- Adolescents who abuse drugs often act out, do poorly academically, and drop out of school. They are at risk for unplanned pregnancies, violence, and infectious diseases.
- Adults who abuse drugs often present some cognitive alterations like thinking clearly, remembering, and paying attention. They often develop poor social behaviors as a result of their drug abuse, and their work performance and personal relationships suffer.

- Parents' drug abuse often means chaotic, stress-filled homes, as well as child abuse and neglect. Such conditions harm the wellbeing and development of children in the home and may set the stage for drug abuse in the next generation.

We should distinguish dual pathology from substance induced disorders. The identification of substance-induced versus independent psychiatric symptoms or disorders has important treatment implications and often constitutes a challenge in daily clinical practice. Similar patterns of comorbidity and risk factors in individuals with substance induced disorder and those with independent non-substance induced psychiatric symptoms suggest the two conditions may share underlying etiologic factors (Blanco *et al.*, 2012). Addictive drugs or exposure to gambling will not lead to addictive behaviors or drug dependence in most individuals but only in vulnerable ones.

2. Discussion

2.1. Etiologic Models of Comorbidity

- Theory of self-medication: The drugs relieve some symptoms. Drug use is defined as a secondary factor and the choice of drug is not casual.
- Model biological dysfunction: in according to the neurotransmitter more involvement, it predisposes some specific psychiatric diseases.
- Model socialization explained by a better social acceptance, less stigma and better social function with consumption.
- Mixed model: the initiation of the drug is performed by environmental factors but maintenance is caused by the reinforcing ability of the drug.

2.2. Neurobiological Background

Some research suggest that Addiction may be caused by long-term changes in brain function as a result of drug aggression (repeated drug use), by genetic predisposition and by environmental facts associated with drug use (learning term). Therefore, to understand the basis of addiction also requires understanding the physiological mechanisms of neuroplasticity and an approximation on the basis of the behavior on the psychobiology of drug addiction.

The appearance of addictive behavior is caused by the activation of a number of neuronal groups. There are three regions of the brain which had been proposed responsible for behavioral activation: the amygdala, prefrontal cortex and nucleus accumbens.

The nucleus accumbens was identified with motivation by reward (important in addictive behavior) and the prefrontal cortex is responsible for determining the intensity of the behavioral response. Some recent studies (Nestler, 2005) reveal the existence of a neuronal circuit with glutamatergic interconnections between the amygdala, the nucleus accumbens and prefrontal cortex with dopamine relations to the three regions. It seems that the action of drugs on the

mechanisms involved causes the sensitization of neurons located in the area of reinforcing brain, it causes an abnormal activation that it involves a frequent search of consumption drugs and it reproduce the behavior that defines the addiction. There are persistent changes in presynaptic plasticity in prefrontal cortex and nucleus accumbens. This induces long term potentiation observed in excitatory psinapsis in the mesolimbic dopamine system, especially in the ventral tegmental area (VTA). The changes in plasticity of the mesolimbic dopamine pathways induce by drugs are associated with addictive learning because it produces alterations in discharge of dopaminergic neurons. Therefore, the most sensitive system to electrical stimulation of the neuronal circuitry of the reward is the midbrain dopaminergic system.

One of the most important neurotransmitters in this circuit is the dopamine. The function is to produce a pleasurable sensation if a certain conduct is made. If we do this behavior which produces pleasure, this increases the probability that behavior is repeated because the patient feels a positive sensation. Thus, this behavior is becoming more common in the repertoire of the individual person. In short, the increase of dopamine is associated with behaviors where it is very important of search new items.

The dopamine modulates neuronal activity through two families of receptors: D1 and D2. The chronic drug use causes a reduction of dopamine D2 receptor subtype. The reduction of dopamine D2 receptor subtype can contribute to the maintenance of addictive behavior and occurs in all drugs including nicotine. With chronic use it is generated a dopaminergic dysfunction (receptors decreased D2) that becomes progressively more elevated. Although the subject repeat again and again this behavior to try to achieve the same pleasurable feelings that he had when he began a consumption, it could not get them.

