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Drug Addiction

Edited by Fang Zhao and Meng Li

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Meet the editors

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Contents

Preface

This edited volume is a collection of reviewed and relevant research chapters concerning the developments within the drug addiction field of study. The book includes scholarly contributions by various authors and is edited by a group of experts pertinent to the subject field. Each contribution comes as a separate chapter complete in itself but directly related to the book's topics and objectives.

Chapter 1 is concerned with deep brain stimulation (DBS) in treatment-refractory addiction. Surgical treatment for addiction has been proposed after the success of DBS for the treatment of neurological movement disorders such as Parkinson's disease. In the field of psychiatric diseases, DBS has been used for obsessive compulsive disorder and treatment-resistant depression. The role in addiction has been proposed only recently.

Chapter 2 studies the effects of alcohol on brain development. Approximately 3.3 million deaths worldwide occur every year due to harmful use of alcohol. This represents 5.9% of all deaths. Ethanol metabolites production and their post-translation modification are one of the proposed mechanisms that lead to neuronal toxicity.

Chapter 3 focuses on the relationship between bereavement and addiction, specifically among those patients who have a diagnosis of substance use disorder. Although bereavement research has advanced greatly in the recent years, there are few studies on bereavement among the drug-dependent population.

Chapter 4 overviews nursing care for persons with drug addiction. Persons with drug addiction exhibit symptoms that affect the central nervous system, which lead to both positive and negative symptoms. Drug addiction is a significant problem and needs more treatment and care from multidisciplinary treatment teams.

Chapter 5 deals with molecular-cellular targets of the pathogenetic action of ethanol in the human brain in ontogenesis and targeted therapy aimed at correcting the effect of pathogenic factors.

Chapter 6 investigates emotions and characters of Internet abusers using psychophysiological signals. Because of the Internet and Internet-enabled devices are ubiquitous, the number of Internet users has rapidly increased. Internet addiction is also a fast-growing, serious, and unavoidable problem around the world.

Chapter 7 offers an insight into methadone treatment for heroin dependence. In substitution therapy for the treatment of heroin addiction, methadone is the synthetic opioid agonist of first choice. The results obtained by clinical, laboratory, and psychological complex evaluations in a correlative approach are essential not only in both initiating the methadone treatment and monitoring the detox period but also in the supervision of methadone maintenance treatment.

The target audience of this edited volume comprises scholars and specialists in the field.

Chapter 1

Deep Brain Stimulation in Treatment-Refractory Addiction

Angelo Lavano, Giusy Guzzi, Attilio Della Torre, Donatella Gabriele, Domenico Chirchiglia, Carmelino Angelo Stroscio and Giorgio Volpentesta

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Abstract

Surgical treatment for addiction has been proposed after the successful efficacy of deep brain stimulation (DBS) for the treatment of neurological movement disorders such as Parkinson's disease (PD). In the field of psychiatric diseases, DBS has been used firstly for obsessive compulsive disorder (OCD) and treatment-resistant depression. The role in addiction has been proposed only recently. The target areas for DBS in treatment-refractory addiction are nucleus accumbens (NAcc), lateral hypothalamus (LH), amigdala, lateral habenula (LHb), dorsal striatum, prefrontal cortex (PFC) and subthalamic nucleus (STN). A well-documented rationale for the choice of the target is required in order to investigate the effectiveness, safety and feasibility. NAcc appears to be the most effective and safe target for DBS followed by STN; PFC is another promising target but needs further exploration to establish its suitability for clinical purposes. DBS is not free of risks, so every patient has to be carefully evaluated and precise ethical standards must be defined in the form of inclusion and exclusion criteria.

Keywords: deep brain stimulation, psychosurgery, addiction, nucleus accumbens, nucleus subthalamicus

1. Introduction

The term "psychosurgery" was coined by Egas Moniz in 1935 to indicate the set of surgical procedures performed on the brain to treat diseases and psychiatric symptoms. The goal is to change the behavioral—obviously pathological—aspects, placing not only clinically but also

ethically complex problems. The entry into the neurosurgical practice of neuromodulation methods has opened up a new scenario due to their flexibility and reversibility in their possible application to the treatment of addiction, such as substance abuse, gambling and internet gaming. The term "addiction" generally indicates a model of persistent redundant behaviors despite adverse medical or psychological results. The common element is recurrent problematic behavior accompanied by a preoccupation with the behavior [1, 2]. It is attested that the development of addiction is not simply the effect of the acute impact of the substance or behavior [3–5] but instead represents a state of imbalance in the reward system [6]. Alterations in prefrontal, limbic and cortical areas seem to be involved in addiction and maladaptive behavior not only in animal models but also in human neuroimaging studies [7–9]. The areas most involved in the manifestations of addiction are represented by the dopaminergic connections between ventral tegmental area (VTA) and nucleus accumbens (NAcc), which modulates learning, memory and repetitive behaviors. Stimulation of NACC in animals has proven to control acquired behaviors as a result of alcohol and cocaine consumption [10–12].

2. Neurobiological mechanism

The development of addiction finds its anatomical and neurobiological bases in the so-called neurocircuitry of reward, and it is important to better understand when and how the reward system is activated [13]. The term "reward" is defined as any event that increases the probability of a response with a positive hedonic component. The ascending meso-cortico-striatal dopamine systems seem to have a key role in the rewarding properties of nearly all drugs of abuse [14]. In humans, positron emission tomography studies have shown that intoxicating doses of alcohol and drugs release dopamine and opioid peptides into the ventral striatum [15, 16], activating low-affinity dopamine D1 receptors, which are necessary for the rewarding effects of drugs [17]. This specific circuitry includes not only dopamine and opioid peptides but also γ-aminobutyric acid (GABA), glutamate, serotonin, acetylcholine and endocannabinoid systems that act at the level of either the ventral tegmental area or nucleus accumbens. Balanced circuits result in proper inhibitory control and decision-making and normal functioning of reward, motivation, stress and memory circuits. These circuits also interact with circuits that are involved in mood regulation, including stress reactivity (which involves the amygdala, hypothalamus and habenula) and interception (which involves the insula and anterior cingulate cortex and contributes to the awareness of negative emotional states). Drugs of abuse usurp executive function circuits, motivational circuits and stress circuits via multiple neurotransmitter-specific neuroplasticity circuits. Key neurotransmitters that are implicated in these neuroadaptations include dopamine, enkephalins, glutamate, γ-aminobutyric acid, norepinephrine, corticotropin-releasing factor (CRF), dynorphin, neuropeptide Y and endocannabinoids.

3. DBS for the treatment of addiction

The use of deep brain stimulation (DBS) for the treatment of addiction was fortuitous, starting from observation in some PD patients the escalation of their intake of dopamine replacement

therapeutics in a manner similar in some ways to addiction, a phenomenon known as dopamine dysregulation syndrome (DDS) [18]. Witjas et al. in 2005 described a reduction of the behavioral disorders as well as addiction to dopaminergic treatment in two PD patients who underwent subthalamic nucleus (STN)-DBS [19]. Subsequently, other studies confirmed the resolution of dopamine dysregulation syndrome following STN-DBS for PD [20–22]. In rat models it was demonstrated that lesions of the STN decrease motivation to take cocaine suggesting that STN-DBS might be a therapeutic option for addiction [23]. In 2007, during a DBS procedure of the nucleus accumbens (NAcc) in a heavy drinker patient with agoraphobia and panic attacks, a rapid reduction of the alcohol intake of the patient was observed [24]. Similarly, three additional patients receiving accumbens DBS for other indications were reported to have spontaneously quit smoking [25].

4. Mechanism of action

The mechanism of action of DBS remains unclear. As to the anatomical organization of the nucleus accumbens, it is divided into two major subregions, the core and shell, which differ from each other both functionally and anatomically. The core receives projections from the anterior cingulate and dorsal prelimbic, while the shell receives projections from the infralimbic and ventral prelimbic cortices [26, 27]. DBS of the accumbens shell or core increased c-Fos immunoreactivity, a measure of neuronal activation in these nuclei. c-Fos study indicates that DBS of the accumbens shell activates the infralimbic cortex, which could have contributed to the DBS-induced activation of the shell [12]. DBS applied to either the accumbens core or shell reduced alcohol consumption [11]. In contrast, DBS of the medial accumbens shell, but not the accumbens core, attenuated cocaine priming-induced reinstatement of drug seeking [12]. Moreover, since enhancing neuronal activity in the nucleus accumbens actually promotes the reinstatement of cocaine seeking [28, 29], DBS-induced inactivation of the nucleus accumbens via depolarization inactivation and/or activation of inhibitory neurons may be responsible for the attenuation of cocaine reinstatement [30–32]. Electrophysiological studies showed that accumbens DBS attenuated the spontaneous activity of cortico-accumbal glutamatergic neurons but also stimulated cortical interneurons, apparently via recurrent inhibition [33]. However, GABA agonist-induced inactivation of the infralimbic cortex attenuated the reinstatement of cocaine seeking induced by a priming injection of cocaine [12], which is consistent with accumbens DBS indirectly activating GABAergic interneurons. These results suggested that DBS of the accumbens shell produced complex effects throughout the circuit in which the shell is embedded. It is generally agreed that cocaine self-administration results in aberrant activity in the cortico-accumbal system and it appears that normalization of this system is one of the main effects of accumbens DBS [34, 35].

5. Targets

The proposed target areas for DBS in treatment-refractory addiction are several but well-documented rationale for the choice of the target is required in order to investigate the effectiveness, safety and feasibility.

5.1. Nucleus accumbens (Nacc)

There is considerable preclinical evidence to support a role for the nucleus accumbens in mediating the motivational effects of conditioned stimuli associated with the drug leading to its anticipation. DBS in the NAcc has been successful in treating the behavioral component in addiction disorders and substance abuse [36, 37]. Ablative surgeries targeted at the NAcc have been used for several years (between 2000 and 2004) in China with mixed results, but a relapse rate of 50% and ethical concerns now limit the use of destructive procedures in the treatment of addiction [38–40]. The limited outcome and the consecutive side effects (poor concentration, poor short-term memory, aconuresis, changes in sexual desire and decreased interest to various degrees) are nevertheless expected considering the preclinical data investigating the role of the nucleus accumbens. However, there is no clear evidence for a specific alteration of the nucleus accumbens in addicted individuals. Despite the reserves considered earlier, few clinical studies are considering application of DBS in the accumbens of addicts and therefore as first indication with successful results as for example on one case of heroin addiction [41, 42]. Clinical data about the efficacy of NAcc stimulation exist in the literature in small case series. In two single case studies, two patients who underwent bilateral NAcc stimulation for heroin addiction experienced abstinence from opioids to the last follow-up, respectively, at 6 years and 6 months [42, 43]. A similar outcome was observed in other two separate cases of patients with chronic, severe alcoholism who were treated with DBS in the NAcc reporting abstinence at 1 year [24, 25, 44]. In a single case of NAcc DBS for obsessive compulsive disorder (OCD), quit smoking was reported [45], but a subsequent analysis of 10 patients who received DBS of the NAcc for OCD, TS, or anxiety found that only three patients achieved nicotine abstinence within 30 months [46]. These case reports show the potential for treatment of substance abuse disorders with DBS of the NAcc, but randomized and blinded studies are lacking. However, DBS of NAcc, as any other basal ganglia targets, can be associated with unpredictable limbic symptoms such as mania and depression [47]. A recent study showed that the DBS of different NAcc subregions had different effects on a natural reward such as the motivation for food intake. Specifically, the stimulation of the lateral shell decreased the motivation to food while the stimulation of the core was without effects [48]. According to some authors, there would be a different response of NAcc neurons to natural rewards with respect to secondary rewards to drug intake even if it was not possible to demonstrate a preferential localization of such neurons in the core or in the shell [49]. The NAcc shell is unlikely to be a good candidate for DBS, considering the empirical evidence for its detrimental effect on general motivation and impulse control [50]. In conclusion, the NAcc DBS seems to be able to exercise a significant control over drug abuse and behavioral components mostly in alcohol and oppiate addictions; therefore, alternative structures have been considered for DBS with limited preclinical empirical or theoretical support.

5.2. Lateral hypothalamus (LH)

The hypothalamic drive control of food-motivated behavior has been extended to drug reward [51]. The lateral portion of the hypothalamus (LH) may be a possible target in the treatment of addiction as it has been demonstrated at this level of important transcriptional modifications in subjects with compulsive drug intake and significant control of alcohol intake following radiofrequency stereotactic lesions of the ventromedial nucleus [52].

The side effects of hypothalamotomy consist of amnesia, vegetative crisis and reduction of libido and sexual desire [41]. The unconventional electrical stimulation of LH in rats while reducing the stimuli that induce the use of cocaine does not change the motivation for its intake [53]. Therefore, electrical stimulation of the posterior hypothalamus seems to have similar effects to the lesion producing a reduction of cocaine intake but preserving the processes of motivation [54]. The lack of effectiveness on motivation and possible severe adverse effects make lateral hypothalamus a target that cannot be used in addiction at the moment.

5.3. Amygdala

Amygdala is involved in the process of evaluating the positivity or negativity of experience and in the formation of connections between experience and other signals becoming the center of emotional memory and learning [55]. In humans, the reduction of amygdala volume has been related to increase in desire for alcohol and cocaine intake and greater tendency to relapse [56], while in rats its functional block leads to increase in compulsivity of cocaine intake and seeking and reduction of its anxiety-producing effect [57, 58]. However, DBS of the amygdala does not find a clinical application in the treatment of addiction at present, even if it has been proposed by some authors [59].

5.4. Lateral habenula (LHb)

The lateral habenula (LHb) is a critical brain structure modulating aversive and rewarding behaviors through the GABAergic and glutaminergic efferent projections to the ventral tegmental area (VTA) by means of the fasciculus retroflexus (FR). The selective degeneration of this bundle in drug abuse led to a possible use of deep brain stimulation for the treatment of this condition. In rats, deep brain stimulation of LHb with low-frequency (10 Hz)-high-frequency alternate stimulation (100 Hz) attenuates cocaine self-administration, extinction training and reinstatement of cocaine seeking while conventional high-frequency stimulation did not have any effect and low-frequency stimulation increases cocaine self-administration [60]. The effect of unconventional LHb DBS on cocaine reinforcement may be due to reduction of the cocaine-induced increase in glutaminergic input to the VTA.

5.5. Dorsal striatum

Recent studies documented that deep brain stimulation of the dorsolateral caudate/putamen significantly attenuates cocaine seeking following chronic cocaine self-administration and withdrawal in rats [61] and also an increase of gray matter in both the ventral and the dorsal striatum in human addicts [62]. The application of DBS in the dorsal striatum may induce undesirable hypokinetic symptoms similar to Parkinson's disease symptoms due to the spread of current to the close motor regions.

5.6. Prefrontal cortex (PFC)

Cingulotomies have been performed for the drug-dependence treatment in order to interrupt obsessional thoughts about drug use. Significant complications have progressively been

documented like impaired motivation, attention and executive functions [55, 56], in addition to very low effectiveness over addictive behaviors. Recent data showed decreased prefrontal activity on fRMN in drug-abuse patients and increased compulsive behavior after DBS of the lateral orbital cortex. The latter effect makes this procedure counterproductive [63].

5.7. Nucleus subthalamicus (STN)

High-frequency stimulation of the subthalamic nucleus (STN) in Parkinsonian patients is reported to induce primarily motor effects but also psychiatric effects. The likely explanation for these effects is the partitioning of the STN into sensorimotor, associative and limbic anatomo-functional territories. The sensorimotor territory (posterolateral) is the target for PD, while the associative-limbic territory (anteromedial) is the target for OCD. STN-DBS has not yet been tested in addicts, but there are clinical observations in PD patients after STN-DBS, reporting craving for sweet food in some cases or decreased addictive behavior toward DAergic treatment [19–22]. To date, there is no report of STN-DBS effects on any form of addiction in OCD patients, but in these patients, the compulsive component of the disease is reduced by the stimulation [64]. STN-DBS may play a role in preventing the loss of control of drug intake in addicts. The interest on STN-DBS in the treatment of addiction is based on clinical reports and preclinical data obtained in rats subjected to either lesion or DBS of STN. The stimulation of this target is able to dissociate various rewards, decreasing the motivation for the drug without diminishing other forms of motivated behaviors. This ability is demonstrated in two original studies. The first study documented the opposite effect of STN-DBS on the motivation for cocaine and for the natural reward; the other study proved that the stimulation of this target reduces motivation for cocaine while increasing motivation for sucrose, emphasizing the potential beneficial effects of STN-DBS for the treatment of cocaine addiction [23, 65]. Moreover, it was demonstrated that lesions of STN decreased incentive motivation (seeking behavior) for cocaine while inducing the opposite effect (facilitating incentive motivation) for food [23, 65–68]. This result suggests that STN-DBS may not be appropriate for all forms of addiction, but this remains to be investigated in other models of alcohol addiction. Therefore, STN represents a potentially effective target for the treatment of addiction that can decrease the desire for some drugs without influencing other motivated behaviors.

6. Conclusion

Ethics in the history of psychosurgery has played a secondary role in experimentation due to the lack of effective medical therapy for mental disorders. The highest ethical standards for the use of DBS should be applied. The great suffering of patients and their poor quality of life, as well as the high social costs, are in favor of the use of this method in patients resistant to pharmacological therapy. Some fundamental ethical problems are mostly extendable to all clinical interventions as well as to neurostimulation procedures in neurological and psychiatric disorders. The reversibility of the method and the potential benefits are important ethical arguments for the use of DBS in addiction. On the other hand, DBS is not free of

risks (hemorrhages, infections, battery life), so every patient has to be carefully evaluated, and precise ethical standards must be defined in the form of inclusion and exclusion criteria. Beyond the negative parabola of psychosurgery, a rational scientific solid, a precise experimental protocol and adherence to a rigid ethical code are key factors to ensure the success of these researches. As to the target, the nucleus accumbens is very promising. We must keep in mind when choosing new optimal neural targets that likely the local and surrounding DBS influences might depend on the stimulated structure and its specific afferents, efferents, cell types, ratio of projection neurons to interneurons and transmitter systems.

Declaration of interests

We declare no competing interests.

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Chapter 2

Effect of Alcohol on Brain Development

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Additional information is available at the end of the chapter

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Abstract

In the world, 3.3 million deaths occur every year due to harmful use of alcohol; this represents 5.9% of all deaths. Ethanol metabolites' production and their post-translation modification are one of the proposed mechanisms that lead to neuronal toxicity. The projected neurochemical changes in chronic alcohol drinkers may be due to an imbalance between excitatory and inhibitory neurotransmitters. Interaction of alcohol with GABA and glutamate receptors (NMDA and AMPA) resulted in diverse adaptive changes in gene expression through neuronal pathways leading to alcohol toxicity. Alcohol consumption in an individual leads to biochemical changes that are correlated with complex inflammatory signaling pathways such as phosphorylation of proteins, synthesis of nitric oxide (NO), NF-kappaB and MAP kinase pathways in certain regions of the brain. Ethanol exposure activates neurons and microglial cells that lead to release of neuroimmune factors like high-mobility group box 1 (HMGB1), toll-like receptor 4 (TLR4) and certain cytokines involved in immune responses leading to neuroimmune signaling in the brain. Epigenetic modification of DNA and histones may lead to neuronal gene expression, thus regulating ethanol toxicity. Researchers attempt to modulate therapies that can help to foil alcohol toxicity and support the development of original neuronal cells that have been injured or degenerated by alcohol exposure.

Keywords: brain, alcohol, epigenetic, alcohol-responsive genes (ARGs), immune responses

1. Introduction

1.1. How alcohol is absorbed into the body?

Some people drink socially and do not get addicted while others do. The ground behind the alcohol drinking is related to psychological, physiological, genetics and social factors.

When people consume alcohol, about 20% is absorbed in the stomach and almost 80% is absorbed in the small intestine. Alcohol absorption is related to the two main factors:

a. concentration of alcohol and

b. heavy meal consumption before drinking. An empty stomach will fasten the alcohol absorption.

Absorbed alcohol enters the blood stream and is carried all through the body. Upon reaching the body, simultaneously the body works to eliminate it. The 10% of alcohol is removed by the kidneys (urine) and lungs (breath). Left-out alcohol is oxidized by the liver, converting alcohol into acetaldehyde first and then further converted to acetic acid.

1.2. Alcohol metabolism and distribution

Alcohol is absorbed in the stomach and intestines through the blood stream and crosses the blood-brain barrier (BBB) after consumption. Alcohol is metabolized through the mitochondrial cytochrome P450 (CYP2E1) and catalase in the liver or the brain. In the brain, alcohol metabolism by CYP2E1 produces acetaldehyde and alcohol is considered to be the only source of acetaldehyde. The rest of the acetaldehyde may go through the brain by an enzyme called alcohol dehydrogenase (ADH) which is found in the liver and helps in conversion of alcohol to acetaldehyde. Target of alcohol is considered to be ADH. Alcohol binds through its hydroxyl (—OH) group and zinc atom on ADH [1]. Disulfiram (antabuse), one of the first approved treatments for alcoholism, showed its mechanism by inhibiting the ADH enzyme. When taken regularly, disulfiram decreases the drinking capacity because of the aversive effects [2].

2. Alcohol and the brain

2.1. How does alcohol act at the neurological level?

Brain chemistry is affected by alcohol through alteration of neurotransmitters. Neurotransmitters are chemical messengers that send out the signals all through the body and control thought processes, behavior and sensation processes. Neurotransmitters are either excitatory (excite brain electrical motion) or inhibitory (decrease brain electrical motion). Alcohol increases the effects of the inhibitory neurotransmitter GABA in the brain. GABA causes the lethargic movements and garbled speech that often occur in alcoholics. At the same time, alcohol inhibits the excitatory neurotransmitter glutamate, which results in a suppression of a similar type of physiological slowdown. In addition, alcohol also increases the amount of chemical dopamine in the brain center, which creates the feeling of pleasure after drinking alcohol. Just after a few drinks, the physical effects of alcohol become perceptible. These effects are linked to blood alcohol concentration (BAC) (**Table 1**). The level of BAC rises when the body takes up alcohol faster than it can release it.

In the brain, various centers have been affected due to alcohol, both upper and lower order. As the BAC increases, more centers of the brain are affected (**Figure 1**) [3]. The order in which brain centers are affected by alcohol consumption is as follows:

1. cerebral cortex
2. limbic system
3. cerebellum
4. hypothalamus and pituitary gland
5. medulla (brain stem)

2.1.1. Long-term effect of alcohol on the brain

Continuous or excessive drinking can lead to undeviating injury, causing the brain to shrivel. This leads to deficiency in fibers that transfers the information between neuronal cells. Excessive alcohol leads to a condition called **Wernicke-Korsakoff syndrome** (deficiency of thiamine) [4]. Alcohol interference leads to this deficiency, as it blocks the way of vitamin B absorption in the body. Symptoms of the Wernicke-Korsakoff syndrome are mental perplexity, lack of fine movements, memory and learning problems.