In neuroimaging and especially with the use of technology PET (positron emission tomography) we can observe the decrease of dopamine D2 receptors in the striatum in addicted individuals which is correlated with dopamine hypofunction.

The polymorphism in the DRD2 gene (with TaqIA1 allele) is associated with:

- Reward deficiency syndrome: it determines an alteration in the mesolimbic reward system which is related with the craving of reward.

- Low capacity of Dopaminergic stimulation: TaqIA1 allele determines the reduced availability of DRD2 postsynaptic in the reward system. The need to find sources of intense stimulation (impulsive and addictive behavior) to get the right level of Dopaminergic stimulation (Cleck y Blendy, 2008).

In preclinical studies where adenovirus carrying the gene encoding dopamine receptors (D2) within Nac rats is inoculated. It's possible to observe an over-expression of DR D2 reduce alcohol self-administration in rats. Rats with levels of DR lower striatal D2 have high levels of impulsivity. Therefore this consumption increases the compulsiveness.

The impulsivity is one of its components and predisposing to addiction (Volkov and Fowler, 2000). The behavioral

response to drugs for increased dopamine produces three effects:

1. To acquire a major incentive (pleasure)
2. More attention to drug-related stimuli, such as odor, certain visual signs, etc., producing similar statements which you feel in your consumptions. This activates the dopaminergic mesolimbic circuit would act to facilitate the resumption of consumption
3. To improve craving of the drug and to promote to binge consumption which helps the relapse in the search of behavior (Cecilio Alamo, 2004)

The chronic use of drugs makes disturbances in the brain function, in control of impulses and assessment of the judgments and risks. When a person becomes addicted (chronic administration), the irrepensible urge which experiencing to get drugs and the relapse are related with a change in the excitatory transmission. In this moment glutamatergic pathways play an essential role with glutamate release in the nucleus accumbens. In the first exposure in most likely drugs, preclinical data from animal research suggest that it produces an increase in dopamine release. However, with chronic use this release is much smaller or could not occur.

Model of Volkow, Fowler and Wang

It's necessary to find models to know exactly brain function. Several models have been proposed, one of the most recognized it is the model of Brain Circuits proposed by Volkow, Fowler and Wang. It is defined by these characteristics:

- 1- Reward circuits (Stimulation): amygdala, ventral striatum and ventral cingulate. There is significance in environmental stimuli. It is related with dopamine and endogenous opioids
- 2- Motivation circuits (Motivation): orbitofrontal and anterior cingulate cortex. There is a behavioral response with an environmental stimulus, relative to dopamine.
- 3- Inhibition circuits (Control): lateral orbitofrontal cortex, anterior cingulate and dorsolateral prefrontal cortex. They are related with the blockade of misbehavior even if they are desired.
- 4- Memory circuits (Memory): nucleus accumbens, amygdala, caudate and putamen and hypothalamus. Where repetitive behavior patterns are formed

Two situations are described, noting different activation pathways:

a) In a situation of chronic consumption with an environmental stimulus related to the addictive substance. The reward circuits are activated plenty. Furthermore automatic behavior patterns (generated in the memory circuits) are activated. This creates a strong motivation to take the substance. Inhibition circuits (weakened by consumption) can not hinder such reasons which produce a high risk of consumption.

b) In a situation of chronic consumption with an environmental stimulus unrelated to the addictive substance. Reward circuits are nearly activated because they are hyperstimulated by consumption. Therefore, there is a low

motivation to perform behaviors designed to bring the natural reinforcement. The control circuits are altered by chronic and they are unable to mobilize resources to avoid consumption. Thus, natural environmental stimuli lose the ability of increase the reinforcement, and indirectly, the desire for consumption.

2.3. Animal Models of Addiction

Another ways to try to understand the mechanism of addiction is the use of animals models. In preclinical research are working with the assumption that if the drugs reduce drug abuse use in animals, they may have therapeutic potential in humans.

Humans and animals are self-administered the same kinds of drugs, and it is this self-administration by the animal of a drug which is defined as a positive reinforcer. Not all drugs of abuse have the same ability to generate dependency, and even some may say that just generate it. Hallucinogens no psychostimulant, for example, rarely cause addictive behavior. At the other end, heroin or cocaine are extremely powerful to lead to these behaviors.

Animal models using drug self-administration procedures and conditioned place preference are most commonly used to study the reinforcing effects of drugs. For example, this animals maintain behaviors such as pressing levers or go to certain places. If these behaviors lead to a presentation of the drug, which rather reminds us the search behavior of the drug in humans.

Study self-administration in animals allows us to establish clear links between preclinical findings and substance abuse in humans. It can be used to evaluate drugs that may be useful as antagonists or substitute agents, or produce aversive effects capable of reducing consumption. Generally models self-administration has been found to have a very high predictive value assessing susceptibility to substance abuse in humans. Therefore, treatments can be reduce drug self-administration in laboratory animals, they should reduce the consumption of drugs in humans (Robert N et al., 2007). Drugs can be assessed in the different phases of self-administration (procurement, maintenance, termination and reinstatement) and you can check whether a particular drug is especially useful during some of these stages. These experimental models help us to discover drugs that could be beneficial to treat consumption. Besides, they help us to study the factors involved and define the neuroanatomical and neurochemical substrates.

2.4. Role of Neurotransmitter Systems in Addictions

The drugs interact with neurochemical processes which mimic, increase or antagonize the function of endogenous neurotransmitter systems. Therefore it would be action on each of these neurotransmitter systems where the different substances of abuse exert their action. They will be the new potential targets of treatments.

Neurotransmitter systems involved are:

- Dopaminergic system
- Opioid system

- Cannabinoid system
- Serotonergic system
- Cholinergic system
- GABA system

Table 1. Neurotransmitters on which exert their action different drugs.

Location	Neurotransmitter	Drug
N. accumbens	Dopamine	Cocaine and amphetamines
Amygdala	Serotonin	
Ventral tegmental area	Dopamine	Opiates
N. accumbens	Opioid peptides	
Ventral tegmental area	Dopamine	Nicotine
N. accumbens	Opioid peptides	
Amygdala		
Ventral tegmental area	Dopamine	THC
	Opioid peptides	
Ventral tegmental area	Dopamine	
N. accumbens	Opioid peptides	Alcohol
Amygdala	Serotonin, GABA, glutamate	

Source: Modified: San, L. 2004

The dopaminergic and serotonergic system has the greater role (they mediate the final action of different drugs). It has been shown that the selective destruction of dopaminergic neurons mesolimbocortical system eliminates self-administration. Numerous drugs including ethanol, THC, nicotine, cocaine and amphetamines are increased extracellular dopamine concentration in the nucleus accumbens. So the dopamine receptor antagonist drugs reduce the reinforcing properties and increase self-administration (eg. Classical neuroleptics). The opposite action is performed by the opioid receptor agonists "mu" or "delta", which increases dopamine release in the nucleus accumbens and it gives them their reinforcing property.

In the action of serotonin system it's possible to see how the denervation of brain serotonergic pathways increases self-administration. And if we manage SSRI drugs or serotonin (5-HT) directly into the nucleus accumbens, this decreases self-administration. Hypofunction of 5-HT is related with impulsivity, craving, and depression during the abstinence. Some drugs, as cocaine, amphetamine or ethanol increase serotonergic neurotransmission in the mesolimbocortical area.

Therefore, we may understand addiction as a brain disease, which pathologically altered regulation of cell functions and neural circuits. They are involved some neurotransmitters such as serotonin, norepinephrine, dopamine and GABA (gamma-amino-butyric acid), but depends on the drug. In general, all drugs of abuse affect the neurotransmitter dopamine in one way or another because normally neurotransmitters modulate each other.

-Psychostimulants promote the release of dopamine in the nucleus accumbens through projections sent from the ventral tegmental area. Opioids act on mu opioid receptor subtype inhibiting GABAergic interneurons in the ventral tegmental area. It results in a stimulation of dopaminergic neurons of this area that project to the nucleus accumbens.

-Alcohol exerts its effects through interaction with various neurotransmitter systems among which, in addition to

dopamine, GABA, glutamate and the endogenous opioid system.

-Nicotine exerts its action by nicotinic acetylcholine receptors, which appear to be regulated by several neurotransmitter systems, including dopamine, serotonin and opioids.