Euphoria (BAC = 0.03–0.12%)	**Excitement (BAC = 0.09–0.25%)**	**Confusion (BAC = 0.18–0.30%)**	**Stupor (BAC = 0.25–0.4%)**	**Coma (BAC = 0.35–0.50%)**	**Death (BAC more than 0.50%)**
They become more self-assured or brave.	They become lethargic.	They become woozy and may walk unsteadily.	They can barely move at all.	They are unconscious.	The person usually stops breathing and dies.
Their awareness period shortens.	They have a problem in understanding or recalling things (even recent events).	They may be highly emotional, destructive, reserved or overly loving.	They may lapse in and out of consciousness.	Their reflexes are depressed.	
They may look flushed (red).	They do not respond to situations as quickly	They cannot observe clearly.	They cannot respond to stimuli.	They feel cold.	
Their conclusive power is not as good.	Their body movements are uncoordinated.	They are drowsy.	They cannot stand or walk.	Their breathing is slower and shallower.	
They have trouble with fine movements, such as writing.	They start to lose their sense of balance easily.	They have garbled speech.	They may vomit.	Their heart rate may slow.	
	Their vision becomes dim.	They have clumsy movements.		They may die.	
	They may have problems in sensing things (hearing, tasting, emotion, etc.).	They may not feel tenderness as readily as a sober person.			

Table 1. The effect of alcohol exposure on the brain.

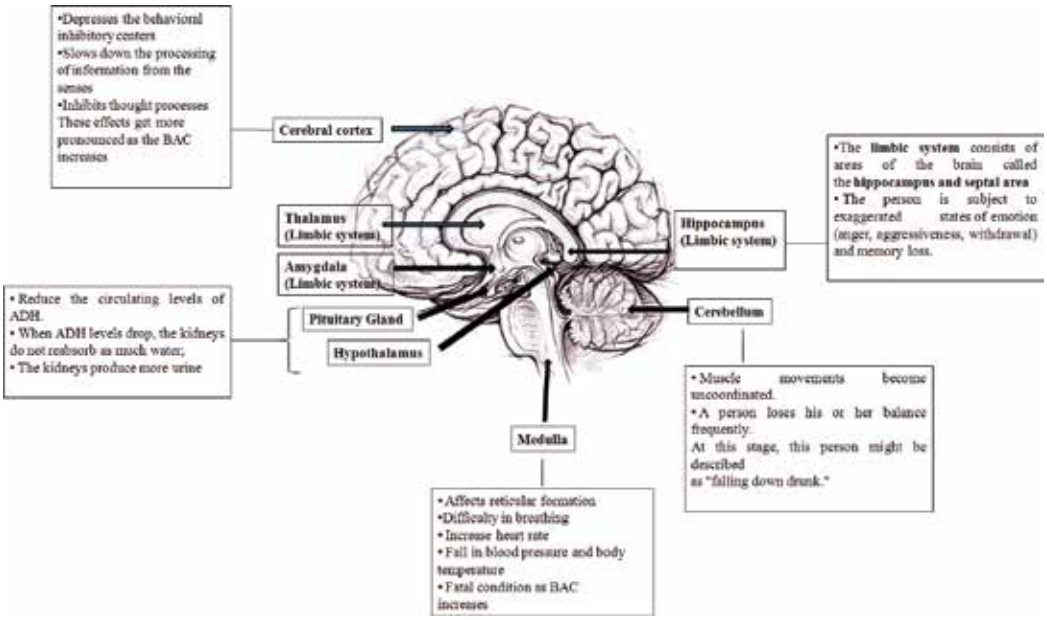

Figure 1. Effect of alcohol on various brain centers.

Heavy or continuous consumption of alcohol can lead to the liver injury. The liver is the chief organ responsible for converting alcohol into nontoxic byproducts and taking them out of the body. Excessive alcohol consumption leads to prolonged liver dysfunction which may also harm the brain, leading to a severe fatal brain disorder known as **hepatic encephalopathy** [5]. Studies have confirmed that at least two toxic substances, **ammonia and manganese,** play an important role in the progress of hepatic encephalopathy.

Treatment—Strategies that have been used to treat or prevent the development of hepatic encephalopathy are as follows:

1. L-ornithine L-aspartate: it lowers the concentration of blood ammonia
2. Artificial livers: it clears patients' harmful toxins present in the blood [6]
3. Liver transplantation [7]

2.1.2. Alcohol and the developing brain

Alcohol consumption during pregnancy can lead to changes in the physical, learning and behavioral effects in the developing brain and it is known as **fetal alcohol syndrome (FAS)** [8].The brains of these people may have less size (i.e., microencephaly) and also a small amount of brain cells (i.e., neurons) that function accurately resulting in long-lasting problems in learning and behavior.

Treatment: Researchers are looking forward to treat or prevent brain damage, such as associated with FAS.

1. In-vivo studies yielded a result showing antioxidant therapy and vitamin E which is used for treating FAS.
2. Treatment with l-octanol (paradoxically an alcohol itself) on developing mouse embryos significantly reduced the rigorousness of alcohol's effects [8].
3. NAP and SAL have the same property as octanol. They both help in protecting nerve cells against a variety of toxins [9].
4. A compound called MK–801 that blocks glutamate that helps with alcohol withdrawal [10].

2.2. Alcohol-induced neurotransmitters and its effect on the neurons

2.2.1. Glutamate

Glutamate receptors include metabotropic glutamate receptor (mGlu), *N*-methyl-D-aspartic acid (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Glutamate exhibits its action on binding to these receptors, resulting in the activation of G-proteins which further leads to amplification of phospholipase C, diacylglycerol (IP3DAG) and calcium-dependent protein kinases [11].

During alcohol drinking, there is a release of excessive glutamate leading to neuronal cell death. This occurs through two pathways:

1. Activation of glutamate receptors causes toxicity [12], resulting into Ca^{+2} ion influx, Na+ influx, nitric oxide (NO) generation and depolarization of mitochondria. This will lead to untenable elevations in ATP, mitochondrial collapse, dendritic beading and depolymerization of microtubule [13].
2. Oxidative toxicity to glutamate [14].

A study has been carried out on 13 abstinent young alcoholics showing a major increase in glutamate to creatine ratio by proton magnetic resonance spectroscopy and magnetic resonance imaging [15]. Furthermore, an alteration in glutamate is linked to altered short memory loss. Immediate administration of alcohol (acute dose) prior to the microdialysis experiment would end up into an increased glutamate release. Earlier studies showed that administration of either 2 or 3 g/kg ethanol to immature rats elicits a decrease or no modification in the release of glutamate into the N-acetyl cysteine (NAC) [16]. Researchers showed that there is a genetic component that probably contributes to the brain injury occurring in "binge drinking" alcoholics [17]. In binge drinking, alcohol models, there are no reports of increased NMDA receptors [18]. In one study, "binge- drinking" individuals with compensated alcoholic cirrhosis, dosing 80 g of ethanol, showed a transient increase in serum nitrates and nitrite resulting in an increase in NO production in certain tissues (liver and brain) [19]. During the period of chronic alcohol toxicity, basal concentration of glutamate seems to be normal in various regions of the brain though blood alcohol levels are high as 2 g/l [20].

During chronic alcohol consumption, NMDA receptor (NMDAR1 and NMDAR2B) levels seem to be increasing in numbers and decreasing in sensitivity [21] in the nucleus [22], the striatum [23] and the hippocampus [20].

2.2.2. Gamma-amino-butyric acid

It is a chief inhibitory neurotransmitter. GABA binds to $GABA_A$ receptors, resulting in hyperpolarization of the cell membrane and inhibition of neural activity. Increased GABA release upon alcohol administration results due to inhibiting its degradation [24]. Alcohol intoxicity and alcohol's anti-anxiety reduce due to decrease in $GABA_A$ receptor activity. Chronic alcohol exposure decreases extrasynaptic GABA-mediated tonic current recorded from neurons in the hippocampus and cortex [25], and this corresponds to a decrease in extrasynaptic $GABA_A$ receptors containing the d subunit in hippocampus [26]. Benzodiazepines (the positive allosteric modulator of $GABA_A$) are considered to be a standard for treating alcohol detoxification owing to their anticonvulsant and anxiolytic pharmacological profile. Improper alcohol interactions have shown some concern about their abuse and dependence responsibility. Therefore, researchers are trying to find out potential anticonvulsant agents as alternatives, that is, gabapentin and topiramate [27, 28].

2.2.3. Dopamine

Transmission of dopamine is linked via two groups of G-protein-linked receptors: D1-like (D1 and D5 receptors) and D2-like (D2, D3 and D4 receptors). These receptors are classified on the basis of adenylatecyclase activity (stimulation or inhibition). Dopamine plays a central role in mediating alcohol compensation through mesocortical and mesolimbic pathways [29]. During chronic alcohol consumption, the release of dopamine depends on the large amount of the alcohol consumption, which gives pleasurable effect of alcohol intake. Reduction in dopamine release is observed during alcohol withdrawal. This ultimately reduces noticeable neuronal cells, leading to dysphoria and depression as a major part in the motivational and behavioral changes [30]. Chronic alcohol drinking has been reported to produce constant neurological changes in transmission of dopamine within the mesoaccumbens reward circuitry, including increased basal extracellular levels of dopamine in the NAC [31], increased firing rate in the ventral tegmental area (VTA) dopamine neurons [32] and changes in the function of dopamine receptor [33]. In comparison, withdrawal from chronic alcohol drinking due to increased dopamine uptake levels resulted in decreased VTA dopamine neuronal activity [34], and reduced basal levels of dopamine in the ventral and dorsal subregions of the striatum, possibly due to enhanced dopamine uptake [35]. The aripiprazole (D2 dopamine receptor agonist) has shown some effectiveness in treating dependence of alcohol [36].

2.2.4. Serotonin

Serotonin exerts its known role in regulating various behaviors (e.g., feeding, sleep/arousal, aggression), mood and emotional behavior [37] via several metabotropic (5-HT1 and 5-HT2 subtypes) and ionotropic (5-HT3) receptors throughout the brain depending on the consumption of alcohol [38]. Alcohol elevates serotonin release in the central nervous system (CNS) affecting emotion, temper and thoughts. The 5-HT3 receptor function is altered by ethanol consumption through its actions on receptor proteins [39]. Chronic alcohol exposure reduces serotonin levels in several brain regions [40]. Researchers have focused on the treatment for alcohol dependence and comorbid depression [41], post-stress disorder [42] and anxiety [43].

Inhibition of serotonin reuptake was done through fluoxetine. The milnacipran blocks both serotonin and norepinephrine reuptake. Both fluoxetine and milnacipran are found to be effective in reducing alcohol consumption in the rats model [44]. Consumption of alcohol (5%) every third day for 18 days leads to disturbance in serotonin function within the nucleus accumbens [45] (**Tables 2** and **3**).

2.3. Biochemical changes associated with alcohol intoxicity

Alcohol consumption in an individual leads to biochemical changes that are correlated with complex signaling pathways such as phosphorylation of proteins, synthesis of nitric oxide (NO), NFκBand MAP kinase pathways in certain regions of the brain [48].

2.3.1. Generation of free radicals

Alcohol-induced brain damage may occur due to generation of free radicals [49] by acetaldehyde intoxicity [50] or microsomal ethanol oxidizing system (MEOS) [51]. This can be minimized, if there would be a reduction in glutathione (cytoprotection) in the specific regions of the brain which is affected.

2.3.2. Changes in phosphorylation

Cell signaling events depend on phosphorylation of proteins (phosphorylation: protein kinase and dephosphorylation: protein phosphatases). During intoxication in hippocampal dentate gyrus,

Neurotransmitters	Effect of alcohol in the brain	References
Glutamate	Inhibits glutamate receptor function	[13, 14]
GABA	Potentiates GABA receptor function	[24]
Dopamine	Increases dopamine concentration	[31]
Serotonin	Decreases serotonin neurotransmission	[39]

Table 2. Neurotransmitters and its effect on the brain system.

Neurotransmitters	Drug found to reduce alcohol consumption	References
Glutamate	Amitriptyline	[46]
GABA	Benzodiazepines (positive allosteric modulator of $GABA_A$)	[27, 28]
	Gabapentin (anticonvulsant)	
	Topiramate (anticonvulsant)	
Dopamine	Aripiprazole (D2 dopamine receptor agonist)	[36]
Serotonin	Fluoxetine and milnacipran	[44]
	Dansetron (5-HT3 receptor antagonist)	[47]

Table 3. Neurotransmitters-associated drug to reduce alcohol toxicity in the brain.

the total phosphorylated c-AMP response element-binding protein (CREB) immunoreactivity is reduced in both chronic or binge drinking. In rat cerebellum, the dose of 3 g/kg alcohol (acute) shows an increase in a phosphorylated form of CREB. Research showed that protein phosphatase inhibitor (DARPP-32), when it undergoes phosphorylation changes, plays a crucial role in reducing ethanol inhibition of NMDA receptors [52].

2.3.3. Transcription factors

They are the first signaling proteins which are regulated through sensitive cysteine residues, which need to be reduced to its function. Earlier studies showed that production of reactive oxygen species (ROS) is responsible for the activation of NFκB [53]. Later *in vitro* studies showed that exogenous hydrogen peroxide is responsible for NFκB activation [54]. In the cortex, one study reported activation of NFκB in chronically alcoholized rats [55]. It was quite clear that NFκB was down-regulated in comparison to acute alcohol drinking. One study showed no NFκB activation in binge alcohol drinking models, when given anti-oxidants (furosemide and butylatedhydroxytoluene) to prevent neuronal degeneration [56].

2.4. Epigenetic mechanism

It is an efficient mechanism for gene regulation by altering the packaging of DNA within chromatin through interactions with histones. CREB requires phosphorylation to initiate transcription of pro-survival neuronal factors (**Figure 2**). A study revealed an increase in CREB (a regulator for plasticity of neurons), increase in H3-H4 (a central histone tetramer) acetylation and inhibition of HDAC (histone deacetylases) activity in a rat amygdala when given an acute dose of ethanol for 15 days. A trichostatin (HDAC inhibitor) was used to treat the rats, resulting in deacetylation of H3-H4, CREB inhibition, reduced NPY expression and HDAC activation in the rat amygdala [57].

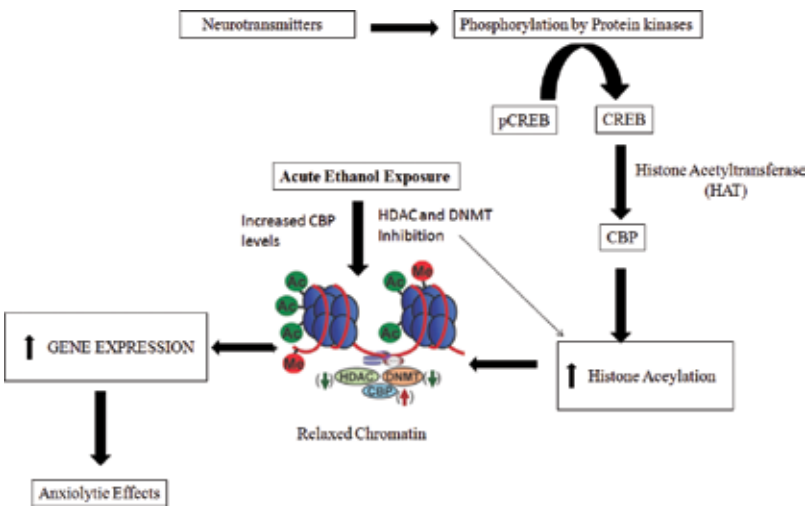

Figure 2. Epigenetic modifications associated with alcoholism.

2.5. Genome profiling of alcohol-responsive genes

With recent technologies like direct sequencing and gene microarray, studying individual genes along with entire genome of an organism has been made possible.

2.5.1. Microarray study

First genome microarray studies were performed in post-mortem alcoholics' human brain; results revealed that myelin related genes expressed in oligodendrites (from frontal cortex) showed downregulation in the brains of human alcoholics compared with brains from control individuals [58], suggesting neuronal dysfunction. In the prefrontal cortex area of the brain, there were 54 genes which were upregulated and those belong to the class of heat shock protein, including *HSP70–2, CRYAB, HSP27–1* and *HSP40–1* in alcoholic abusive individuals [59]. An old study revealed that 100 mM ethanol (2 days) given to NG108–15 hybrid cell line determined that a number of genes were induced by heat shock and a few were induced by ethanol only. Heat-shock cognate proteins *Hsc 70* and *Hsc 110* were recognized as ethanol-inducible genes [60]. When *C. elegans* was given a high dose of ethanol, it showed activation of *glr-2*, a gene that encodes a subunit of the AMPA glutamate receptor subunit (homologous to mammalian GluR2) within 15 min [61]. Cultured cortical neurons given 75 mM of ethanol for 5 days showed increased levels of gene expression of *Hsp84, Hspa8* and *Hsp70* [62]. In a whole brain, when C57BL/6J and DBA/2J mouse strains were given acute doses of different ethanol preferences, they revealed downregulation of *Erbb3*, *Mobp* and *Nkx2-2* (myelin-related genes) [63].

The researcher performed a genomic level along with a microarray experiment on neurons of mouse corticals given 60 mM ethanol or heat treatment at 42°C. Microarray results showed upregulation of a large number of genes by ethanol and heat shock [64]. Among the pool of genes, there were nine genes which showed greater than 50% stimulation. It includes.

- gene-encoding proteins involved in synaptic neurotransmission: *Syt1* and *Spnb2;*
- gene-encoding proteins involved in synaptic plasticity and synaptic formation: glycoprotein m6a (Gpm6a), neurogranin (*Nrgn*) and cadherin 13 (*Cdh13*);
- and gene-encoding proteins involved in microtubule assembly, microtubule-associated protein 1B *(Mtap1b)* [64].

2.5.2. Analysis of quantitative trait loci

A quantitative trait loci (QTL) refers to the trait that varies in degree and can be attributed to the interactions between two or more genes and their environment. Possible QTLs have been identified through microarray studies for alcohol uptake. An analysis is done across inbred mouse strains identified a group of genes for alcohol preference QTL on chromosome 9. These genes include *Arhgef12*, *Carm1*, *Cryab (heat shock protein)*, *Cox5a*, *Dlat*, *Fxyd6*, *Limd1*, *Nicn1*, *Nmnat3*, *Pknox2*, *Rbp1*, *Sc5d*, *Scn4b*, *Tcf12*, *Vps11* and *Zfp291* [65].

2.6. Activation of multiple neuroimmune genes in human alcoholic brains

In human brain-slice cultures, multiple ethanol-induced cytokines are released. Among all, monocyte chemotactic protein-1 (MCP-1) showed increased levels in the amygdala, nucleus accumbens, VAT and hippocampus [66]. In alcoholic brains, elevated levels of TLR 2, TLR3, TLR4 and HMGB1 (high-mobility group box 1) were found in the orbital frontal cortex (OTC) [67]. Release of HMGB1 leads to disruption of synaptic plasticity which causes hyperexcitability of neurotransmitters due to ethanol exposure. There is an increased level of IL-1β inflammatory marker in an alcoholic brain (hippocampus) causing neuro-degeneration [68]. RAGE (HMGB1 receptor) has shown an increased level in an alcoholic brain [69].

2.6.1. Role of microglia

Exposure to alcohol causes activation of microglia along with the proinflammatory cytokines, leading to neuronal inflammation and toxicity [70]. Alcohol exposure causes accumulation of microglia in the brain which occurs through activation of TLRs leading to increased HMGB1 expression [71]. Alcohol-induced neuronal apoptosis leads to stimulation of the transcription factor AP-1 and release of IL-1β, IL-6 and transforming growth factor β (TGF-β1) [71]. An in vitro study revealed that microglial TNF-α production plays an important role in neuronal toxicity [72]. Neuronal cell death occurred due to chronic alcohol exposure which leads to upregulation of the NF-κB expression, which in turn leads to release of TNF-α resulting in neuronal apoptosis [73].

In vivo studies in the cortical and hippocampus region of the brain showed increased levels of NADPH oxidase, superoxide and microglial activation, which is correlated with alcohol-induced ROS production [74]. In vitro studies revealed that upon alcohol exposure, microglia-conditioned cells showed increased ROS production and induced oxidative stress in cultured hypothalamic neuronal cells; this leads to neuronal apoptosis [75]. Alcohol-induced elevation of TGF-β1 levels in neuronal cells is accompanied by a host of molecular and chemical changes such as increase in E2F1 protein expression, mitochondrial proapoptotic proteins bak, bad and bcl-xs and E2F1 protein expression and simultaneously decrease in cyclin D1, cyclin-dependent kinase-4 expression and antiapoptotic protein bcl-2 leading to neuronal apoptosis [76] (**Figure 3**).

2.7. The brain and immune responses

The interface between the brain and the immune system is bidirectional. Recent findings have revealed that alcohol causes the release of HMGB1 in the gut, which in turn activates TLR4

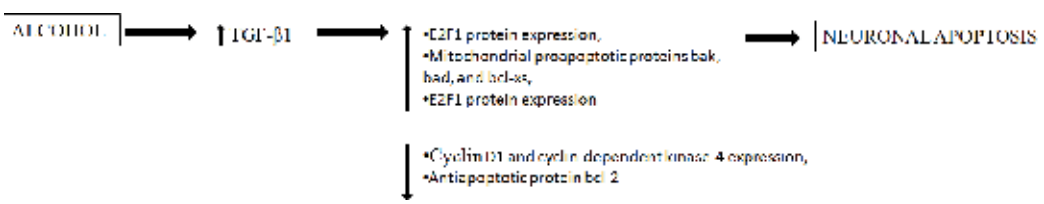

Figure 3. Alcohol-induced elevation of TGF-β1 levels in neuronal cells is accompanied by a host of molecular and chemical changes related to cell death.

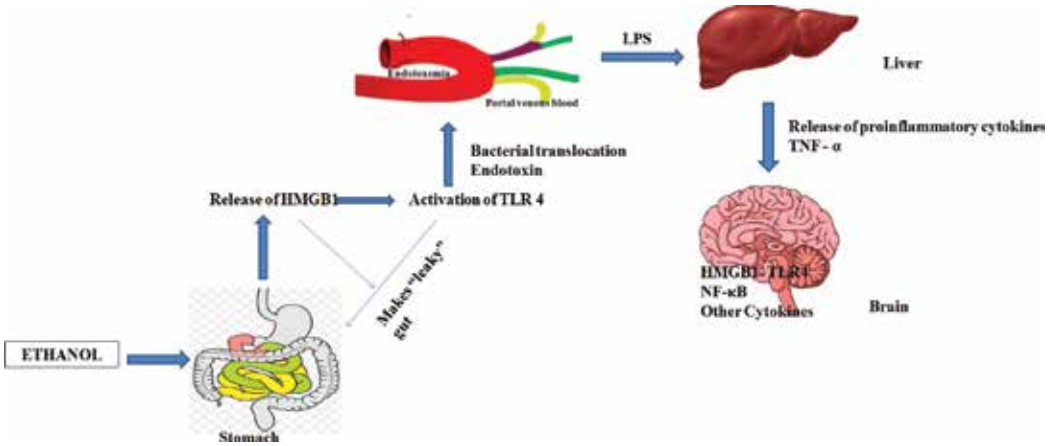

Figure 4. Alcohol influences neuroimmune signaling via its effects on the gut.

resulting in an increased gut permeability. As a result, there is activation of proinflammatory cytokines in the liver, which leads to induction of TNF-α and other cytokines in the blood. Researchers found that LPS induced increases in serum TNF-α as well as proinflammatory cytokines, leading to induction of the gene in the brain [77]. This proinflammatory cytokines in the blood are then transported across the blood–brain barrier (BBB) by their receptors [78]. For example, 2 to 3 g/kg ethanol when administered into the stomach results in the activation of innate immune response in the gut [79]. This damages the tight junction present in the gut resulting in an opening of the sites where gut bacteria and their endotoxins (LPS) can easily enter the blood stream leading to the liver, where they can activate proinflammatory cytokines (**Figure 4**). Increased proinflammatory cytokines responses, which affects the brain through TNF-α and other cytokines [80]. The brain response to the proinflammatory cytokine MCP-1 is quite longer than that found in the liver and blood [81]. An in vivo study showed an increased LPS induction of proinflammatory cytokines (TNF-α, IL-1β and MCP-1) only in the brain but not in the liver and blood after ten daily doses of alcohol [81]. In the liver, the researcher suggested that the anti-inflammatory cytokine (IL-10) inhibits NF-κB which was increased after 1 week of ethanol treatment but decreased in the brain [81]. After 10 days of ethanol (5g/kg/day) administration to mice model, this study showed sensitization to TLR3 agonist Poly:IC which induces proinflammatory cytokines in the brain for 24 hours [74].

3. Conclusion(s)

Alcohol is an anxiolytic and soothing drug. Chronic alcohol consumption leads to determined molecular and cellular modification in the brain system. It is comprehensible that GABA and glutamate neurotransmitters play a crucial role in alcohol toxicity, neuronal toxicity and neuronal cell death. Ethanol exposure triggers the activation of various gene expressions involved in apoptosis, in oxidative stress and in the cell cycle. Upregulation of genes by ethanol includes heat shock proteins and proteins related to synaptic neurotransmission,

synaptic plasticity and synaptic formation. Downregulation of genes by ethanol includes protein synthesis, myelination and the ubiquitin-proteasome pathway. Chronic ethanol exposure increases HMGB1–TLR4 and NF-κB signaling which leads to improved NF-κB target genes' expression. This results in determining neuroimmune responses to ethanol toxicity that releases HMGB1 or directly stimulates TLR and/or NMDA receptors. An epigenetic mechanism will show potential towards drug dependence by changing the DNA protein structure. Microglial cells will arbitrate the effect of alcohol toxicity on neurogenesis. The progression towards the neurobiologic techniques including micro array, QTL and proteomics will provide some anticipation for researching the molecular and cellular mechanisms that act as a keystone for the understanding of neuronal toxicity and enlightening new therapeutic gene targets for this public health burden.

Conflict of interest

We have no conflict of interest to declare.

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Chapter 3

Bereavement and Substance Use Disorder

Laura Masferrer and Beatriz Caparrós

Additional information is available at the end of the chapter

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Abstract

In the present chapter, we focused on the relationship between bereavement and addiction, specifically among those patients who have a diagnosis of substance use disorder. Although bereavement research has advanced greatly in recent years, there are few studies on bereavement among the drug-dependent population. The substance use disorder population often report life stories marked by painful experiences and loss. Different studies have remarked on the relationship between bereavement and substance use. Highlighting the possible relationship between the loss of a significant person and a substance use disorder could help to build a theoretical background as well as to improve the dishabituation treatment in addiction centers.

Keywords: bereavement, grief, substance use disorder, alcohol dependence, cocaine dependence, heroin dependence

1. Introduction

In this review, we focused on the association between bereavement and those people who have a diagnosis of substance use disorder (SUD). Carrying out an accurate review of what other previous studies had found on this subject is necessary to establish the basis for doing research on this topic. The current state of knowledge with respect to bereavement and having a diagnosis of SUD was the objective of this chapter. Bearing in mind the possible association between the loss of a significant person and SUD could be useful to describe a theoretical background, which enhances the addiction framework on which the dishabituation treatments rely on.

The mental illness of SUD is a biopsychosocial phenomenon [1]. Addiction involves problems at different levels, such as traumatic experiences during childhood [2], economic instability, unemployment [3], marital problems, accidents, court proceedings [4, 5], social exclusion [6, 7],

physical complications as well as medical complications, and high psychiatric comorbidity [8, 9]. Therefore, the SUD population is highly vulnerable than the general population and often presents life stories marked by suffering and loss.

Bereavement is a life-event that everybody experiences during their lives, but for some individuals, it is often associated with a period of intense suffering with an increased risk of developing mental and physical health problems [10]. Hence, when it happens to vulnerable people with psychiatric comorbidity, the result may be complications in the grief process. In this regard, different studies have reported a link between losing a significant person and drug consumption among substance users [11–13].

Both conditions (having an SUD diagnosis and having experienced a loss of a significant person) have implications in known brain mechanisms. Scientific evidence has suggested that not only does the use of substances cause changes in brain structure and functioning but it is also relevant to understand the influence of bereavement on a biological level. According to Luecken [14], parental death is a powerful early life experience with the potential to alter the development of biochemical, hormonal, emotional, or behavioral responses to the environment and later life stressors. Following the paragraph from Luecken [14]: "Maternally separated rodents and primates show neurobiological alterations that indicate permanently altered sensitivity to drugs of abuse and consume significantly more alcohol than mother-reared animals both before and after stress exposure" [15, 16], suggesting that disrupted care during development may form a neurobiological basis for vulnerability to substance abuse later in life. Cortisol dysregulations are also associated with the increased risk of substance abuse, externalizing and internalizing disorders, and behavioral precursors to illness [17, 18].

In this chapter, a review of the main quantitative studies related to these two complex topics, the diagnosis of SUD (especially alcohol, cocaine or heroin) and bereavement, has been carried out.

2. Relationship analysis between bereavement and addiction

Several authors have noted the possible relationship between the loss of a significant person, complications in grief, and substance abuse [11, 13]. This section showed the results of the review of quantitative scientific literature about the relationship between the diagnosis of an SUD (especially alcohol, cocaine, or heroin) and bereavement.

Table 1 described the quantitative studies, which have analyzed the relation between bereavement and SUD. The columns specify: the authors and the date of publication, the type (where "B" means bereavement and "SLE" stressful life events where bereavement was included as a specific SLE), the objective of the study, the sample characteristics or participants, the instruments used, and the main results indicating if there is an evidence of the relationship between bereavement and addiction.

The aspects and variables contemplated and analyzed in different investigations are numerous. As can be seen from the table, the main variables studied were:

Authors (Date) Country	Type*	Purpose of study	Sample characteristics	Method	Results (Is there any evidence of a relationship between loss and addiction?)
Birtchnell [24] UK.	B	Examine the prevalence of parental death	N = 6795 patients aged 20 or over N = 3425 of control group	The psychiatric sample was interviewed and the control group answered a post survey	Yes, relationship between early parental death and alcoholism was found only in female patients. The diagnosis most significantly associated with early bereavement was among the depressives and the alcoholics
Blankfield [26]. Australia	SLE&B	Assess the different ways in which loss effected patterns of alcohol consumption	N = 50 alcoholic patients (aged from 19 to 61 years) "Loss" included: death, separation, or divorce and unexpected losses	MAST	Yes, loss can affect the pattern of alcohol consumption. The onset of alcoholism after loss could perhaps reflect a precipitant factor which unmasks the predisposition in a stable phase of the individual concerned
Blankfield [20]. Australia	B	Examine the patterns of establishment of alcohol dependence in widows	N = 37 widows who had not remarried. N = 85 nonwidows	MAST	Yes, the older women with no family history or the women with an alcoholic spouse have a higher risk factor
Bowser et al. [29]. USA	B	Ascertain the relationship among intravenous drug users between high levels of HIV risk-taking and both a) death of significant others experienced before age 15 and b) unresolved mourning	N = 592 participants (out-of-treatment intravenous drug users) (71.4% male) (Aged from 19 to 67) Primary losses = before 15 years	CFBQ/CIDUS	Yes, relationship between death and addiction was shown. Unexpected deaths experienced early in life and inadequate mourning as factors in progressively higher adult HIV risk-taking. 26.4% experienced one or more sudden deaths of adult family members before age 15. Significant relationship between those who under-mourned and being sexually abused as children. The earlier deaths respondents experienced, the higher was their sex trading. Those with incomplete mourning

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Authors (Date) Country	Type*	Purpose of study	Sample characteristics	Method	Results (Is there any evidence of a relationship between loss and addiction?)
					had the highest level of heroin and cocaine injection
Dennehy [23]. UK	B	Determine the incidence of bereavement, that is, loss of a parent by death, in a psychiatric population	N = 1020 patients from 3 psychiatric hospitals (433 men and 587 women) diagnosed as depressive, schizophrenic, alcoholic and drug addicted and other	Interview	Yes, significant incidence of parental death and addictions were found. There was a significant incidence of death of mother under 15, but no significant loss at a particular age was seen. Male alcoholics also showed an excess of loss of father between the ages of 10–15. Among the drug addicted, there was significant excess of loss of both parents of female drug user before the age of five
Furr et al. [28]. USA	B&SLE	Examine the self-reported losses experienced throughout life in individuals currently receiving treatment for SUDs	N = 68 addicted patients divided into: adult residential program (n = 14); substance abuse comprehensive outpatient (n = 6); substance abuse intensive outpatients (n = 34) and aftercare (n = 14)	Experience of loss in Addictions Inventory	Yes, loss was an issue that may appear during any phase of addiction counseling but authors are prudent and avoid establishing causal relationship
Furukawa et al. [36]. Japan.	B	Examine the relationship between early parental loss and subsequent development of alcohol dependence among Japanese men	N = 75 men with alcohol dependence in treatment N = 52 healthy controls without any lifetime psychiatric disorder	PISA	No relationship between childhood parental loss and alcohol dependence was found. When stratified for sex and age, there was no statistically significant difference between the patients and the controls in the rates of maternal or paternal death or separation before the age of 16 years
Hamdan et al. [34]. USA.	B	Examine whether the incidence of alcohol and substance abuse is higher in parentally bereaved	N = 235 youth participants whose parents died of suicide, accident or sudden natural death	Longitudinal population-based study. Validated scales covering	No, the relationship between parental bereavement and pathological youth alcohol and

Authors (Date) Country	Type*	Purpose of study	Sample characteristics	Method	Results (Is there any evidence of a relationship between loss and addiction?)
		youth and, if so, what might explain this increased incidence	N = 178 demographically similar nonbereaved youth	psychopathology, self-esteem, social support and ways of coping	substance use was not statistically significant. However, bereaved youth had an increased incidence at an earlier time to onset of SUD relative to nonbereaved controls. Bereaved youth were at a greater risk of SUD than their nonbereaved counterparts
Hilgard and Newman [22]. USA.	B	Determine the prevalence of parental loss by death in childhood among schizophrenic and alcoholic patients compared with a nonpatient community sample	N = 1561 schizophrenic patients (631 males and 930 females) and N = 929 patients (678 males and 251 females); N = 1096 (478 males and 618 females) for control group All participants aged between 20 and 40 years	Control survey Alcoholics admission records	Yes, results established certain relationships between parental loss in childhood and the development of mental illness in adult life. Statistically significant difference in the incidence of death of both parents between young male alcoholics (aged 20–29) and the controls but no significant difference in the rate of death of either father or mother between older alcoholics and the controls
Kaplow et al. [19]. USA.	B	Examine the potential differences in the presence of psychiatric symptoms between parentally bereaved children, children who experienced the death of another relative and nonbereaved children	N = 172 parent-bereaved youth; N = 815 youth who experienced the death of another relative; N = 235 nonbereaved youth, aged 11–21 years	C-GAS/CAPA	Yes, a greater proportion of bereaved youth showed drug problems after the loss. SLE may lead to substance abuse through individuals' poor coping skills and vulnerability to depression
Kendler et al. [21]. USA.	B&SLE	Examine the impact of parental loss due to death and separation on risk for major depression (MD) and alcohol dependence (AD).	N = 5070 twins participants from same-sex and 2118 participants from opposite-sex twin pairs ascertained from a population-based registry	Cox Proportional Hazard and Nonproportional Hazard models	Yes, relationship between parental loss and alcoholism was demonstrated. Consistent sex differences in the association with parental loss were seen for Alcohol Dependence but not Major Depression. Parental separation was associated with a substantially increased risk for Alcohol

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Authors (Date) Country	Type*	Purpose of study	Sample characteristics	Method	Results (Is there any evidence of a relationship between loss and addiction?)
					Dependence in females but not in males. The loss in childhood of a parenting figure due to death does not appear to be pathogenic for Alcohol Dependence.
Masferrer et al. [27]	B	Explore the loss of a significant person	N = 196 SUD patients	Self-constructed questionnaire	Yes, 83.2% patients stated that after suffering the loss, they increased drug consumption.
Masferrer et al. [42]	B	Determine the presence of CG symptoms among an SUD sample	N = 196 SUD patients N = 100 control patients	ICG	Yes, the presence of CG symptoms was 34.2% among SUD patients in comparison to 5% in the control group
Murphy et al. [33]. USA	B	Analyze if loss has a role in those alcohol dependent people who died by suicide	N = 50 participants postmortem description	Interview the nearest available relative (the spouse of the victim mainly) in 2 phases.	Yes, loss as a predictor of suicide among alcoholics. 26% of alcoholics had experienced a loss of close interpersonal relationship within 6 weeks of their death and 50% for the entire year
Pilling et al. [30]. Hungary	B	Analyze the relationship between bereavement and alcohol consumption accounting for time and gender differences on a national representative sample	N = 466 participants (aged 18–75 years) who had lost a close relative in the past 3 years	Slightly modified Hungarian version of AUDIT	Yes, a link between bereavement and alcohol problems was found. Among bereaved men, the risk of alcohol related problems tends to be higher (than nonalcohol)
Risser et al. [25]. Austria	B&SLE	Describe family characteristics of drug-related deaths	N = 51 (have experienced at least one drug overdose and 53% of them had contact with therapeutic institutions)	Interviews with relatives of deceased drug users	Yes, there was a relation between SLE and drug abuse. 80% of drug users were reported to have experienced a traumatic event (parents' divorce or the death of a parent) during their childhood). The Mean age at death was 24.6 years. Those who experienced a traumatic event during their childhood started to smoke earlier.

Authors (Date) Country	Type*	Purpose of study	Sample characteristics	Method	Results (Is there any evidence of a relationship between loss and addiction?)
					Drug abuse may be an indication of dysfunction within the family system.
Rugani et al. [31]. Italy	B&SLE	Assess the life events (loss and traumatic) before and after the dependence age of onset (DAO) and their responses to these events	N = 82 heroin-dependent patients in treatment (aged from 17 to 61 years)	DAH-RS/TALS-SR	Yes, SLE and addiction was linked. Loss events and potentially traumatic events were present, and tend to increase, in passing from the before- to the after- DAO period. During the before-DAO period, "the death of a close friend or relative," "divorce" and "being neglected or abandoned" were rated by patients as the most important events. Exposure to SLE seems to strongly increase the risk of becoming drug-addicted.
Stikkelbroek [37]. Netherlands	B	Examine association between parental death during childhood and adult psychopathology	N = 7076 participants (aged from 18 to 64 years)	CIDI/ MOS-SF-36 Cross-sectional and prospective study	No, few indications that there was a significant increase in mental disorders in adulthood after the death of a parent during childhood. A small decrease was found in the lifetime prevalence of substance abuse for parentally bereaved compared to no parental bereavement. Parental death before the age of 16 was not associated with a younger age of onset of mental health problems.
Tennant & Bernardi [35]. Australia	B&SLE	Examine if both narcotic users and alcoholics are more likely to have experienced the death of a parent or prolonged separation from one or both parents in childhood than a control group of nonaddicts	N = 70 heroin dependent patients and N = 40 alcohol dependent in treatment N = 123 controls (patients and accompanying relatives)	MiniMental State Examination/ Zung Depression Inventory/PBI	Yes, there was a relationship between loss and alcoholism, although it was not significant. More alcoholics and addicts reported maternal loss than controls (no statistical difference). Separations from both parents

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Authors (Date) Country	Type*	Purpose of study	Sample characteristics	Method	Results (Is there any evidence of a relationship between loss and addiction?)
					were significantly more common in both alcoholics and addicts than in controls. However, parental deaths were not associated with addiction
Wilcox et al. [32]. USA	B	Examine the risk of suicide, psychiatric hospitalization, and violent criminal convictions among offspring of parents who died from suicide, accidents, and other causes	N = 44,397 offspring of suicide decedents, N = 41,467 offspring of accident decedents, N = 417,365 offspring of parents who died by other causes, and N = 3,807,867 offspring of alive parents	Population-based data from multiple Swedish national registers were linked from 1969 to 2004.	Yes, parental deaths were linked with addiction. Offspring of suicide decedents had an especially high risk of hospitalization for suicide attempt. Child survivors of parental suicide were at particularly high risk of hospitalization for drug disorders and psychosis

MAST = Michigan Alcoholism Screening Test; CIDUS = Collaborative Intravenous Drug Users Study questionnaire; CFBQ = The Coleman Family Background Questionnaire; PISA = psychiatric initial screening for affective disorders; C-GAS = Children's Global Assessment Scale; CAPA = Child and Adolescent Psychiatric Assessment; ICG = Inventory of Complicated Grief; AUDIT = Alcohol Use Disorders Identification Test; DAH-RS = Drug Addiction History Rating Scale; TALS-SR = Trauma And Loss Spectrum-Self Report Instrument Questionnaire; CIDI = Composite International Diagnostic Interview; MOS-SF-36 = Medical Outcomes Study Form-36; PBI = Paternal Bonding Instrument.
* Type of article: B = bereavement; SLE = stressful life events.

Table 1. Quantitative studies about the relationship between bereavement and addiction.

a. *The family relationship or proximity to the deceased person*. Most studies identified the loss of significant people, such as the father, the mother, or the husband. One example of these studies is a longitudinal epidemiological study, which examined differences in psychiatric symptoms between young parents (N = 172), youth who experienced the death of another relative (N = 815), and non-mature youth (N = 235). A large proportion of bereaved youth showed drug problems after the loss. According to the results, the impact of parental death on children must be considered in the context of pre-existing risk factors [19]. Some years later, Blankfield [20] conducted further research comparing similar age-grouped widows (n = 37) and nonwidows (n = 85) who were in treatment in a unit of alcohol dependence. The results suggested that the widows of alcoholics who had unresolved marital conflicts or who become socially isolated are more vulnerable to abnormal grief responses. She pointed out the premorbid personality style (more solitary lifestyle) as a risk factor for complications afterwards. On the other hand, the death of an alcoholic spouse could be a more powerful factor than family history in triggering the same dependence for their widows or social isolation for others.

b. The *gender* of people who have suffered loss is also a variable that has been very important in many studies and has contributed different results, as Kendler points out [21]. Consistent sex differences in the association with parental loss were seen for alcohol dependence. For example, Hilgard and Newman [22] compared the incidence of death of a parent among 929 alcoholic patients from a state hospital and 1096 controls from a community nearby. They found a statistically significant difference in the incidence of both father and mother death between young male alcoholics and controls. Dennehy [23], comparing the data for 1020 psychiatric patients (depressive, schizophrenic, alcoholic, drug addicted, other) with the expected incidence of loss of parents calculated from the data census, found that there was a significant incidence of death of mother for those who were under 15 at the time. Male alcoholics also showed an excess of loss of father between the ages of 10–15. Among the drug addicted, there was significant excess of loss of both parents of female drug users before the age of 5.

c. The *age at the time of loss* of the person has been a very frequently studied factor. In this sense, losses at early ages seem to have a very important impact on the evolution of people in relation to addiction problems and other disorders. This is the point obtained from the research carried out by Birtchnell [24], involving patients with various psychiatric diagnoses (depressive, neurotic, psychotic, alcoholic and personality disorders) and a control group drawn from the general population. The author found that early morning affected only female patients. The diagnoses most significantly associated with early bereavement were depressive and alcoholism. The most crucial period for parenting was age 0–9 years old. Risser et al. [25] stated that 80% of addicted patients had experienced at least one traumatic event during their childhood (mean age at the event was 7.8 years), such as the loss of a parent or parents' separation. Also, those patients who experienced a traumatic event during their childhood began to smoke at a significantly lower age.

d. *Impact on substance consumption patterns*. In some studies, such as Blankfield [26], the different ways in which grief-affected patterns of alcohol consumption was analyzed.

After assessing 50 inpatients of an alcohol and drug treatment center, it concluded that the loss can influence the pattern of alcohol consumption in different ways as the intake can be started, remain unaltered, increase, or even decrease. She also described that the onset of alcoholism after loss could perhaps reflect a precipitating factor that unmasks the predisposition in a stable phase of the individual concerned. Moreover, 83.2% of SUD patients (alcohol, cocaine, and heroin dependence) stated that after suffering a loss of a significant person, they increased drug consumption [27]. On the other hand, Furr et al. [28] differentiated between different types of losses: losses prior to addiction, losses while abusing substances, and losses associated with entering treatment. They interviewed 68 addicted patients using a self-report instrument. They concluded that the loss was an issue that may appear during any phase of addiction counseling but authors are prudent and avoid establishing causal relationship.