-Cannabinoids primarily exert their reinforcing action on CB1 receptors ATV, basal ganglia, hippocampus, cortex and cerebellum. The endocannabinoid system also has anatomical and functional connections with the opioid and the dopaminergic system mainly.

- Synthetic drugs also promote the release of serotonin, and dopamine in the nucleus accumbens and other structures from nerve terminals coming from the ventral tegmental area.

2.5. Diagnosis

The reliable and valid identification of comorbid psychiatric diagnoses is very problematic. There are no biological markers for detection and the diagnostic criteria used are low specific. Some drugs can mimic other mental disorders which increase the difficulty of diagnosis. Moreover, some patients often deny the addiction and the professional can see a higher psychiatric symptoms caused by toxic effects of drugs, and can be confusing and delaying the diagnosis.

Despite the high rates of comorbidity, the fundamental problem of a dual diagnosis disorder is the tendency to not diagnose it, with the consequences this may have in the face of suitable treatment. Besides, the symptoms of substance use disorder and mental disorder constantly fluctuate in frequency and intensity. It's necessary to have a longitudinal view of the course of a dual disorder with a flexible and comprehensive approach, to use the therapeutic resources that we are considered appropriate in each time and to regard the therapeutic aspects of addiction and the aspects of mental disorder.

To improve the diagnosis, we first should establish the relationship between psychopathology and drug abuse. For this, the use of biomarkers appears as a very useful possibility, it's necessary to dispose of information from family members and make a good medical examination. It is also important to distinguish between drug-induced symptoms with symptoms are not related by them. At the end, we must establish the chronology of symptoms, identify family and personal history and we note after the withdrawal drug the symptoms not go away.

2.6. Patient Characteristics

These patients are at least three of the four difficulties:

1- The symptoms and signs of the patient can have a direct impact on the interview process and induce the patient to distort information.

2- The patient may suffer cognitive impairment, which along with his lack of insight cover its true condition.

3- The patient can be deceive intentionally about essential information.

In addition, such patients present many clinical problems

for the management, treatment and overshadow the prognosis. The earlier onset of mental illness, lower compliance and refractory to treatment, and higher rates of relapse and higher rates of hospitalization. They exhibit more aggressive behaviour, with increased legal problems and in the community are most vulnerable.

All these features indicate that the Severe Dual Pathology are major risk factors to produce a worse outcome. The most important items are: the presence of relevant disabilities, to be refractory to antipsychotics, the comorbidity and the personality disorders associated (Ochoa E, 2001).

2.7. Consequences in the Clinic

They have a more torpid course, especially related with discontinuations treatment and with most ineffective effects of the drugs. There are more need for going to the hospital and this increases the spending. It is more frequency of violence when they are in the hospital. The delay in diagnosis causes contradictions between professionals about the technical strategies of therapeutic approach (Kessle et al., 2003).

2.8. Partnership with Psychotic Disorders

There are multiple data reveal about schizophrenia the existence of a mesolimbic dopaminergic hyperfunction relates to the positive symptoms of the disease (delusions, hallucinations, aggressiveness, verbiage, etc.). It is known that this pathway enhancing agents such as psychostimulants, provoke psychotic symptoms, sometimes indistinguishable from schizophrenia. The blocking agents, such as antipsychotics, improve positive symptoms. Therefore it appears to be a neurobiological link between substance abuse and schizophrenia which its base is the "mesolimbic dopaminergic hyperfunction."

The relationship between schizophrenia and addiction is not casual (Khantzian, 1985; Meyer, 1986; Dixon et al., 1991; Perez Casas, 1995). It could be reduced to two explanatory models:

- Vulnerability model: dependence as causal and predisposing factor for psychiatric disorders (Westermeyer 1992; Arias 1999). It has been more family history of schizophrenia in patients with acute psychosis consuming THC (McGuire et al., 1995). More psychotic experiences after consuming THC in patients with more probability of psychosis. (Verdoux et al., 2003; Henquet et al., 2005). There are a high sensitivity in patients with schizophrenia cognitive impairment induced by THC (D'Souza et al., 2005).