Moreover, some results also emphasized the fact that substance use was a strategy used as a coping mechanism in certain traumatic vital circumstances. According to Bowser et al. [29], drug abusers may be people with a variety of background traumas and these accumulated traumas, and respondents and their families' inability to deal with or process emotions, were what motivates their self-medication and extremes in life-threatening and risk-taking behavior. In this regard, they reported that 26.4% of 592 participants experienced one or more sudden deaths of adult family members before the age 15. The same research showed that those drug dependent people with incomplete mourning had the highest level of heroin use and injection of cocaine. According to the study, almost half of the respondents (48%) used heroin as an adaptive attempt to regulate and control high anxiety at the same time as a way of managing stressful life events. Related to stressful life events, the authors claimed a significant relationship between those who under-mourned and being sexually abused as children. Moreover, the earlier the death that respondents experienced, the higher was the likelihood that they would become involved in the sex trade.

e. The *type of substances* consumed has also been studied. Different studies have focused primarily on alcoholism and have found a link between bereavement and alcohol problems. Among bereaved men, the risk of alcohol-related problems tends to be higher than nonalcohol [30], although other types of drugs have undergone a study. Among the heroin-dependent patients sample, loss events and potentially traumatic events were present and tend to increase in passing from the before- to the after-dependence age of onset period. During the prior-dependent age of onset period, "the death of a close friend or relative," "divorce," and "being neglected or abandoned" were rated by the patients as the most important events. Exposure to stressful life events is associated with an increase in the risk of becoming drug addicted [31].

f. *Suicide*. At this point, we can include aspects related to the way the person died, such as the study by Wilcox et al. [32], which showed that parentally bereaved youths were found to show higher rates of alcohol and substance abuse symptoms than their nonbereaved counterparts. The results described the association between parental death and addiction. Offspring of suicide decedents had an especially high risk of hospitalization for suicide attempt. Child survivors of parental suicide were at particularly high risk of hospitalization for drug

disorders and psychosis. From another aspect, the loss could be a predictor of suicide among alcoholics, as noted in the study by Murphy et al. [33], in which 26% of alcohol dependent patients who died by suicide had lost a close interpersonal relationship within the previous 6 weeks and 50% during the whole previous year.

Previous studies described relationships between loss and mourning, in different analyzed variables, but the data was controversial because it is also important to indicate studies that did not find this association, or found that it was very weak [21, 34]. For example, Tennant and Bernardi [35] studied 40 alcoholic patients who were admitted to a specialized in-patient facility and 123 controls attending general medical practitioners and found that childhood parental loss through separation but not through death, was significantly more common among alcoholics than in controls. Some authors have also reported nonsignificant associations between parental death and alcoholism [21, 36]. In a Japanese study, Furukawa et al. [36] examined the relationship between early parental loss and subsequent development of alcohol dependence among Japanese men. They did not find a statistically significant difference between patients and controls in the rates of maternal or paternal death or separation before the age of 16. Along the same lines are the results of the Hamdan study [34], in which the relationship between parental bereavement and pathological youth alcohol and substance use was not statistically significant. However, unemployed youth had an increased incidence and an increased risk of SUD than their nonbereaved counterparts.

More recently, Stikkelbroek et al. [37] found few indications that there was a significant increase in mental disorders in adulthood after the death of a relative during childhood. A small decrease was found in the prevalence of alcohol abuse for the parentally bereaved compared to no parental bereavement. Parental death before the age of 16 was not associated with a younger age of onset of mental health problems.

It is highly important to bear this information in mind because, as different retrospective studies [19, 32, 36] point out, the circumstances surrounding parental loss, including economic privation, conflict, parental hostility, neglect, distress, and disruption are more important in the prediction of psychopathology than parental bereavement *per se*. When looking for risk factors, a multidimensional perspective must be taken, examining both individual and family variables [38]. For example, there is evidence that the lack of adequate parental care following the death is a more powerful predictor of later adult impairment than the simple fact that a parent has died [39]. Further investigation will be needed to establish consistent patterns of parental deprivation and that such patterns *per se* may not indicate exact modes of causation, but may well be of considerable etiological significance when taken in conjunction with other objective factual data [40].

3. Limitations of the quantitative studies

When arriving to this point, it is clear that the subject we are dealing with has great theoretical and methodological complexity. For example, the different terminology used relative to bereavement, such as grief or abnormal grief responses, as Blankfield [20] pointed out.

Despite the fact that we can find some recent research, some of the articles are from the late 70s and 90s. For this reason, dated studies also affect the concept and model of bereavement. In the few studies where the conceptual framework is defined, this is based on the popular model of Kubler-Ross stages [41]. Today, different limitations of models based on stages are well known.

At the methodological level, in many of the presented studies, there is a comprehensive and detailed description of both the sample and the procedure or statistical analysis. In this sense, it is worth noting that there are few studies that consider the relationship between these two constructs: SUD and bereavement. On the other hand, it should also be pointed out that in some cases they are evident and that some studies present some problems of scientific rigor and validity. Due to the characteristics of SUD patients, it is difficult to collect data, so some studies presented small size of the samples. As Hilgard and Newman [22] pointed out, some studies were characterized by poorly defined and incomplete samples.

In relation to the assessment of different variables, the psychometric tests assess the psychopathology, personality, alcohol and drug use or dependence, self-esteem, social support, coping strategies, trauma-life history, and paternal bonding, but in general there is a lack of information about the measurement of bereavement. Few studies have measured the symptoms of complicated grief, except Masferrer's research [42], in which 34.2% of SUD patients reported symptomatology of CG.

Another technique used which can cause a bias is retrospective call, as Hilgard and Newman [22] described. This outlines the different hazards involved in using old hospital records to derive statistical information and also the retrospective call depends on participants' memories, which could be different from reality.

Another important aspect to note is that, as Gregory [40] summarized, it is very common for the control groups to have been casual (medical students, hospital orderlies, not equated for age, sociodemographic factors that could be important). In most of the cases, the main characteristics of the sample are defined by two categories: (a) patients, which means that the person is attending a treatment and (b) participants, people who are not attending any treatment. This categorization may not identify addiction cases. They are not receiving treatment and may be included in a control group if this variable is not controlled in some way.

Locations of the vast majority of the studies cited were in the U.S.A. Six research studies were from Europe. Only one study was from Japan and two from Australia. This point is closely related to cultural variables that can be involved, both in relation to consumption and loss. More transcultural research on this topic is needed.

In many of the studies presented, a deterministic vision could be obtained, in the sense that a linear and direct relationship between loss and addiction were described. Therefore, it is essential to be cautious with the interpretation of the outcomes. It should be remembered that an SUD diagnosis is much more complex, complicated, multifactorial, and even dynamic than simple cause–effect relationships. In this regard, the studies do not consider other etiologic factors involved in addiction, so it is relevant to take into account the limitations from a reductionist point of view. From a psychodynamic approach, addiction is understood as a

secondary phenomenon as a symptom and not as a mental disorder itself. In this sense, there is a danger of diminishing, minimizing, or downplaying all that addiction entails.

Following Furr et al. [28] and Beechem [43], it is also important to distinguish between **different kinds of losses**: prior to SUD diagnosis, while abusing substance and those losses associated with entering addiction treatment centers. Moreover, some studies focus on bereavement **before** SUD diagnosis. It will be important to consider also bereavement during the SUD process.

However, despite the shown limitations of these studies, we cannot underestimate them because each of them includes a contribution to the complex, complicated, and difficult field of addiction treatment.

4. Conclusion

This review presents different research studies which show the relationship between stressful life events and addiction over a wide range of years of publication. The majority of the revised quantitative studies support the hypothesis that there is evidence of a relationship between bereavement and addiction. According to Rugani etal. [31], the addiction might be affected by traumatic life events but it also has an impact on their development. Highlighting the possible relationship between the loss and the SUD could help to build a theoretical background. At a therapeutic level, it would be useful to take into account the bereavement of a significant person to improve the dishabituation treatment. However, a few of the studies [21, 34, 36–37] showed no relation between these two constructs. More research is needed to support and describe the bereavement phenomenon related to the addiction framework to support the inclusion of grief psychotherapy for those patients at risk of developing CG symptoms in addiction treatments.

Considering the studies shown, we can conclude that loss could have a role in the process of addiction. Because loss can have different influences on the pattern of drug consumption (precipitating the initiation of consumption, intake remaining unaltered, increasing or decreasing), it is important to be cautious. Loss could be a factor but more research is needed to clarify what kind of factor it is [26].

It would be significant to be able to understand the specific interplay of bereavement in the patient's personal situation and hopefully be able to develop even more effective and personalized treatment for each specific personal situation [44].

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Chapter 4

Nursing Care for Persons with Drug Addiction

Ek-uma Imkome

Additional information is available at the end of the chapter

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Abstract

Persons with drug addiction (PDDs) may exhibit symptoms affecting the central nervous system. Multidisciplinary treatment teams may offer the most updated treatment and care. Pharmacotherapy is one standard treatment, effective in managing psychotic symptoms with supportive psychosocial interventions. As part of the health-care team, nurses deal with PDD on a 24-hour basis. Quality nursing care is essential for improving quality of life, health status, and continued abuse-free status of PDD.

Keywords: nursing, drug addiction, nursing process, intervention, motivation interview, family therapy

1. Introduction

Drug addiction comorbidities are common in persons with psychiatric disorders. About 55% of persons with psychiatric disorders who are medicated with antipsychotics have drug addiction [1] that precipitate and exacerbate psychotic symptoms. Inability to lessen or stop drug use because of psychotic symptoms and their neurological impact creates significant health problems. An estimated 50–75% [2, 3] of persons with drug addiction also have psychiatric disorders, and up to 31% of individuals with psychiatric disorders have a history of drug addiction [4]. Recurrent relapse and the high level of drug addiction have been associated with an increased prevalence of psychotic symptoms [5].

The evidence of drug addiction has evolved in several ways. Lifetime use rates appear to have increased, and early remission from drug addiction disorders is now common. Sustained drug-free remission is well documented, although rates are still low. Research on drug addiction is leading to knowledge in many areas, including characteristics of drug addiction,

reasons for persons with drug addiction (PDDs) seeking substances, effects of different substances upon symptoms, and obstacles to drug use recovery. Dependent drug abusers were noted to be three times likelier to experience psychotic symptoms than nondependent counterparts. This indicates that PDDs are at particularly high risk for psychotic relapse [6].

Drug addiction may contribute to enhanced vulnerability by disrupting neural substrates mediating positive reinforcement. Deficits in cognitive control have been documented in a number of clinical populations with drug addiction. Behavioral and neural profiles occur, including hallucinations, delusions, signs of distractibility, and altered patterns of neural activation involving dopamine-rich frontostriatal brain regions [5, 7].

Drug addiction impacts physical symptoms, including emotional shifts, increased psychosis, cognitive confusion, family conflicts, financial problems, and legal difficulties. This suggests that drug addiction may initially provide relief, but longer term use exacerbates psychiatric symptoms. Individuals also noted that the advantages of quitting include improved physical symptoms, higher self-esteem, and increased social relationships. This suggests that individuals were aware of the impact of drug addiction on psychiatric symptoms and interpersonal relationships. Individuals reported that disadvantages of quitting drugs include withdrawal symptoms, relapse cycles, loss of substance-abusing friends, cravings, and pressure to abuse drugs.

PDD struggle with lifelong addictions to prescription drugs, taken to cope with life events presented physical and psychological stress. As a team, professional nurses working in hospital and community care should be sensitive to PDD and identify strategies for addressing their issues. Positive nursing outcomes improve their quality of life.

2. Reasons for drug addiction

Studies pinpoint five general explanations for high rates of PDD:

1. Achieving and increasing feelings of intoxication [8, 9].
2. Relieving negative emotional states such as frustration, fear, anxiety, depression, for relief from fatigue or boredom, and as a break from daily routines with altered states of consciousness [3, 10, 11].
3. Enhancing socialization skills through self-medication for positive and negative symptoms and decreasing dysphoria associated with psychotic symptoms and negative side effects from antipsychotic medications [8].
4. Responding to peer pressure, relieving negative effects such as depression, and experimenting [9].
5. While there is some evidence for the self-medication hypothesis, most research does not support theories that drug addiction occurs to decrease psychiatric symptoms or cope with negative side effects of medications [5, 8, 9, 12].

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3. Effects of drug addiction

Drug addiction affects biological, psychological, and social condition of mental and emotional states, stimulating pleasure centers of the brain. Psychotic symptoms of drug addiction follow:

3.1. Impact on physiology

Much evidence suggests that drug addiction negatively and directly affects underlying neuropathology of psychiatric disorders. This may enhance addiction vulnerability by disrupting neural substrates mediating positive reinforcement; increasing hallucinations, delusions, and signs of distractibility; and displaying altered patterns of neural activation involving dopamine-rich frontostriatal brain regions, injury, human immunodeficiency virus (HIV), hepatitis, cardiovascular, liver, and gastrointestinal diseases. In the longer term, drug addiction impairs daily life by disrupting frontostriatal reward-learning signals. Intravenous drug abuse may induce psychotic symptoms by significantly attenuating the reward prediction error signal in the limbic striatum and the incentive value signal in the ventromedial prefrontal cortex. Drug-induced behavioral changes may occur leading to lower rates of reward-related reinforcement learning (RL). The degree to which drugs disrupt encoding of incentive values in the ventromedial prefrontal cortex and posterior cingulate correlates with the degree to which drugs induce mild psychotic symptoms [3, 5, 7]. According to Bernacer et al. [10], (a) "disturbance in the ways that affected individuals evaluate stimuli and learn associations leads to mistaken evaluation of irrelevant phenomena as motivationally salient and to faulty association of unconnected ideas and events, ultimately leading to the emergence of characteristic alterations in perceptions and beliefs."

3.2. Impact upon psychology

Drug addiction exacerbates social alienation and increases potential for violent lashing out and low self-esteem, along with poor coping skills. Under these circumstances, emotional, social, or symptom-related cues can provoke recourse to available substances and suicidal ideation. They may also contribute to psychosocial instability, self-image issues, and achievement motivation. In some cases, social hostility and rejection may result. Friends and family of persons also experience distress, tension, and conflict in these relationships. Interpersonal conflicts are often associated with dual diagnoses. Friends and families may be frustrated with ongoing substance misuse that the users themselves may not see as problematic [13–16].

3.3. Impact on socialization

Short-term impact may devastate the lives of persons and severely disrupt families. Persons may withdraw from their environment with regressive behavior, fail to engage with others, or even notice physical illness and pain [3]. Social exclusion and homelessness may ensue. In the longer term, psychosis and its potential disruption of the capacity to fulfill social roles can result in further burdens. Severe, untreated symptoms may result in social, familial, and occupational

dysfunction. Severe symptoms are likely to result in patient stigmatization of self and loved ones, inadequate clinical care and rehabilitation, and the stigma of shame and family burden. Many family members hide their relationships or consider the illness to be a source of stigma when a relative suffers from PDD. Those in contact with dual-diagnosis persons may also experience distress, tension, and conflict within these relationships. Interpersonal conflicts are often associated with dual diagnoses [3, 15, 17, 18].

3.4. Impact upon treatment adherence

Rates of treatment noncompliance may decrease, reducing motivation for change and making engagement more difficult. Persons may drop out of long-term programs, retard progress, and destabilize illnesses, contributing to psychosocial instability [16, 19].

4. Treatment modalities of PDD

Professional nurses have observed that PDDs have a low tolerance for stressors and a narrow repertoire of coping skills, some of them unhelpful even in the short term. These PDDs frequently develop idiosyncratic avoidance methods to manage positive symptoms such as delusions and hallucinations. These methods may become habitual and generalized. Research has suggested the following treatment modalities:

4.1. Pharmacotherapy

Antipsychotics are a standard treatment for PDD, effectively managing symptoms. Case studies demonstrate that the antidepressant olanzapine may reduce psychotic symptoms induced by drug addiction. Dopamine antagonists have also demonstrated effectiveness in decreasing drug addiction. Research has shown that psychotic symptoms are associated with changes in brain chemistry. Antipsychotic medications restore the brain's natural chemical balance, reducing or eliminating psychotic symptoms. Medications may require weeks to work. Conventional antipsychotics are dopamine antagonists and target one of five subtypes of dopamine receptors in the brain. Dopamine 2 (D2) receptor antagonism in the mesolimbic tract improves hallucinations and delusions, but the conventional antipsychotic blockade of all D2 receptors causes other problems. Antagonizing D2 receptors in the mesocortical dopamine pathway worsens negative symptoms including avolition, anhedonia, alogia, and affective flattening. Atypical antipsychotics antagonize serotonin 5HT2A receptors as well as D2 antagonism seen with conventional antipsychotics. Serotonin affects dopamine differently in each of the four pathways. In the nigrostriatal pathway, serotonin antagonism increases dopamine release, resulting in fewer reports of movement disorders. Serotonin antagonism in the tuberoinfundibular pathway eliminates serotonin's ability to increase prolactin levels, mitigating the effect of two blockades in this pathway. In the mesocortical pathway, where serotonin 2A receptors predominate, antagonizing serotonin increases dopamine. This is thought to be responsible for improved cognition, affection, and motivation seen with antipsychotics. Weak serotonin 2A antagonism in the

mesolimbic tract cannot reverse dopamine antagonism; D2 receptors remain blocked, and hallucinations and delusions decrease. Pharmacotherapy remains the main effective treatment for PDD.

4.2. Supportive psychosocial interventions

Supportive psychosocial therapies have been used as adjuncts to pharmacotherapy [20] and psychoeducation programs to alleviate residual symptoms; improve social functioning, quality of life, and medication adherence; and reduce relapse and rehospitalization. Details of supportive psychosocial intervention follow:

4.2.1. Individual approaches

4.2.1.1. Motivational approaches

Motivational counseling works according to the idea that motivation for change is dynamic rather than static. Professional uses may influence change by developing a therapeutic relationship to increase therapeutic alliance, developing insight, and coping skills to resolve ambivalence and change health-related behavior. Professional nurses follow five motivational approach principles:

- Expressing empathy through reflective listening
- Identifying discrepancies between patient goals or values and behavior
- Avoiding argument and direct confrontation
- Coping with resistance
- Supporting self-efficacy

4.2.1.2. Cognitive behavioral therapy (CBT)

Bellack and DiClemente [footnote] outline a treatment protocol acknowledging that behavioral change is a longitudinal process consisting of several stages. "Escalating symptoms and other warning signs must be recognized, cravings coped with, coming up with healthy alternative activities developed, drug addiction lapses normalized, lapse or relapse plans developed, and cognitive restructuring counteracting positive beliefs about substance use devised." Barriers to significant personal changes include lack of motivation, impaired cognition, and social skill limitations. Low motivation, energy levels, and mood, common within this group, may arise from medication, illness, or constrained life circumstances. They provide obvious challenges for engagement, goal setting, and therapy continuance. Deficits in attention, concentration, and abstract thinking, as well as thought blocking, may impede information processing, problem-solving, and realistic planning. Underdeveloped social interaction skills required to meet people and maintain relationships may result in the absence of a healthy social support system to sustain persons through change processes, as well as in difficulties resisting pressure from substance-using peers (**Table 1**).

Many studies of cognitive behavioral therapy (CBT) and motivational interviewing (MI) with contingency management or standard care, comprising 6 months of supportive group therapy, revealed positive outcomes [15].

4.2.1.3. Family support

Family support may enhance individual and group treatment with case management or assertive community with enhanced substance use treatment services to reduce or eliminate drug addiction [21].

4.2.1.4. Relapse prevention

Relapse prevention strategies have been widely shown to be effective [22]. Behavioral change is difficult, but change related to drug addiction is even more difficult because of chemical imbalance in the brain thereby induced. Persons rarely make sudden or drastic behavioral changes and maintain them with no return to previous behavior.

4.2.2. Group intervention

4.2.2.1. Group dynamic

Positively, group interactions for PDD have the potential to change social attitudes and behaviors and are generally cost-effective. For decades, structured behavioral and social skill training was utilized to rehabilitate persons with long-term mental illnesses to overcome difficulties in concentration and learning. As Horsfall et al. [23] noted "At the micro-level, programs encourage participants to explore thoughts and expectations that are a help or hindrance, as well as address interpersonal stressors and supports." Such programs aim to improve conversational skills and social functioning and develop problem-solving skills, such as overcoming practical problems with self-care, money management, shopping, cooking, and employment readiness. Substance abusers have to learn to recognize high-risk

Nursing aims	Nursing strategies
Enhance self-control	• Goal setting • Functional analysis of drug addiction antecedents and consequence • Self-monitoring • Learning alternative coping skill
Enhance behavior contracting	• Creating a written agreement with the patient that specified targeted patient behavior and consequences
Enhance social skills	• Learning skill for forming and maintaining interpersonal relationship, assertiveness, and say no from drug
Contingency management	• Patients receiving incentives or rewards for adaptive behavior or meeting specific behavioral goals. It is based on principles of operant conditioning, which posit that behavior that is followed by positive consequences is more likely to be repeated. It supports the view that positive incentives are more effective in producing improved outcomes than negative consequences

Table 1. Nursing strategies to enhance self-control, self-efficacy, and social skills in CBT.

situations (such as carrying money and proximity to easy drug access locations and people) and to participate in role play to develop personalized ways of avoiding or extricating themselves from those situations. "Realistic relapse-prevention approaches have to be tailored to each participant's abilities and style" [23].

4.2.2.2. Self-help groups

Self-help groups often play important and meaningful roles for persons with dual diagnoses, offering essential social support from others who understand the difficulties of remaining sober. They provide a structure for daily living and commitment to stopping drug abuse. Research reveals that PDDs who consistently attend self-help groups for at least 1 year achieve reduced drug addiction outcomes [4, 22].

4.2.2.3. Assertive community treatment (ACT)

ACT is a structured health-care service approach to working with dual-diagnosis PDDs, particularly by adapting a conventional model of case management to the needs of the PDD cohort [4]. Usual case manager responsibilities include developing a working alliance with PDDs, linking them to relevant other services, and functioning as an advocate for these services with health professionals [22].

4.2.2.4. Case management

Case managers are central to PDD engagement, treatment, and retention. A study of standard outpatient case management found that case management is effective in preventing hospitalization and drug abuse relapse [24, 25].

4.3. Treatment principles

From research published over the past decade, Drake et al. [23] outlined ten principles essential for effective treatment of PDD, including engagement strategies, motivational counseling, stage-wise interventions, active treatment, long-term program retention, integrated mental illness and drug addiction treatments, and relapse-prevention strategies. Further comprehensive services such as peer support, family education and interventions, liaison with the criminal justice system, housing, and vocational rehabilitation should also be available, along with specialized programs for those with more complex disorders, cognitive impairment, and treatment resistance, as well as for minority groups [23]. In addition, services need to be flexible in order to cater to actual consumer needs, given their real-life circumstances. Hence, there is likely to be a "window of opportunity" for effective prevention or reduction of drug use shortly after a first psychotic episode.

4.4. Potential treatment models

Sequential, parallel, and integrated service models are applied for persons with drug addiction and dual diagnoses. Firstly, they are treated for one condition by sequential treatment. Secondly, person with dual diagnoses was treated by the parallel model at the same time [23].

Integrated treatment is a combination of treatment modalities from the psychiatric and mental health-care team that focus on conditions simultaneously and work with the coordinated interaction between service providers, or they are working together as one team in the hospital [24, 26]. The integrated programs require mental health staff to coordinate a range of approaches, such as detoxification, medication management, CBT, and MI—which is often problematic due to limited resources and the absence of well-defined guidelines.

In summary, recommendations for treating PDD covered three broad areas: screening, assessment, and planning; psychosocial and pharmacological treatment; and systems of service provision, with the fundamental issue being that of coordinating across federal and state departments and across area health services and individual agencies. The initial focus when developing treatment plans must be on encouraging a therapeutic alliance with the PDD and on offering MI, CBT, contingency management, skills training along with education and support for family and caregivers, relapse prevention, case management, and promoting positive health support from others (including family members and non-substance-using friends). Furthermore, the use of atypical antipsychotic medications may facilitate adherence since they are associated with fewer side effects and have been shown to benefit persons with PDD. Regardless of whether services follow integrated or parallel models, multidisciplinary treatment team should be well coordinated, take a team approach, have specialist-trained personnel (including 24-hour access), include a range of program types, and provide for long-term follow-up [4, 20, 25].

5. Vulnerability-stress model of drug addiction

The major focus of this paper was focused on nursing intervention in perspective of two types of human responses—reactions to actual health problems or illness (health-restoring responses) and concerns about potential health problems (health-supporting responses) [28]. The vulnerability-stress model determines the factors that affect schizophrenic psychotic symptoms and integrates a holistic perspective in which both biological and psychological variables explain the onset, course, and psychotic symptoms. Additionally, this model illustrates the interaction between four factors, which can be further subdivided [28, 29] as follows:

5.1. Personal vulnerability factors

The factors of the model are dopaminergic dysfunction, reduced available processing resources, autonomic hyperactivity, and schizotypal personality traits. The dopaminergic dysfunction will reduce the activation of processing resources and affect tonic autonomic hyper activation. The interaction of the personal vulnerability factors and personal protectors leads the vulnerable individual to develop prodromal symptoms of drug use. However, the personal vulnerability factors are associated between the inherited genetic factors and/or early biological factors [28]. These factors have been thought to contribute to vulnerability to congenitally compromise brain structure and function.

Therefore, nurse should be aware with the assessment about biological factors such as genetic drug use to design nursing intervention.

5.2. Personal protective factors

These factors include (i) coping skills and self-efficacy and (ii) antipsychotic drug and self-efficacy: for this study, the researcher used the terms of medical use self-efficacy to describe self-efficacy as confidence in one's ability to perform a given task such as taking antipsychotic medications as prescribed.

Nurse should be concerned that the strength of self-efficacy for appropriate antipsychotic use plays an important role to take antipsychotic, continue on treatment program, and balance neurotransmitters in the brain, especially dopamine and norepinephrine, which decrease psychotic symptoms. Thus, psychoeducation of medication self-efficacy program is needed.

Moreover, coping is a behavioral and cognitive effort to cope with situations that are appraised as stressful in PDD's life and the pressure from family members because they often lack the information-processing skills to process optimum behavioral alternatives and the social skills to put these strategies into action [27, 29–31]. For this reason, nurse should enhance coping skills, medication self-efficacy, information-processing skills,and social skill in PDD by designing program interventions that possibly help to make information-processing skills easier than the past by implementation via information system and interactive system such as website, Facebook, and mobile phone.

5.3. Environmental protective factors

These factors include effective family problem-solving and supportive psychosocial interventions.

Effective family problem-solving refers to the ability of family members to solve their problems, not only the individual problems of PDD but also the problems of all family members, which are always related to the conditions of each individual's life, his or her household, the neighborhood or town, and the larger community [5].

Social support: stress factors can exacerbate the psychotic symptoms. Therefore, the support from family, friends, medical specialists, or clinical practitioners represents the key components in helping persons to raise the protective factors for the reduction of symptoms severity.

Supportive psychosocial interventions: the combination of pharmacotherapy and psychosocial intervention has been recommended for treatment of PDD to reduce psychotic symptoms, and the individuals can be effectively engaged and continue the treatment [32]. In order to meet the goals of intervention in terms of reducing the stress of the patient, provide support for relapse prevention, promote adaptation of patient to living in the community, and facilitate continued decrease in symptoms and consolidation of remission, social support and supportive psychosocial interventions are recommended for the nursing role.

5.4. The environmental potentiates and stressor

According to the model, the environmental potentiates and stressor compose of the critical or emotionally over-involved attitudes toward the patient, an overstimulating social environment, and stressful life events.

The critical or emotionally over-involved attitude toward the patient is, namely, expressed emotion; according to this alternative model, there might not be a causal relationship between the highly expressed emotion (EE) of significant others and relapse; they might be jointly related to a third variable (severity of illness). Combine these two models by postulating feedback loops from behaviors of patient to attitudes and behaviors of significant others, thereby creating bidirectional influence patterns [29, 30].

This model views the social environment as stressful life events and highly expressed emotion. The occurrence of key life events leading to a high level of environmental stress interacts with preexisting biological vulnerability factors and increases the likelihood that psychotic symptoms will return. Additionally, critical and emotionally over-involved attitudes at least partially represent responses to the heavy burden that mental illness places on significant others and that the persons who have a more severe, relapse-prone form of illness place the heaviest burden on significant others.

For stressful life events, empirical data indicated that stressful life events rule on independent of the patient's behavior are more common in the weeks immediately before relapse. Additionally, the initial findings showed the roles of stress factors in other aspects of the early course of drug use that have significant associations with social functioning. Moreover, stressors in the form of stressful life events are realized as factors that interact with preexisting vulnerability characteristics to produce vicious circles, which lead, in turn, to psychotic episodes.

All of expressed emotion, both negatively expressed emotion and positively emotional expressed emotion, and stressful life events were included in nursing implementation for PDD.

5.5. Outcomes

This model indicated that the outcomes were social function, psychotic symptoms, and occupational functioning.

Social function (social dysfunction) is a hallmark characteristic of PDD that has important implications for the development, course, and outcome of illness. Additionally, social dysfunction generally worsens over the course of the disorder and is often resistant to drug treatment [31, 32].

Psychotic symptoms are a central element of drug use and are the outcome factors that reverse to other factors. Coping, self-efficacy, EE, stressful life events, and social functioning lead to the severity of psychotic symptoms that are exacerbated by drug use.

Occupational functioning of drug use is associated with a significant decrease in such functioning. "Less than 20% of individuals with PDD can maintain regular employment, and there is a relationship between psychotic symptoms and occupational functioning among PDD." Empirically derived factor structures have shown that symptoms fall into five components. One such factor structure is derived from the following components: positive, negative, hostility, cognitive, and emotional discomfort.

Occupational functioning is defined as competency with one's task performance associated with valued roles, sense of self-satisfaction, productivity, communication/interaction skills, leisure and rest in response to demands of the internal and/or external environment, and

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environments, where context, temporal factors, and physical and psychological phenomena are inseparable (**Figure 1**).

In conclusion, the prevalence of PDD can be as high and create vulnerability for drug use. Providing optimal care and intervention for this population such as (a) awareness and assessment about biological factors, (b) enhanced personal skill (coping skills, medication self-efficacy, information-processing skills, and social skill), (c) supportive psychosocial interventions, (d) social support, (e) expressed emotion program, (f) social function intervention, and (g) occupational functioning program, these all require development and implementation of a best practice protocol.

6. Nursing care for persons with drug addiction

Nursing interventions are helping PDD acknowledge the drug addiction and facilitating development of effective coping skills, medication self-efficacy, information-processing skills, occupational skill, and social skill by using the nursing process to (a) assessment information and health-care needs of PDD and (b) identified nursing diagnosis based on NANDA International (NANDA-1) classification system. Nursing diagnosis of PDD includes acute confusion, ineffective coping, and dysfunctional family process:

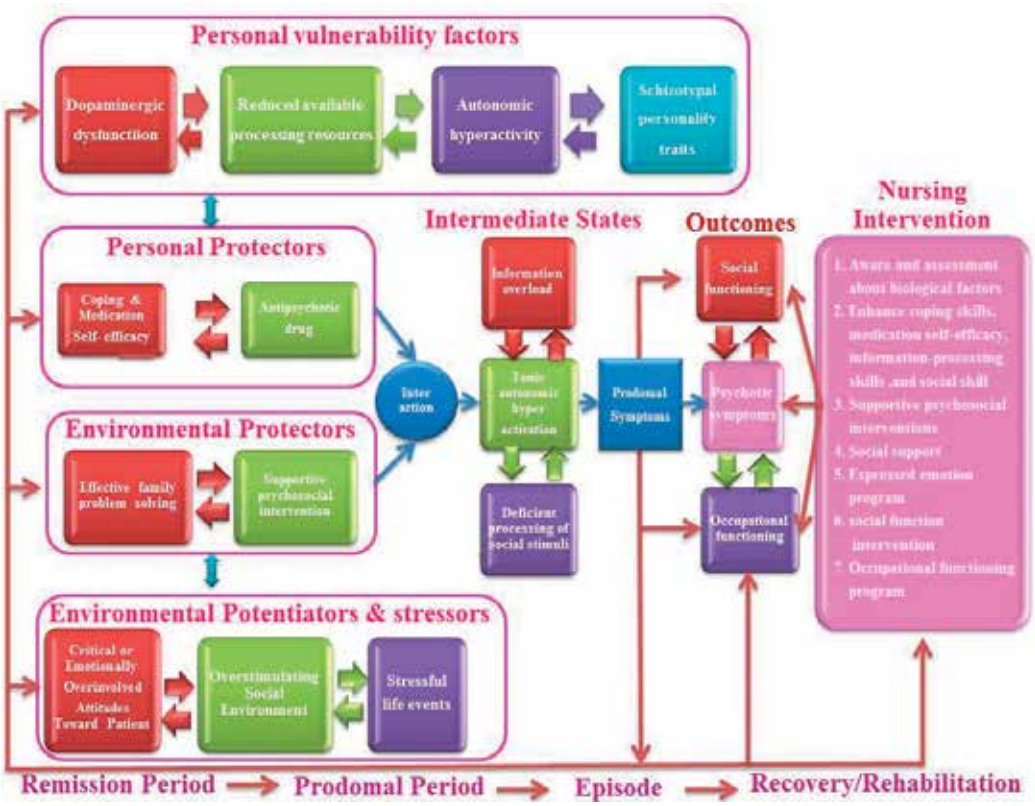

Figure 1. Vulnerability-stress model of nursing intervention for PDD adapted from vulnerability-stress model [28–30].

1. Supportive psychosocial interventions
2. Social support
3. Expressed emotion program
4. Social function intervention
5. Occupational functioning program

Professional nurse is working as an integral part of the multidisciplinary treatment team in caring of symptomatic care, limits setting, structured support, psychoeducation, and referrals for continuing care in the community. Family and caregivers are significant in the treatment program to be the part of resolving the problem and feelings surrounding the persons' drug use to facilitate recovery sessions.

6.1. Nursing diagnosis: disturbed sensory perception (specify: visual, auditory, kinesthetic, gustatory, tactile, olfactory)

Change in the amount or patterning of incoming stimuli accompanied by a diminished, exaggerated, distorted, or impaired response to such stimuli.

6.1.1. Assessment data

- Positive psychotic symptoms
- Disorientation
- Fear
- Low concentrate
- Cannot perform personal hygiene or grooming

6.1.2. Nursing outcomes

• Immediate	Persons with drug addiction will: • Be oriented to person, time, place, and situation • Establish a balance of rest, sleep, and activity • Establish adequate nutrition, hydration, and elimination • Perform in self-care activities
• Stabilization	Persons with drug addiction will: • Maintain adequate, balanced physiologic functioning • Communicate effectively with others
• Community	Persons with drug addiction will: • Demonstrate independence in self-care activities • Manage chronic illnesses, if any, effectively • Avoid the use of drugs or other precipitating factors

6.1.3. Implementation

1. Assessment data include hallucinations, disorientation, fear, low concentrate, and ability to perform to personal hygiene or grooming.
2. Be alert to the PDD's physical needs because of crucial. He or she may not attend to hunger, fatigue, and so forth.
3. Observe the PDD's patterns of food and fluid intake; monitor and record intake, output, and daily weight. Adequate nutrition is important for the PDD's well-being.
4. Monitor the PDD's elimination patterns by using PRN medication to the PDD to maintain bowel regularity. Constipation is a frequent side effect of major tranquilizers.
5. Calming activities before bedtime facilitate rest and sleep. Institute relaxing, quieting activities before bedtime (tepid bath, warm milk, quiet environment).
6. Present reality by spending time with the PDD to facilitate reality orientation because your physical presence is the reality.
7. Reorient the PDD to person, place, and time as necessary, by using the PDD's name often and by telling the PDD your name, the date, the place and situation, and so forth because reminding the PDD of surroundings, people, and time increases reality contact.
8. Evaluate the use of touch with the PDD. Touch can be reassuring and may provide security for the PDD.
9. Be simple, direct, and concise when speaking to the PDD. Talk with the PDD about concrete or familiar things; avoid ideological or theoretical discussions. The PDD's ability to process abstractions or complexities is impaired.
10. *Direct activities toward helping the PDD accept and remain in contact with reality; use recreational or occupational therapy when appropriate. The greater the PDD's reality contact and involvement in activities, the less time he or she will deal in unreality.
11. Provide information and explanations to the PDD's family or significant others.

The family or significant others may have difficulty understanding that psychotic behavior is related to medical illness.

7. Evaluation of nursing outcomes

7.1. Nursing diagnosis: ineffective denial

Conscious or unconscious attempt to disavow the knowledge or meaning of an event to reduce anxiety and/or fear, leading to the detriment of health.

7.1.1. Assessment data

- Dose and frequency of drug use or dependence
- Insight

- Blaming others
- Help-seeking
- Accepting personal responsibility
- Poor self-perception
- Intellectualization

7.1.2. Nursing outcomes

•	Immediate	Persons with drug addiction will: • Participate in treatment program • Identify negative effects of his or her behavior on others • Abstain from drug use • Verbalize acceptance of responsibility for own behavior
•	Stabilization	Persons with drug addiction will: • Express acceptance of drug dependence as an illness • Maintain abstinence from chemical substance • Demonstrate acceptance of responsibility for own behavior • Verbalize knowledge of illness and treatment plan
•	Community	Persons with drug addiction will: • Follow through with discharge plans regarding employment, support groups, and so forth

7.1.3. Implementation

1. Assessment data include minimization of drug use or dependence, blaming others for problems, reluctance to discuss self or problems, poor insight, failure to accept responsibility for behavior, viewing self as different from others, and rationalization of problems (intellectualization).

2. Avoid the PDD's attempts to focus on only external problems (such as marital or employment problems) without relating them to the problem of substance use. The problem of substance use must be dealt with first because it affects all other areas.

3. Encourage the PDD to identify behaviors that have caused problems in his or her life. The PDD may deny or lack insight into the relationship between his or her problems and behaviors.

4. Do not allow the PDD to rationalize difficulties or to blame others or circumstances beyond the PDD's control. Rationalizing and blaming others give the PDD an excuse to continue his or her behavior.

5. Consistently redirect the PDD's focus to his or her own problems and to what he or she can do about them. You can facilitate the PDD's acceptance of responsibility for his or her own behavior.
6. Encourage other PDD in the program to provide feedback for each other. Peer feedback usually is valued by the PDD, because it is coming from others with similar problems.
7. Positively reinforce the PDD when he or she identifies and expresses feelings or shows any insight into his or her behaviors and consequences. You convey acceptance of the PDD's attempts to express feelings and to accept responsibility for his or her own behavior.
8. Evaluation of nursing outcomes.

7.2. Nursing diagnosis: ineffective coping

Inability to form a valid appraisal of the stressors, inadequate choices of practiced responses, and/or inability to use available resources.

7.2.1. Assessment data

- Stressful life crisis
- Isolative behavior
- Low self-esteem
- Impulse control
- Superficial relationships
- Effective problem-solving skills
- Ineffective coping skills
- Inability to form and maintain intimate personal relationships
- Avoidance of problems or difficult situations

7.2.2. Nursing outcomes

•	Immediate	Persons with drug addiction will: • Express feelings directly and openly • Engage in realistic self-evaluation • Verbalize process for problem-solving • Practice nonchemical alternatives to dealing with stress or difficult situations
•	Stabilization	Persons with drug addiction will: • Develop a healthful daily routine regarding eating, sleeping, and so forth • Verbalize increased self-esteem, based on accurate information

•	Community	Persons with drug addiction will: • Demonstrate effective communication with others • Demonstrate nonchemical methods of dealing with feelings, problems, and situations • Participate in follow-up or aftercare programs and support groups

7.2.3. Implementation

1. Assessment data include stressful life crisis, isolative behavior, low self-esteem, impulse control, superficial relationships, effective problem-solving skills, ineffective coping skills, inability to form and maintain intimate personal relationships, and avoidance of problems or difficult situations.

2. Encourage the PDD to explore alternative ways of dealing with stress and difficult situations. The PDD may have little experience dealing with life stress without chemicals and may be learning for the first time how to cope, solve problems, and so forth.

3. Help the PDD develop skills in defining problems, planning problem-solving approaches, implementing solutions, and evaluating the process. You can provide knowledge and practice of the problem-solving process in a nonthreatening environment.

4. Help the PDD express feelings in acceptable ways, and give positive reinforcement for doing so. You are a sounding board for the PDD. Your feedback encourages the PDD to continue to express feelings.

5. Involve the PDD in a group of his or her peers to provide confrontation, positive feedback, and sharing of feelings. Groups of peers are a primary mode of treatment in drug addiction treatment, and provide honesty, support, confrontation, and validation, based on common experiences.

6. Focus attention on the "here and now": what can the PDD do now to redirect his or her behavior and life? The PDD cannot change the past. Once he or she acknowledges responsibility for past behavior, it is not helpful or healthy to ruminate or feel guilty about the past.

7. Avoid discussing unanswerable questions, such as why the PDD uses substances.

Asking why is frustrating as well as fruitless; there is no answer.

8. Guide the PDD to the conclusion that sobriety is a choice he or she can make

Sobriety, including abstinence from all substances, is associated with greater success in recovery.

1. Help the PDD view life and the quest for sobriety in feasible terms, such as "What can I do today to stay sober?" The PDD have many barriers to success in abstinence. External stimuli and internal stimuli are the big deal to challenge their self-control to say no and stop using drug.

2. *Refer the PDD to a chaplain or spiritual advisor of his or her choice, if indicated. The PDD may be overwhelmed with guilt or despair. Spiritual resources may help the PDD maintain sobriety and find social support.
3. *Teach the PDD and significant others about prevention of hepatitis and HIV transmission, and refer them for testing and counseling if appropriate. PDD who use substances are at increased risk for hepatitis and HIV transmission by sharing needles and by sexual activity, especially when judgment is impaired by drug use.
4. *Refer the PDD to vocational rehabilitation, social services, or other resources as indicated. The PDD may need a variety of services to reestablish successful functioning.
5. *Refer the PDD and significant others to join motivation interview session or other support groups in the community or via the Internet as indicated. Many PDDs and significant others benefit from continued support for sobriety after discharge. *Note:* There are many different groups modeled on the basic 12-step program, including gay, lesbian, and non-Christian groups.
6. *Refer the PDD for treatment for other problems as indicated. Drug dependence often is associated with posttraumatic behavior, abusive relationships, and so forth.
7. Evaluation of nursing outcomes.

8.1. Nursing diagnosis: risk for injury

At risk of injury as a result of environmental conditions interacting with the individual's adaptive and defensive resources.

8.1.1. Assessment data

8.1.1.1. Risk factors

- Feelings of hostility
- Fear
- Cognitive deficits
- Emotional impairment, mood alteration, and drastic mood swings
- Integrative dysfunction
- Sensory or motor deficits
- Inability to perceive harmful stimuli
- Confusion
- Uncooperative, hostile behavior
- Disorientation
- Seizures

- Hallucinations
- Delusions
- Physical pain or discomfort
- History of combative or acting-out behavior
- Disturbances of concentration, attention span, or ability to follow directions

8.1.2. Nursing outcomes

• Immediate	Persons with drug addiction will: • Be safe and free from injury • Demonstrate decreased aggressive or hostile behavior • Respond to reality orientation • Verbally express feelings of fear or anxiety • Not harm others or destroy property • Be free from toxic substances
• Stabilization	Persons with drug addiction will: • Demonstrate adherence to the treatment regimen • Verbalize knowledge of drug abuse as a disease • Verbalize risks related to drug ingestion • Verbalize plans for further treatment, if indicated
• Community	Persons with drug addiction will: • Abstain from the use of substances • Accept referral to drug abuse treatment • Participate in treatment or follow-up care as needed

8.1.3. Implementation

1. Assessment data include feelings of hostility, fear, cognitive deficits, emotional impairment, integrative dysfunction, sensory or motor deficits, inability to perceive harmful stimuli, mood alteration, drastic mood swings, confusion, uncooperative, hostile behavior, disorientation, seizures, hallucinations, delusions, physical pain or discomfort, history of combative or acting-out behavior, disturbances of concentration, attention span, or ability to follow directions.

2. Place the PDD in a room near the nurses' station or where the staff can observe the PDD closely. The PDD's safety is a priority.

3. It may be necessary to assign a staff member to remain with the PDD at all times. One-to-one supervision may be required to ensure the PDD's safety.

4. Institute seizure precautions as needed, according to hospital policy (padded side rails, airway at bedside). You should be prepared for the possibility of withdrawal seizures.

5. Restraints may be necessary to keep the PDD from harming himself or herself. If the PDD cannot be protected from injury in any other manner, restraints may become necessary. Restraints are not to be used punitively.

6. Do not moralize or chastise the PDD for substance use. Maintain a nonjudgmental attitude. Remember that substance use and substance abuse are illnesses and out of the PDD's control at this time. Moralizing belittles the PDD.

7. Talk with the PDD using simple, concrete language. Do not attempt to discuss the PDD's feelings, plans for treatment, or possible changes in the PDD's lifestyle while the PDD is influenced by the drug or in acute or severe withdrawal. The PDD's ability to process abstractions is impaired during withdrawal. You and the PDD will be frustrated if you attempt to address interpersonal or complex issues at this point.