Cocaine addicts have eleven times higher risk of mental disorder. Between 53-68% have experienced any psychotic symptoms or transient episode of paranoia in relation to consumption (Rigter y cols., 2004). The cocaine modifies the

clinical presentation of schizophrenia: depressive symptoms, paranoid subtype predominates and motor disturbances.

Stimulant users have more than seven times risk of psychotic experiences and psychosis especially the patients with vulnerability (Tien and Anthony 1990). This can become true psychosis later (Sterling et al. 1994)

- Self-medication hypothesis: individuals with mental illnesses can begin by trial and error, to use and abuse of substances as self-medication. Thus they attempt to alleviate the symptoms of the disease, which they produce a greater risk like the addiction. Around a third of these, consumption can become an addictive disorder. Comorbidity is greater when there are criteria for dependence.

The dual diagnosis is close to the model of genetic and biological vulnerability, where neurobiological systems in abnormal functional status predisposes different psychopathological phenotypes. This status produces changes which make the most pleasant substances for this profile individuals. These alterations, genetically determined, are corrected by use of substances. Schizophrenia patients may have genetic load for both disorders and certain drug in these types of patients precipitate psychosis.

Psychopathology of psychotic disorders may be a risk factor for addiction. Some drugs such as opiates themselves have antipsychotic activity (it can delay the diagnosis). In the case of cannabidiol have atypical antipsychotic profile and it may attenuate mimetic psychosis and anxiogenic effects of 9-THC. Probably the drug intends to offset neurobiological deficits of schizophrenia.

The pattern of consumption is done based on the symptoms, so the choice of the substance is not random. (Table 2)

Table 2. Patterns of drug use in psychotic patients.

Drugs	Estimated prevalence (%)
Cocaine	22-30
Amphetamines	10-65
Nicotine	90
Caffeine	90
Alcohol	20-60
Cannabis	12-42
Opiates	4-12

It is observed more frequent consumption of alcohol, cannabis and stimulant. It is usual intake two or three drugs at the same time.

There are differences in patients diagnosed with schizophrenia with or without substance use disorders (SUD). Onset of symptoms usually precedes average about two years of the onset of an addiction. (P Tender, 2000). 33% of patients, substance abuse is before the first psychotic episode. (Lambert M, 2005). Other differences are listed in Table 3.

Table 3. Clinical differences between Schizophrenia and Dual diagnosis.

	SCHIZOPHRENIA	SCHIZOPHRENIA AND SUD
Age of onset	Higher	Minor
Symptomatology	Positive and negative symptoms	More positive and less negative symptoms
Hospitalizations	Less	More and longer lasting (revolving door phenomenon)
Risk of aggressive behavior	Greater than general population	Much higher than the general population
Long-term prognosis	Variable	Worse when alcohol consumption is associated

Assessment of psychosis with comorbid substance abuse should be made based on the NICE guideline (2011) as follows:

- Recognize psychosis in patients with addictive disorder
- Building a therapeutic relationship.
- Work motivation.
- Primary care: referrals to specialists
- Mental Health: Do not exclude the treatment of patients by the SUD
- Network Drugs: Joint work with Mental Health
- Since the revenue plan further coordination.

3. Conclusions

A long-term drug use leads to a change of behavior based on the dopamine which changes in glutamate during development of addiction. Drug treatments that prevent glutamate release also prevent drug-seeking (antagonists glutamate receptors). So the pharmacological agents which regulate the prefrontal glutamatergic impulse to the nucleus accumbens may improve the regulation of excessive motivational importance to stimuli that predict the drug availability, and the diminished ability of individuals addicted to inhibit consumption. These are fundamental characteristics of the direct terminal and determining addiction relapse.

The final assessment in relation to the specific treatment plan is decided with reference to the results of recent research, clinical experience and patient preferences to propose interventions that have evidence of effectiveness. We must consider the parameters of action in health care are related with scientific advances and the development of technology. At the same time there are changes in the profile of addicts who seeking treatment for drug addiction in care units (new consumption, entry age, educational level... etc.). For these reasons it is necessary the constant updating to know and manage the new therapeutic strategies.

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