8. Reorient the PDD to person, time, place, and situation as indicated when the PDD is confused or disoriented. Presentation of concrete facts facilitates the PDD's reality contact.

9. Decrease environmental stimuli (bright lights, television, visitors) when the PDD is agitated. Avoid lengthy interactions; keep your voice soft; and speak clearly. Your presence and soft tones can be calming to the PDD. He or she is not able to deal with excessive stimuli.

10. Reassure the PDD that the environment is safe by briefly and simply explaining procedures, routines, and so forth. The psychotic PDD frequently acts out based on fear as a means of protecting himself or herself.

11. Protect the PDD from harming himself or herself by removing the items that could be used in self-destructive behavior or by restraining the PDD. The PDD's physical safety is a priority.

12. Remove the PDD to a quiet area, or withdraw your attention if the PDD acts out, provided there is no potential danger to the PDD or others. Decreased attention from you and others may help to extinguish unacceptable behavior.

13. Set limits on the PDD's behavior when he or she is unable to do so if the behavior interferes with other PDDs or becomes self-destructive. Do not set limits to punish the PDD. Limit setting is the positive use of external control to promote safety and security.

14. Evaluate the PDD's response to the presence of family and significant others. If their presence helps calm the PDD, maximize their visiting time, but if the PDD becomes more agitated, limit visits to short periods of time with one or two people at a time.

15. Evaluation of nursing outcomes.

8.2. Nursing diagnosis: ineffective health maintenance

Inability to identify, manage, and/or seek out help to maintain health.

8.2.1. Assessment data

- Fear
- Drug addiction and dependence

- Physical discomfort
- Sleep disturbances
- Low self-esteem
- Ineffective coping strategies
- Feelings of apathy
- Physical symptoms (impaired nutrition, fluid, and electrolyte imbalance)

8.2.2. Nursing outcomes

- Immediate — Persons with drug addiction will:
  - Establish nutritious eating patterns
  - Establish a balance of rest, sleep, and activity
  - Establish physiologic homeostasis
- Stabilization — Persons with drug addiction will:
  - Maintain physiologic stability
  - Verbalize knowledge of prevention of HIV transmission
  - Agree to participate in a treatment program
- Community — Persons with drug addiction will:
  - Follow through with discharge plans regarding employment, legal involvement, family problems, and financial difficulties
  - Abstain from alcohol and drugs

8.2.3. Implementation

1. Assessment data include fear, drug addiction and dependence, physical discomfort, sleep disturbances, low self-esteem, ineffective coping strategies, feelings of apathy, and physical symptoms (impaired nutrition, fluid, and electrolyte imbalance).

2. *Obtain the PDD's history, including the kind, amount, route, and time of the last drug use. Consult the PDD's family or significant others to obtain or validate the PDD's information if necessary. *Note:* The PDD may report an inaccurate estimate of drug use (either minimized or exaggerated). Baseline data can help you anticipate the onset, type, and severity of physical withdrawal symptoms.

3. Be aware of PRN medication orders to decrease physical symptoms. Do not allow the PDD to be needlessly uncomfortable, but do not use medications too liberally. The judicious use of PRN medications can decrease the PDD's discomfort but must be used cautiously, as the PDD is already experiencing drug effects.

4. Blood test and urine specimens are needed for drug screening on admission.

5. Laboratory tests may need to be surrendered to authorities.

6. Monitor the PDD's intake and output and any pertinent laboratory values, such as electrolytes. The PDD in withdrawal is at risk for fluid and electrolyte imbalances.

7. Encourage oral fluids, especially juice, fortified malts, or milk. If the PDD is vomiting, intravenous therapy may be necessary. Milk, juice, and malts provide a maximum of nutrients in a small volume. Fluids usually are tolerated best by the PDD initially.

8. Talk with the PDD quietly in short, simple terms. Do not chatter or make social conversation. Excessive talking on your part may be irritating to the PDD in withdrawal.

9. Be comfortable with silence. You may touch or hold the PDD's hand if these actions comfort or reassure the PDD. Your physical presence conveys your acceptance of the PDD.

10. Encourage the PDD to bathe, wash his or her hair, and wear clean clothes. Personal cleanliness will enhance the PDD's sense of well-being.

11. Assist the PDD as necessary; it may be necessary to provide complete physical care depending on the severity of the withdrawal symptoms. You should attend to the PDD's hygiene only to the extent that he or she cannot do so independently.

12. *Teach the PDD that substance dependence is an illness and requires long-term treatment and follow-up. Refer the PDD to a substance dependence treatment program. A substance withdrawal program deals only with the PDD's physical dependence. Further therapy is needed to address the primary problem of substance dependence.

13. Family and significant others are affected by the PDD's drug use and also need help with their own issues. Dealing with relapses was difficult, and public resources were lacked. The coping strategies that they use were suggestion, religiosity and faith, isolation, and ambivalence in thoughts and attitudes [32]. Therefore, nurse should enhanced coping strategies and knowledge in family members and significant others of PDD as well.

14. Teach the PDD about the prevention of HIV transmission. PDD who use intravenous drugs are at increased risk for HIV transmission by sharing needles and by sexual activity, especially when judgment is impaired.

15. *If the PDD is HIV positive, refer him or her for medical treatment and counseling related to HIV disease. PDD who are HIV positive face the risk of AIDS as well as the loss of friends, family, housing, insurance, employment, and so forth. PDD may be unaware of available medical treatment and supportive resources.

16. Evaluation of nursing outcomes.

9. Conclusion

Quality of life of PDD is the indicator to illustrate the quality of nursing intervention outcomes. Detection of drug addiction is most effective when multiple types of assessment are used. A combination of interview, screening instruments, information from collateral sources, and laboratory tests such as urine test and drug screens should be used.

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Conflict of interest

The author has no conflicting interest to declare.

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Chapter 5

Molecular-Cellular Targets of the Pathogenetic Action of Ethanol in the Human Brain in Ontogenesis and the Possibility of Targeted Therapy Aimed at Correcting the Effect of Pathogenic Factors

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Additional information is available at the end of the chapter

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Abstract

Prenatal exposure to ethanol has an impact on angiogenesis and synaptogenesis and formation of neurotransmitter receptors in the brain of the embryo and fetus. Compensatory mechanism of hypoxia in conditions of prenatal exposure to alcohol involves decrease in the perimeter of the vessel and the area of the vessel in the cross section and an increase in the number of vessels in the brain. A significant effect of prenatal exposure to ethanol on the development of synaptic structures in the developing brain of the fetus was expressed in the slowing down of the formation of synaptic contacts and in the reduction of their number in comparison with the norm. Shaping synaptic contact is one of the leading processes during which largely determine the future integrative brain capabilities. The properties of benzodiazepine receptors in the developing brain of the human's embryo and fetus under prenatal alcohol influence were characterized by a decrease in affinity and an increase in their density as compensatory adaptation of the fetal nervous system to the effects of alcohol. It is reflected on during synaptogenesis in the developing brain and can lay the basis of severe disorders in the unborn child. Alcohol abuse induces neuroadaptive alters of benzodiazepine receptor system in the brain in patients with alcoholism that can modulate $GABA_AR$ and mediation of GABA in the brain, which can cause alcohol addiction.

Keywords: alcohol, alcoholism, embryo, fetus, brain, vessel, synapse, benzodiazepine receptor, GABA

1. Introduction

Prenatal alcohol exposure at moderate and higher levels increases the odds of child behavior problems with the dose, pattern and timing of exposure affecting the type of behavior problems expressed [1, 2]. Disruption in the neural activation of the prefrontal cortex (PFC) and neurobehavioral disorders were detected in children with severe prenatal exposure to alcohol (PAE) [3–6]. The developing brain is extremely sensitive to the effects of ethanol [6, 7]. The use of significant doses of ethanol during pregnancy can result in a combination of profound morphological and neurological changes called fetal alcohol syndrome (FAS) [8, 9].

The use of moderate doses of ethanol can cause abnormalities that are not associated with multiple morphological and neurological damage associated with FAS, but are associated with the development of cognitive deficits and more serious consequences in the offspring, which can be particularly pronounced in puberty [10, 11]. This formed the basis for an expanded diagnostic classification of fetal defects and a new category—neurodevelopmental disorders caused by alcohol. There is a complex relationship between the dose, nature and timing of prenatal exposure to alcohol and problems of child behavior in the future. Fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE) are preventable forms of mental retardation and developmental disability caused by heavy prenatal alcohol exposure.

The human brain is arguably one of the most complicated organism living systems. This elaborate structure originates from a simple neural tube, followed by a series of differentiation processes. The possible contributions of PAE to nervous system malformations must be considered in the context of developmental timing. Neural tube defects typically occur during weeks 3–4 of human gestation [12]. Morphometric characterization of the brain at each stage not only aids in understanding this highly ordered developmental process but also provides clues to detecting abnormalities caused by genetic or environmental factors. Some observations have shown that the development of brain abnormalities: brain microencephaly, neural tube defects, hydrocephalus with various etiology and severity and cerebral vascular lesions, is not associated with complications at birth or as a result of prematurity [12].

Alcoholism of the mother can lead to the development of the FAS or FAE, which is apparent as a complex of disorders in the somatic and mental domains, reflecting impaired nervous system development [13, 14]. A number of authors have shown that the development of this syndrome is mainly due to impaired fetal brain development [15–17], starting from the earliest stages of neurogenesis and brain formation structures, which leads to a delay in migration and differentiation of neurons and some disorders of angiogenesis and synaptogenesis [15, 18–21]. The function of the blood-brain barrier (BBB) in the embryonic brain is mediated by cellular elements—endotheliocytes, developing glial cells and pericytes, and also by the noncellular structures of capillary basal membranes. Elements of BBB are under the direct influence of alcohol, with prenatal exposure to it during pregnancy in conditions of mother's alcohol abuse. In the early stages (5–6 weeks of intrauterine development), the neural tube does not have blood vessels. Neuroectodermal structures are fed from a protein-rich fluid into the neural tube. Due to their rapid growth and increase in mass, nutrients enter the newly formed blood vessels [22, 23].

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At the molecular-cellular level, changes in the nervous system in the formation of alcohol dependence are associated with activation of the processes of synaptic plasticity. With the development of alcohol dependence, stimulation of neuroplasticity is considered one of the reasons for the rapid formation of a behavioral stereotype—addictive behavior. At the same time, long-term consumption of ethanol leads to a permanent disruption of synaptic plasticity, which can cause cognitive impairment, learning and memory problems, and the formation of alcoholic motivation and obsessive directed behavior in experimental animals and people with prolonged use of alcohol [24].

Neurogenesis is the basis for ensuring the plastic function of the brain and is regulated by many factors. Stimulation of neurogenesis is observed in a number of pathological conditions: brain ischemia, trauma, the development of neurodegenerative pathology, the influence of neurotoxic agents, including high doses of alcohol, prolonged use. Neurogenesis is the key adaptive function of the brain, represents one of the most important mechanisms of brain plasticity, which is expressed in an increase in the number of cells involved in the restructuring of neuronal networks. Exposure to ethanol limits early development by delaying or inhibiting the formation of postsynaptic neurons from progenitor neuronal cells (PNA) [19–21, 25].

The effects of ethanol in the early stages of development can disrupt the signaling mechanisms that regulate synaptogenesis. Negative effects of ethanol are associated also with its influences on the lipid component of neuron membranes. As lipotropic agent, ethanol is able to change the essential physico-chemical properties of cell membranes, which is reflected in the current fetal brain synaptogenesis [26, 27]. It has been shown that ethanol triggers apoptotic neurodegeneration [17] in the developing brain, when administered to infant rodents during the period of synaptogenesis, also known as the brain growth spurt period [19, 20]. Prenatal alcohol exposure inhibits neurogenesis [24, 28] and dendritic growth of newborn neurons [18].

The effects of ethanol cause neuronal death, impairment of differentiation, migration of neuronal elements and changes in neuronal plasticity, acting through various receptors and their signaling pathways [29]. Rapidly developing neural networks form synapses, mediate the communication and functioning of a multitude of synapses, through neuromediation part of them associated with a neurotransmitter gamma-aminobutyric acid (GABA), which operates via chloride-permeable GABA type A receptor channels. At an early stage of development, neurons have a high concentration of intracellular chloride, which leads to an outflow of chloride and exciting actions of GABA in immature neurons. Transmission of GABA signals is also established prior to the formation of glutamatergic transmission. Thus, GABA is the main excitatory transmitter in the early stages of development and modulates the cell cycle, the formation of cells and their migration [30–33].

The currently accepted position is that the adverse effects of ethanol are also linked with interactions with specific proteins, ion channels and receptors, leading to changes in their functions [17, 34, 35]. The ability of ethanol to interact with receptor proteins was demonstrated, which contributed to a change in neuronal excitability. GABAergic neurotransmission plays an important role in the mechanisms of action of ethanol. GABA receptors fulfill the inhibitory role in the CNS. $GABA_AR$ is an oligomeric protein complex, which contains various allosteric binding sites that modulate receptor activity, and these allosteric binding sites are the

targets for various agents, including benzodiazepines (BzD) and ethanol. Benzodiazepines, which bind to the specific sites—benzodiazepine receptors (BzDR) on the GABA receptor complex, change its conformation and affinity [35–37]. Sedative and anxiolytic effects of alcohol and benzodiazepines are based on the potentiation of inhibitory effects of GABA by the inactivation of $GABA_A$ receptors. In the experiment, it was shown that the acute effect of ethanol enhances the gain of GABAergic transmission, but chronic alcoholization increases the binding of inverse BzDR agonists and reduces GABAergic function [38, 39]. Recent data point to the existence of a relationship between the actions of ethanol and the functioning of the GABA-BzD-receptor complex.

One of the theories of alcoholism involves a shift in the general excitability of the brain as a result of reduced inhibition processes. $GABA_AR$ are modulated by the main inhibitory neurotransmitter in the central nervous system—GABA, are potential targets for alcohol and mediate the effects of ethanol [40–44]. Alcohol can activate $GABA_AR$, possesses anxiolytic properties, and in connection with its use of this ability is a form of self-medication by patients. Decrease of GABAergic functioning was found in patients with alcoholism and persons with a high risk of alcohol addiction development [44, 45]. The sedative and anxiolytic effects of alcohol and BzD are associated with potentiating of the inhibitory effect of GABA [41, 43]. At current time has not been revealed endogenous ligands for BzDR, as for opiate receptors and others, but their role is very significant in neuropharmacology of inhibitory processes in the CNS. There are cross-reactions (tolerance and dependence) between alcohol and BzD, which confirm the interaction of ethanol with BzDR [38].

In addition to BzDR "central" type (CBR) that associated with $GABA_AR$ and having synaptic localization, known BzDR "peripheral" type (PBR), not associated with $GABA_AR$ and localized in the mitochondrial membrane, more of them are located in the glial cells of the brain.

These receptors make very important function—transfer of cholesterol into the mitochondria; this is limited step in the regulation of the neurosteroids biosynthesis. Neurosteroids are endogenous modulators of the $GABA_A$/BzDR in the CNS [46]. BzD, anxiolytics, anesthetics and alcohol are implementing some of its effects through the PBR and regulating production of neurosteroids and their active metabolites, which are very significant for normal brain functioning [46, 47].

Understanding of the basic signaling mechanisms that regulate the excitability and inhibition of brain processes involved in the formation of alcohol addictive behavioral, the determination of the target of alcohol effects can contribute to the creation of new pharmaceutical preparations to influence these targets and to develop a potentially effective therapies to prevent the consequences of alcohol abuse and withdrawal.

In this regard, it is impossible to overestimate the importance of further studying the processes associated with angiogenesis and synaptogenesis and the formation of receptor systems in the developing human brain, in particular, the GABA-benzodiazepine receptor system under conditions of chronic effects of ethanol, their role in the development of alcohol dependence, which may contribute to further clarification of the etiopathogenesis of the disease and the search for new medications necessary for pharmacotherapeutic correction, and prevention of harmful effects of ethanol.

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2. Neuroplastic features of vascular development, synaptic contacts and formation of benzodiazepine receptors in the developing human fetal brain under conditions of prenatal exposure to alcohol. Adaptive changes in the benzodiazepine receptor system of the human brain under the influence of chronic alcoholization

The study of the effect of mother's alcoholism on the developing fetal brain (prenatal exposure to alcohol) was carried out in the brain tissue of embryos and human fetuses at the 7–15 week of pregnancy in accordance with the requirements of the Ethics Committee and with the consent of patients during abortion procedures under strict medical indications. About 33 embryos and fetuses were obtained from female, suffering from alcoholism and constituted the main study group. The age of women who suffered from alcoholism was 26–39 years old, and the duration of the disease was from 3 to 13 years. In all cases, according to ICD-10 criteria, alcoholism of grade II was diagnosed (ICD-10 F10.201, F10.202). The diagnosis of alcoholism was established in the Department of Addictive Conditions, the Institute of Mental Health, Tomsk National Scientific Medical Center Russian Academy of Science (RASci). The control group included samples of the brain tissue of embryos and fetuses obtained from healthy women who do not have a history of neurological or mental diseases comparable in age. Exclusion criteria were cases of adverse effects on brain development of embryos, namely exposure to radiation, chemicals, certain pharmacological agents and maternal diseases during pregnancy: influenza, rubella, toxoplasmosis and others.

Ultrastructure of synaptic contacts and vessels of the brain tissue from embryonic and fetal brain were examined under JEM-100B and JEM-100CX electron microscopes. Electron microscopy studies addressed the intermediate layer of the wall of the forebrain, which is an accumulation of neuroblast and glioblast (including microglial cells), between which blood vessels start to grow. Morphometric analysis was performed using photographic prints from 6 to 9 cm negatives obtained from the electron microscopes. Some negatives were digitized with the scanner without intermediate paper prints. Scion Image for Windows, developed at the National Institutes of Health by Scion Corporation, was used to assess the areas of presynaptic terminals, their perimeters and the lengths of postsynaptic densities. Quantitative assessments by computerized morphometric analysis were performed by subdividing electron micrographs of embryo brain synapses into four groups, according to the period of embryo development: 7–8, 9–10, 10–11 and 11–12 weeks. This was performed in both the study group and the control group. Analyses involved five cases for each age period in the control and study groups.

2.1. Vesicles in the human developing brain in conditions of prenatal exposure to alcohol

The rapidly growing neuronal structures of the developing brain of the embryo and fetus are powered by a protein-rich fluid in the lumen of the neural tube. Subsequently, this mechanism becomes inadequate when their mass increases, and the task of delivering nutrients and removing metabolic products falls on blood vessels. It is extremely important to assess the degree of alcohol exposure to vasculogenesis of the developing brain fetus under the influence of prenatal alcohol exposure associated with maternal alcoholism [48].

As our studies showed, the vessels in the developing brain of embryos and fetuses for 8–9 weeks of development under normal conditions and in the presence of prenatal exposure to alcohol consisted only of capillaries with thin walls. Endotheliocytes and pericytes are presented on microphotographs, and the lumen of the vessels was open and contained formed blood elements. On the vessels, a basal membrane, consisting of a loose fibrillar material, was visible. Morphological differences in the development of vessels between the embryos of the control and main groups during the 8–9 weeks of pregnancy were not observed. In samples of the brain tissue of the fetuses from the main experimental group, the developmental period of 10 weeks of pregnancy identified erythrocyte stasis in some forming vessels (**Figures 1** and **2**). Our data show that vessels in the human brain start to differentiate into arteries and veins from 10 weeks of gestation (**Figures 3** and **4**). Brain vessels are differentiated into arterioles, capillaries and venules. Capillary basal membranes in the main experimental and control group were already clearly visible at 12 weeks of development (**Figures 5** and **6**). In both groups, we found that the apical surfaces of endotheliocytes remained smooth, with only occasional microvillus and no

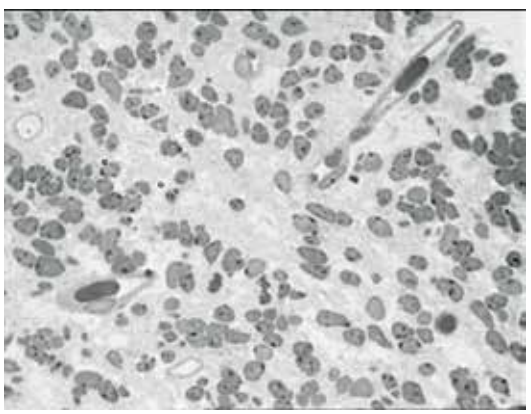

Figure 1. Capillaries of the intermediate layer embryonic brain. Control group, embryo 10 weeks of development. Coloring methylene blue. 740×.

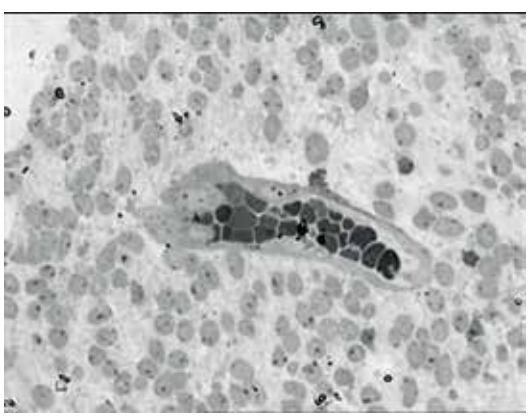

Figure 2. Stasis of erythrocytes in the vessel between the exact layers. Main group, embryo 10 weeks of development. Coloring methylene blue. 740×.

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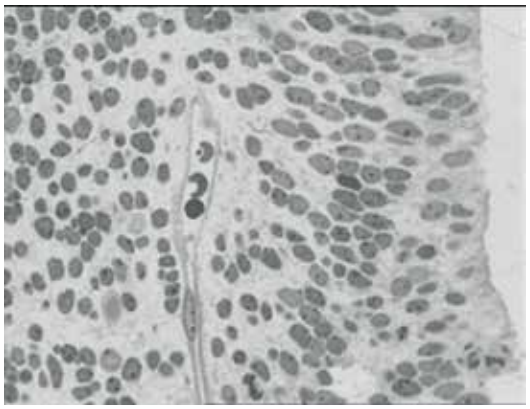

Figure 3. In the center of the picture, the forming venule with the shaped elements of blood in the lumen of the vessel. Control group, embryo 10 weeks of development. Coloring methylene blue, 740×.

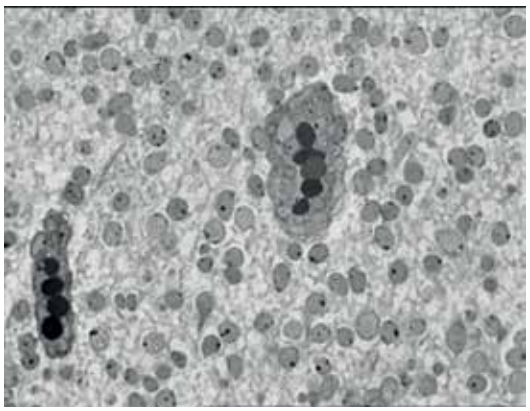

Figure 4. Two arterioles are visible in the field of vision. Control group, embryo 10 weeks of development. Coloring methylene blue, 740×.

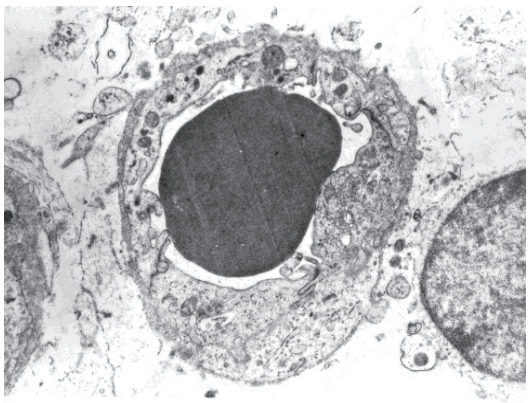

Figure 5. Ultrastructure of the basal membrane and capillary endothelium. The erythrocyte is visible in the lumen of the vessel. Main group, fetus 11–12 weeks of development, 10,000×.

significant protrusions of these cells into lumens, which remained open. We studied quantitative computer morphometric and established a series of characteristics of brain tissues samples in experimental group in comparison with control group (**Table 1**). Mean vessel cross-sectional areas and vessel perimeters in the main experimental group were significantly reduced by 11 weeks as compared with controls. The tendency for these measures to decrease in the experimental group compared with controls persisted at 12 weeks of development. Relative vessel cross-sectional area in samples of brain tissue from the main experimental group was greater than in control group. This measure was significantly greater in this group at 11 and 12 weeks of development. The number of vessels per unit area was significantly increased in the main experimental group at weeks 11 and 12 of fetal brain gestation as compared with control group.

The first blood vessels in the human endbrain are seen at the start of week 7 of embryogenesis in the area of the ganglionic tubercle (the rudiment of the corpus striatum) and rather later in the rudiment of the neocortex (lateral wall of the lateral ventricle). The formation of blood

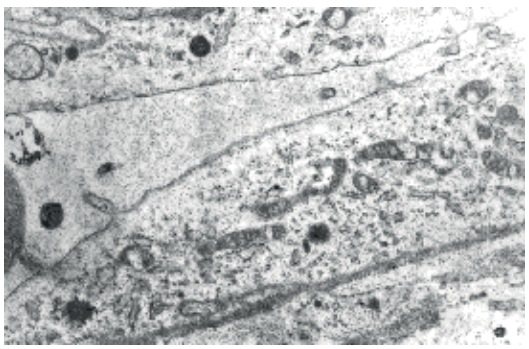

Figure 6. Basal membrane of the capillary without damage to the structure and a fragment of the cytoplasm of the endothelial cell. Main group, fetus 12 weeks of development, 45,000×.

Measure	Control group			Experimental group		
	Week 10	Week 11	Week 12	Week 10	Week 11	Week 12
Mean cross-sectional area of vessels, μm^2	45.61 ± 0.81**	65.73 ± 2.77	59.25 ± 5.38	49.08 ± 2.61	51.82 ± 3.07*	48.26 ± 1.67
Relative cross-sectional area of vessels in brain tissue, %	0.79 ± 0.11	1.26 ± 0.11	1.38 ± 0.2	1.02 ± 0.34	5.96 ± 1003*	7.59 ± 1.44*
Number of vessels per 1 μm^2 cross-sectional area of sections	0.00017 ± 0.000023	0.000189 ± 0.000013	0.00023 ± 0.000025	0.000214 ± 0.000078	0.001137 ± 0.000189*	0.000624 ± 0.000314*
Vessel perimeter, μm	349.44 ± 18.24	492.71 ± 34.28	269.83 ± 26.0	340.58 ± 35.87	292.20 ± 16.87*	244.69 ± 16.41

*Significant difference with control, $p < 0.05$.
**Significant difference compared with fetuses at 11 and 12 weeks of development, $p < 0.01$.

Table 1. Characteristics of brain vessels in normal conditions and in conditions of prenatal exposure to alcohol from week 10 to week 12 of intrauterine development (x ± sx).

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vessels in the neocortical rudiment directly precedes the large scale migration of neuroblasts from the ventricular zone to the area of the cortical plate [22]. At 6–9 weeks of prenatal ontogenesis, developing intracerebral structures are not differentiated into arteries and veins, but have the structure of capillaries, which is consistent with our data. Endotheliocytes of intracerebral vessels are not fenestrated and contain small numbers of transport vesicles. At 8–9 weeks of gestation, vessels acquire basal membranes, which consist of a very loose fibrillar material with low electron density; there are also locations at which the endothelium makes direct contact with the intercellular space. At areas of contact between endotheliocytes and pericytes, interaction of the plasmalemmas of these cell types is seen in the form of mutual invagination [22].

We have shown that the differentiation of vessels into capillaries, venules and arterioles in the developing brain of a person begins in 10–11 weeks of pregnancy. Computer morphometric analysis showed that the main effect of alcohol on the blood vessels in the brain of the fetuses was found during the development of 11 weeks of pregnancy. An increase in the number of vessels per unit cross-sectional area of the fetal brain was observed, while the average cross-sectional area and perimeter of the vessels were reduced. Under conditions of prenatal alcohol influence, brain tissue undergoes hypoxia. Increase in the number of cerebral vessels per unit cross-sectional area is a compensatory adaptive mechanism in the development of this state.

Thus, the influence of alcohol during pregnancy can significantly affect the dynamics of the cerebral circulation in the embryo and fetus, which is manifested by altering the vascularization of the developing human brain.

2.2. Cortical synaptogenesis in the human developing brain in conditions of prenatal exposure to alcohol

As a lipotropic agent, ethanol, is able to change the basic physicochemical properties of cell membranes, which are reflected in the current synaptogenesis of the embryonic brain in order to establish the nature of this effect, we conducted the following studies.

In human embryonic brain in the early period—7–8th week of gestation, the desmosome-like contacts were represented as we observed. Contacting membranes are in their middle part of thickening, which both sides approach to each other, forming a fissure. In these places of the thickening, the membrane can be connected. Electron-dense material is in the field of adhesion. Contacts of this type are found between dendritic processes and neuronal cells. During the development of 9–10 weeks of pregnancy, these types of contacts are less frequent. Contacts with the presence of vesicular elements have been revealed. Synaptic vesicles were rounded and had a bright center, and the diameter of these vesicles was approximately 40 nm. The width of the synaptic space of immature synapses was approximately 20 nm. The length of the area of the sealing membrane reached 0.1–0.15 microns (**Figure 7**). In the transitional stage from synapse-like contacts to their true synaptic form, single synaptic vesicles were visualized near the presynaptic membrane. Such synapses are located mainly at the lower boundary of the intermediate layer of the cerebral cortex (**Figures 8** and **9**). They can already be considered functionally competent.

Figure 7. Contact with uniformly thickened membranes. Main group, the fetus of 10–11 weeks. Magnification 160,000.

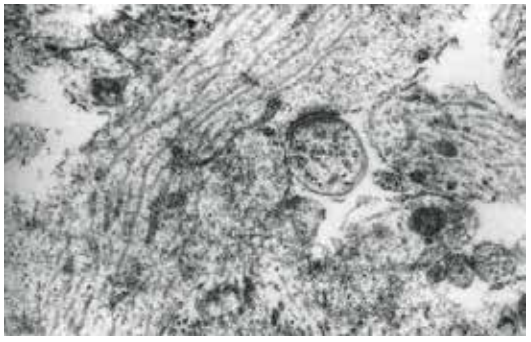

Figure 8. The emerging synapses in the cerebral cortex the intermediate layer brain. Main group, 12-week fetus. Magnification 40,000.

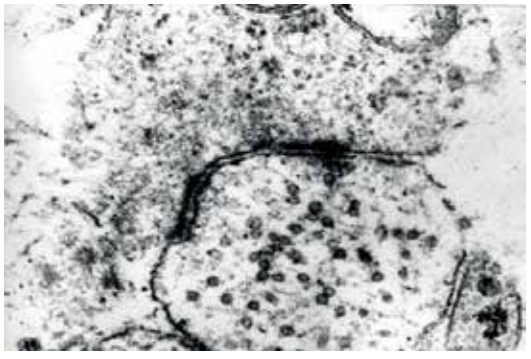

Figure 9. Completely formed functionally competent synapse. Main group, the fetus of 11–12 weeks. Magnification 70,000.

At the stage of fetal development 10–12 weeks, the number of synapses with relatively mature structures increased. They are located in the border of the ventricular and intermediate layers and in the intermediate layer of the cortical plate and nerve cells. In synaptic contacts, all the

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necessary components were found; from the mature synapses, their difference was the smaller number of synaptic vesicles. Synaptic contacts on neuroblasts and glioblasts have fewer synaptic vesicles compared to the synapses of the mature brain. All of the above features were inherent in both the control group and the main group of embryos and fetuses (**Figures 10** and **11**).

In the brain tissue of embryos and fetuses obtained from women suffering from alcoholism, a slowdown in the formation of synaptic structures was observed. Non-synaptic contacts in the samples of the main study group did not differ from those of control in the frequency of occurrence in the brain tissue and in its structure. The fully formed structure of the synaptic contacts is associated with the appearance of synaptic vesicles comparable with structure control; however, the area of the synapse was smaller [49].

The strong evidence we have obtained suggests that the developing brain is vulnerable to the pathogenic effects of ethanol. In the cells of the brain of embryos and fetuses from the main group of the study group, a slowing down of the process of synaptogenesis in comparison

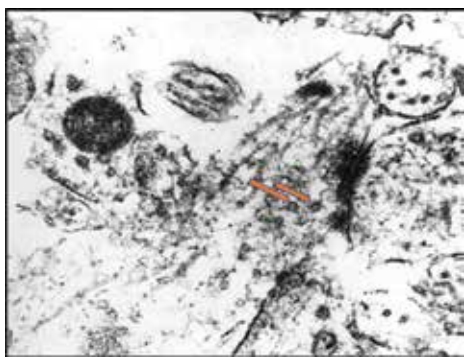

Figure 10. Single synaptic vesicles in the formation of contact, the main group is a fetus of 12 weeks of development, magnified 60,000.

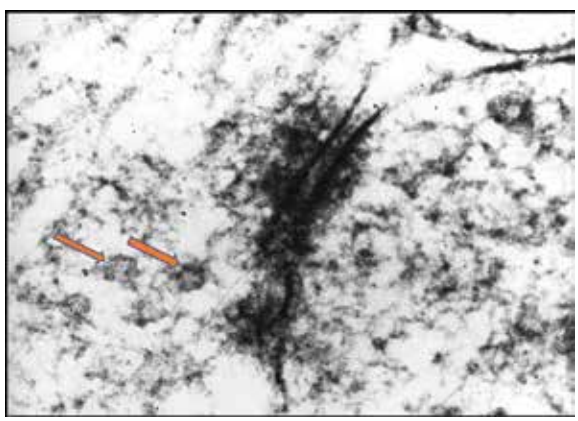

Figure 11. Single synaptic vesicles in the formation of contact, the main group is a fetus of 12 weeks of development, magnified 144,000.

with the norm was revealed, which can be critical for neurotransmitter processes in the developing human brain.

2.3. Morphometric analysis of synapses in the human developing brain in conditions of prenatal exposure to alcohol

Morphometric analysis of synaptic characteristics was performed in the study and control groups, using as a criterion the stage of development of embryos and fetuses.

In the main study group, a significant decrease in all parameters of synaptic structures was revealed in comparison with the control. More detailed analysis of synapse parameters was then performed, taking cognizance of embryo and fetus developmental period (**Figures 12–14**, **Table 2**).

We found that the length of postsynaptic density was lower in the main group compared to the control group already at the 7–8th week of gestation. At the 9th week of pregnancy, we identified synaptic contacts, especially at the upper margin of the middle layer. At this period of brain development, all synaptic parameters studied were significantly smaller in the main

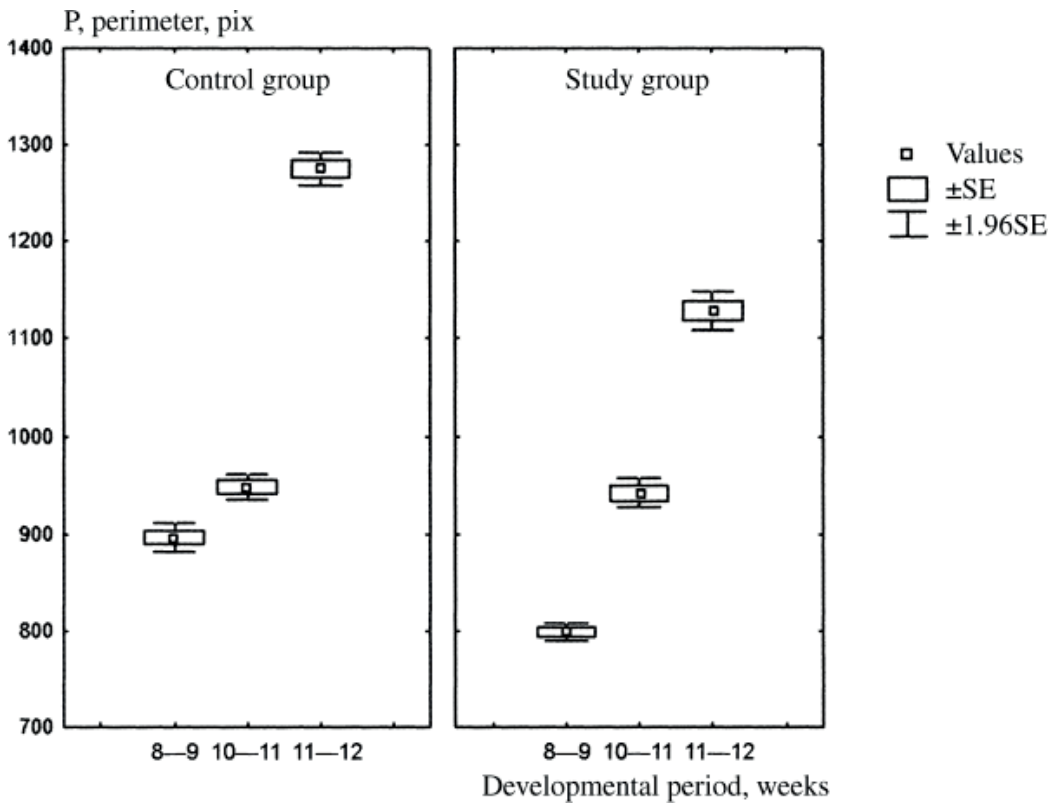

Figure 12. Morphometric values for presynaptic terminal perimeters in the control and study groups at different weeks of development.

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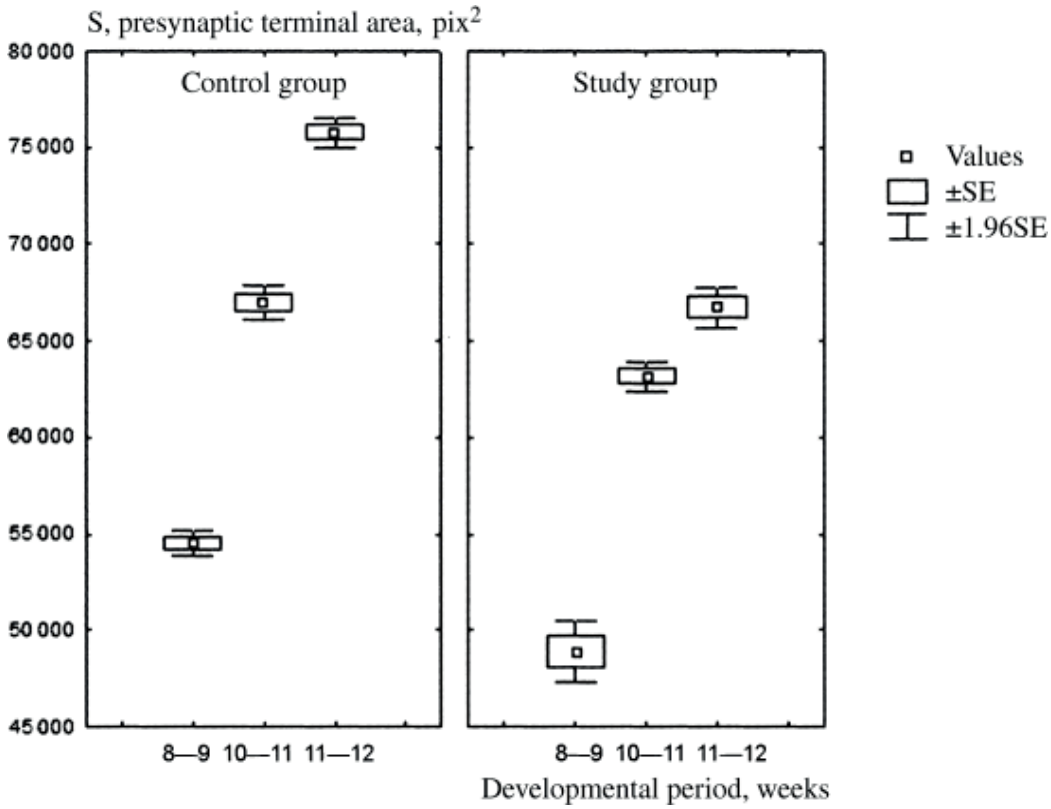

Figure 13. Morphometric values for presynaptic terminal areas in the control and study groups at different weeks of development.

group with respect to the control. At week 10, we also noted a decrease in all parameters of the study at the synapses; however, the presynaptic perimeters did not differ.

At 11–12 weeks of development, there was a more pronounced change in the parameters of synaptic contacts in the main group relative to the control group. Most synapses in the brain of the fetuses of 11–12 weeks of gestation are axodendritic positively bent synapses with some insignificant amount of synaptic vesicles and single mitochondria in the presynaptic terminals of the synapses.

The fully formed structure of synaptic connections with the appearance of synaptic vesicles compared to the control, but synapse core area considerably less resulting computer-morphometric analysis, we identified a delay of synapses and their structural immaturity which is probably due to a direct effect of alcohol on nerve cells, primarily due to its membranotropic action. Our morphometric studies have revealed that the prenatal influence of alcohol has a pronounced effect on the structural organization of synaptic contacts and their parametric characteristics. Our data confirm the data of other researchers obtained in studies in the culture of hippocampal tissues under the influence of a solution of ethanol [50, 51].

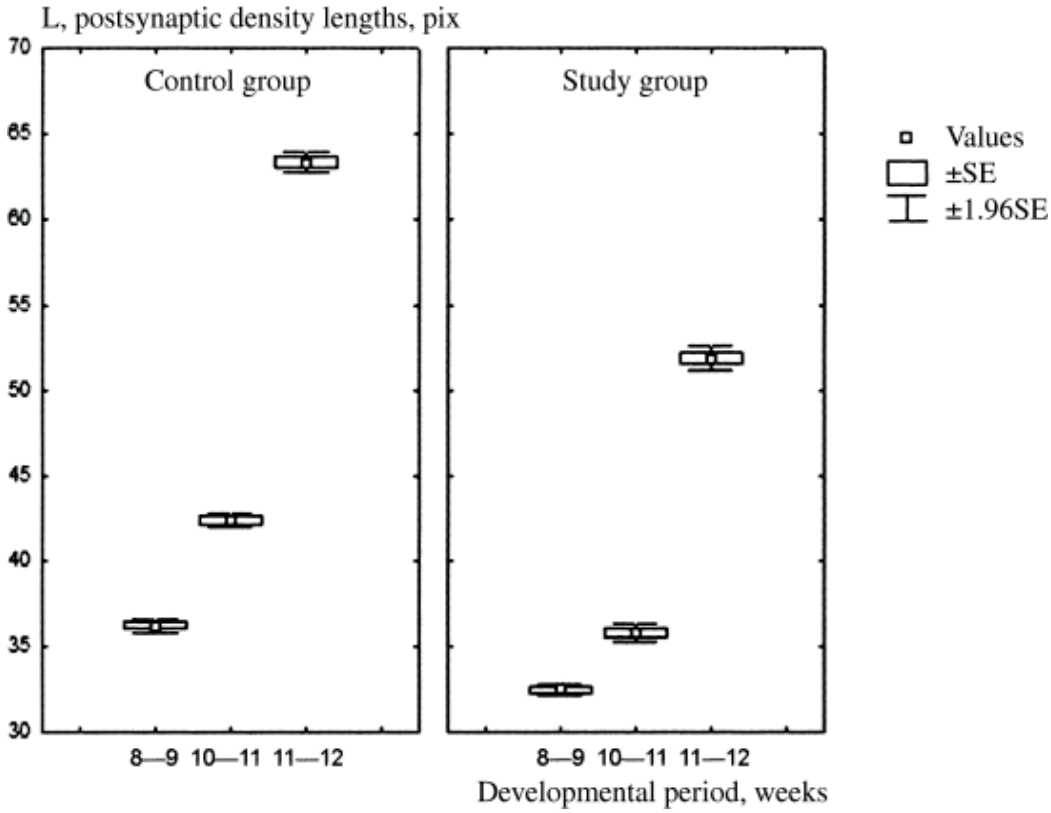

Figure 14. Morphometric values for postsynaptic density lengths in the control and study groups at different weeks of development.

Stage of development	**7–8 Weeks**		**9 Weeks**		**10 Weeks**		**11 Weeks**	
Measure	C M ± SE N = 90	S M ± SE N = 90	C M ± SE N = 210	S M ± SE N = 210	C M ± SE N = 210	S M ± SE N = 210	C M ± SE N = 210	S M ± SE N = 210
Length of postsynaptic density	25.21 ± 3.0	23.56 ± 2.4	36.21 ± 1.56	32.45 ± 1.23*	42.37 ± 1.70	35.80 ± 2.37*	63.33 ± 2.51	51.90 ± 2.88*
Area of postsynaptic terminals	–	–	54.521 ± 2673	48.861 ± 6773*	66.964 ± 3833	63.178 ± 3168*	75.742 ± 3207	66.750 ± 4436*
Perimeter of postsynaptic terminals	–	–	896.28 ± 63.7	798.90 ± 40.09*	948.19 ± 58.2	941.56 ± 64.44	1276.02 ± 73.08	1129 ± 86.87*

Notes: C, control group; S, study group (materials from alcoholic mothers).
*Significant differences between study and control groups ($p < 0.01$).

Table 2. Morphometric parameters of synapses in the human brain at different stages of embryonic development.

Thus, as a result of computer-morphometric analysis, we found a delay of synapses and their structural immaturity, which is probably linked to the direct effect of alcohol on nerve cells in the first place due to its membranotropic action.

2.4. Formation of benzodiazepine receptors of the developing human brain of the fetus in conditions of prenatal exposure to alcohol

To study the formation of benzodiazepine receptors of the synaptic structures of the brain of the developing fetus in normal and prenatal influences of alcohol, BzDR were investigated by radio-receptor binding with [^{3}H]-flunitrazepam using synaptosomal fraction obtained from the brain of fetuses and human embryos. Radioanalysis was performed in a Rack-beta scintillation β-counter. The dissociation constant (K_d) and number of specific binding sites (B_{max}) were determined by analysis of saturation curves in Scatchard coordinates. Linear Scatchard blots were analyzed in all cases which confirm the presence of only a specific population of binding sites. Distributions of parameters did not deviate from the normal, so statistical analysis of the data was performed by parametric variational statistics (Student's test) on Statistika 10.0; differences were regarded as significant at $p < 0.05$. Correlational relationships were assessed by Spearman analysis. Experimental work was carried out in the Department of Clinical Neuroimmunology and Neurobiology of Mental Health Research Institute, Tomsk National Research Medical Center RASci (Tomsk) and in the Laboratory of Clinical Neuromorphology and Laboratory of Clinical Biochemistry of Mental Health Research Center RASci (Moscow). All the studies were approved by the Ethics Committee of the Mental Health Research Institute.

Studies of the properties of human brain BzDR at 8–9 weeks of development showed that specific [^{3}H]-flunitrazepam binding site density (B_{max}) was greater in the study group than the control group (**Figure 15**, **Table 3**). There was a decrease in receptor affinity for the [^{3}H]-flunitrazepam, in the main study group, related to the increase in the value of K_d (**Figure 16**, **Table 3**). The dissociation constant—K_d is inversely proportional to the receptor affinity for their ligand, that is affinity corresponds—$1/K_d$. The observed increases in K_d indicate a decrease in the affinity of the receptors. The data obtained indicate an increase in the expression of receptors with a decrease in their affinity for the ligand in human embryo brains under the prenatal alcohol exposure.

At 10 weeks of gestation, there were not expressive changes in [^{3}H]-flunitrazepam-binding parameters (K_d and B_{max}) in compared groups. However, it should be noted that the dynamics of changes in receptor density is discrete, nonlinear. At this period, slight changes in the binding parameters in the control and experimental groups were noted. Density of receptors increases slightly between the 9th and 10th weeks of fetal development. There is some inhibition of growth in receptor density (**Figure 16**, **Table 3**), especially in the main group. This correlated with morphometric evaluation of synapses: decreases in presynaptic terminal area and postsynaptic density length in the main experimental group relative to the control group (**Table 4**).

Alcohol in the early stages of pregnancy, according to the data, negatively affects the formation of synaptic contacts and benzodiazepine receptors in the human brain, reducing the functional

activity of the brain and its development. We found that from the 12–13 weeks of pregnancy, a significant increase in receptor expression (B_{max}) was observed, and this trend of increasing prescription density continued during the gestation period of 14–15 weeks (**Figures 15** and **16**,

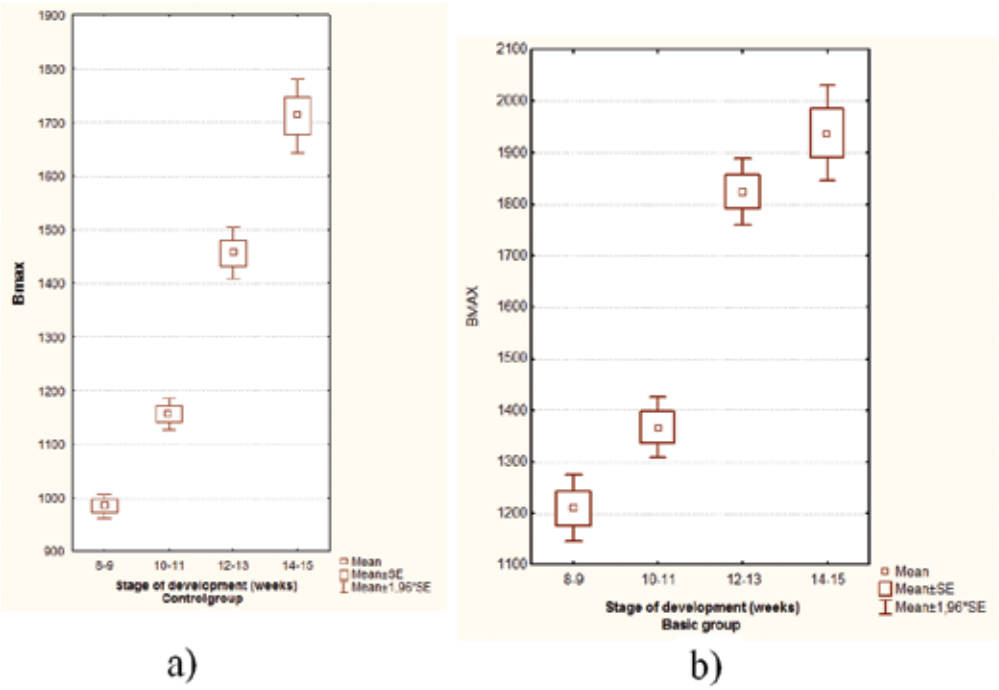

Figure 15. Statistical analysis of [^{3}H]-flunitrazepam binding parameters [B_{max} (fmol/mg of protein) – density of binding sites] with synaptosomal membranes of human embryonic and fetuses brain in the control (a) and study (b) groups in dynamics.

Developmental period, weeks	Control group			Study group		
	B_{max} fmol/mg protein	K_d nM	n	B_{max} fmol/mg protein	K_d nM	n
8–9	984.22 ± 11.64	1500 ± 0.024	9	1210.00 ± 32.79* r = 0.47 p = 0.0001	1591 ± 0.023* r = 0.22 p = 0.014	9
10–11	1156.00 ± 15.22	1700 ± 0.019	8	1367.40 ± 30.38* r = 0.50 p = 0.0001	1792 ± 0.019* r = 0.49 p = 0.04	10
12–13	1456.29 ± 24.17	1900 ± 0.023	7	1824.13 ± 33.51* r = 0.23 p = 0.0001	1982 ± 0.018* r = 0.19 p = 0.014	8
14–15	1712.00 ± 35.24	2120 ± 0.031	5	1938.17 ± 47.28* r = 0.73 p = 0.005	2450 ± 0.068* r = 0.56 p = 0.0027	6

Notes: B_{max}, [^{3}H]-flunitrazepam binding density with synaptosomal BzDR; K_d, ligand-receptor complex dissociation constant ([^{3}H]-flunitrazepam with synaptosomal BzDR). *Statistically significant differences between study and control groups, $p < 0.01$.

Table 3. [^{3}H]-flunitrazepam binding properties with synaptosomal membranes from human embryo and fetus brains (8–15 weeks of development).

Table 3). However, in the experimental group, with prenatal exposure to alcohol, the affinity of the receptors decreased at all stages of the human brain development, and the increase in expression and density of receptors can be considered as compensatory adaptive brain

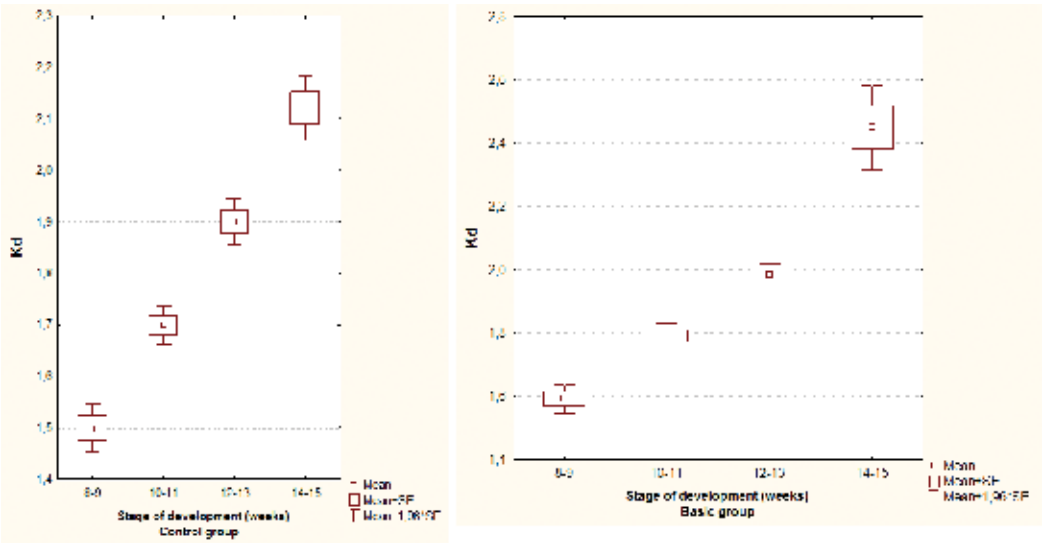

Figure 16. Statistical analysis of [^{3}H]-flunitrazepam binding parameters [K_d (nM) – constant of dissociation ligand-receptor complex] with synaptosomal membranes of human embryonic and fetuses brain in the control (a) and basic groups (b) in dynamics.

Developmental period. weeks	Control group *(M ± SE)*				Study group *(M ± SE)*			
	B_{max}	P	S	L	B_{max}	P	S	L
8–9	984.22 ± 11.64	896.28 ± 63.7 r = 0.80 p = 0.0006 *	54.521 ± 2673 r = 0.79 p = 0.0003 **	36.21 ± 1.56 r = 0.89 p = 0.0004 ***	1210.00 ± 32.79	798.90 ± 40.09 r = 0.78 p = 0.0004 *	48.861 ± 6773 r = 0.64 p = 0.0002 **	32.45 ± 1.23 r = 0.85 p = 0.0007 ***
10–11	1156.00 ± 15.22	948.19 ± 58.2 r = 0.77 p = 0.0004 *	66.964 ± 3833 r = 0.62 p = 0.0002 **	42.37 ± 1.70 r = 0.87 p = 0.0008 ***	1367.40 ± 30.38	941.56 ± 64.44 r = 0.82 p = 0.0006 *	63.178 ± 3168 r = 0.71 p = 0.0001 **	35.80 ± 2.37 r = 0.88 p = 0.0005 ***
12–13	1456.29 ± 24.17	1276.02 ± 73.1 r = 0.83 p = 0.0008 *	75.742 ± 3207 r = 0.76 p = 0.0001 **	63.33 ± 2.51 r = 0.91 p = 0.0003 ***	1824.13 ± 47.28	1129 ± 86.87 r = 0.79 p = 0.0004 *	66.750 ± 4436 r = 0.70 p = 0.0003 **	51.90 ± 2.88 r = 0.83 p = 0.0008 ***

Notes: L, postsynaptic density length; S, presynaptic terminal area; P, presynaptic terminal perimeter; r, correlation between control and study groups between B_{max} and P (*), B_{max} and S (**) and B_{max} and L (***); p, level of significance of correlational relationships.

Table 4. Correlation analysis of morphometric parameters of synapses (presynaptic terminal area perimeter and area, postsynaptic density length) and [^{3}H]-flunitrazepam specific binding site density (BzDR) at different developmental stages.

reaction with decreasing affinity of receptors. The change in receptor affinity is attributed to neuroplastic changes in the tissue of the developing brain due to the chronic effects of alcohol.

In ontogenesis, in the early stages of gestation, the benzodiazepine receptor system of the human brain is normally formed, starting with the 7th week of development. According to the data obtained, the density of BzDR during pregnancy 8–9 – 14-15 weeks increases by almost 200%. During prenatal influence of alcohol, associated with maternal alcoholism, we found that expression of BzDR was higher in comparison with control, at different developmental stages. The data of receptor analysis showed that the density of synaptic BzDR (B_{max}) correlates with the morphometric characteristics of the synapses (**Table 4**). We have shown that the affinity of receptors for the ligand during the development of the brain is somewhat reduced, which indicates the greatest sensitivity of receptors at the earliest stages of development—8–10 weeks of gestation. The prenatal influence of alcohol significantly reduced the affinity of the receptors in the experimental group, which confirms the greatest sensitivity of the BzDR to alcohol at the earliest stage of the formation of the human brain. The results of our study of the human embryonic brain in normal and under the influence of alcohol, which is associated with mother's alcoholism, indicate significant neuroplastic changes in the human brain during the early stages of its growth and development [52, 53].

Neuroplastic changes in blood vessels, synapses associated with GABAergic activity and BzDR receptors, in the developing brain under the influence of maternal alcoholism, are aimed at adapting the nervous system of the embryo and fetus to the phenomena of hypoxia, as well as functional failure of GABAergic neurotransmission. However, these adaptive changes in the human embryonic brain differ significantly from the processes of formation of angiogenesis and synaptogenesis and $GABA_AR$ neurotransmitter system of the normal human brain, which leads to various somatic disruptions and mental disorders, including the development of FAS and PAE.

2.5. Benzodiazepine receptor system in various structures of the human mature brain in patients with alcoholism

Benzodiazepine receptors in different human mature brain of the alcoholics were performed using autopsy material (postmortem) obtained as a result of an urgent autopsy. Samples of autopsy material of the human brain were obtained during urgent autopsy (no later than 6 hours after the onset of death). Samples of the tissue of the prefrontal cerebral cortex, the cerebellar cortex and the head of the caudate nucleus of the brain in persons who were chronically subjected to alcoholization (based on anamnesis) and control subjects were postmortem. Samples of the brain were frozen and stored in thermoses with liquid nitrogen. A total of 126 samples from different areas of the human brain were obtained for the study of radio-receptor binding, including the basic group and the reference control group. In addition to the data of the anamnesis, the objective biological criteria for chronic alcoholization of man (fatty liver, cirrhosis, etc.) were used to form the main group. The control group included patients who did not have neurological and mental illnesses. Autopsy material was obtained only from males, and the age range was 33–54 years. Alcoholic patients were under the supervision by psychiatrists of Mental Health Research Institute and had a diagnosis according to ICD-10: F10.232; F10.302. Patients

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with other psychiatric disorders were not included in this study. The study included only patients whose lethal outcome occurred as a result of acute heart failure and not subjected to resuscitation measures.

The separation of tissue from human brain samples into membrane fractions (synaptosomal and mitochondrial) was carried out by preparative ultracentrifugation. The resulting membrane fractions were frozen and stored at t = −80° C. Investigation of the properties of BzDR "central" type (CBR) and BzDRs "peripheral" type (PBR) was performed by the radioreceptor assay of binding synaptosomal and mitochondrial membranes with selective ligands. We used the parametric method (t test) using Statistika 10.0.

The experimental part of the research was carried out by us in the Laboratory of Neurobiology Mental Health Research Institute (Tomsk) and Laboratory of Clinical Biochemistry Research Center for Mental Health Sciences (Moscow). All ongoing studies were approved by the Ethics Committee.

(I) A study of the binding characteristics of the selective ligand [^{3}H]-flunitrazepam with synaptosomal fractions of membranes obtained from various regions of the human brain (postmortem) has shown that the properties of synaptosomal BzDR differ in the structures of the brain studied. The highest affinity of CBR was detected in the caudate nucleus and the lower affinity receptors have been identified in the cerebral cortex (the region of the prefrontal cortex) and in the cerebellar cortex (**Figure 17**, **Table 5**).

The density of the receptors in the brain structures studied was also different: the maximum receptor density (B_{max}) was detected in the caudate nucleus, in the cerebral cortex (the region of the prefrontal cortex) and in the cerebellar cortex (**Figure 18**, **Table 5**). Thus, the results obtained by us testify to the heterogeneity of the CBR in various areas of the human brain in the control group. A comparative analysis of the

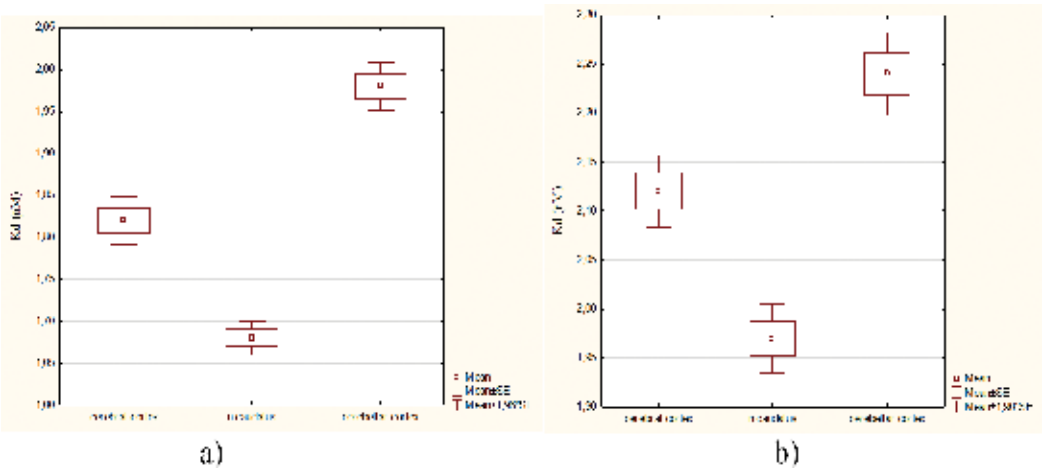
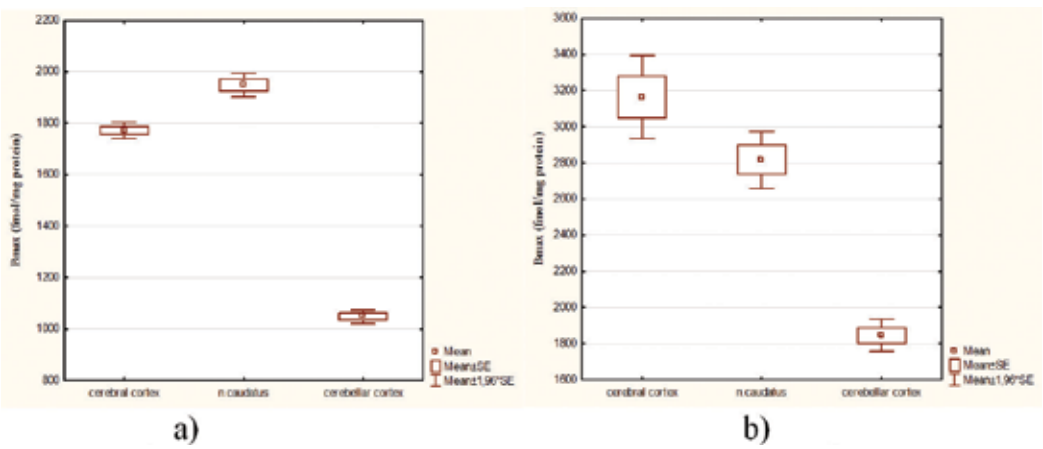


Figure 17. Statistical analysis of [^{3}H]-flunitrazepam binding parameters [K_d (nM) – constant of dissociation ligand-receptor complex] with synaptosomal membranes in different areas of the human brain in control group (a) and study group (b) (alcoholic patients).

Area of the brain	[^{3}H]-flunitrazepam binding to synaptosomal membranes				[^{3}H]-PK-11195 binding to mitochondrial membranes			
	Control group (n = 21)		Study group (n = 21)		Control group (n = 21)		Study group (n = 21)	
	K_d^1 (nM)	B_{max}^1 (fmol/mg protein)	K_d^1 (nM)	B_{max}^1 (fmol/mg protein)	K_d^2 (nM)	B_{max}^2 (fmol/mg protein)	K_d^2 (nM)	B_{max}^2 (fmol/mg protein)
Prefrontal cortex *{M ± SE}*	1.82 ± 0.07	1772 ± 79	2.12 ± 0.09*	3165 ± 565*	2.45 ± 0.17	1824 ± 11	3.12 ± 0.13**	2245 ± 168**
N. caudatus *{M ± SE}*	1.68 ± 0.05	948 ± 112	1.97 ± 0.09*	2817 ± 386*	1.12 ± 0.09	724 ± 36	2.31 ± 0.16**	1895 ± 77**
Cerebellar cortex *{M ± SE}*	1.98 ± 0.1	1048 ± 67	2.24 ± 0.21*	1845 ± 217*	2.61 ± 0.21	1209 ± 98	3.32 ± 0.19**	2479 ± 123**

Notes: B_{max}^1, density of binding sites [^{3}H]-flunitrazepam with synaptosomal membranes; K_d^1, constant of dissociation ligand-receptor complex [^{3}H]-flunitrazepam with CBR; B_{max}^2, density of binding sites [^{3}H]PK-11195 with mitochondrial membranes; K_d^2, constant of dissociation ligand-receptor complex [^{3}H]PK-11195 with PBR; n, the number of cases studied. *Statistically significant difference indicators binding [^{3}H]-flunitrazepam and **[^{3}H]PK-11195 between study and control groups, $p < 0.05$.

Table 5. Properties of [^{3}H]-flunitrazepam and [^{3}H]PK-11195 binding to the synaptosomal and mitochondrial membranes from different areas of the human brain in alcoholic patients and control.



a) b)

Figure 18. Statistical analysis of [^{3}H]-flunitrazepam binding parameters [B_{max} (fmol/mg of protein) – density of binding sites] with synaptosomal membranes in different areas of the human brain in control group (a) and study group (b) (alcoholic patients).

kinetic characteristics of the binding of [^{3}H]-flunitrazepam showed a significant increase in the K_d values in the studied brain structures in the patients of the main group as compared to the patients in the control group, which indicates a decrease in receptor

affinity. The largest changes in K_d were found in the cerebral cortex, the caudate nucleus and, to a lesser extent, in the cerebellar cortex (**Figures 17** and **18**, **Table 5**). Thus, the changes revealed by us indicate a decrease in the affinity of CBP in the brains of patients under the exposure of chronic alcoholization and an increase in their density in relation to the control group, which can be compensatory adaptive in nature [54].

(II) A comparative analysis of the PBR properties in the study of the binding of [^{3}H]PK-11195 to the mitochondrial fraction of membranes isolated from various regions of the human brain showed that the degree of manifestation of changes in the PBR properties is not the same in the studied brain structures of patients who had alcoholism according to anamnesis. The greatest changes of PBR in comparison with the control were detected in the caudate nucleus and the cerebellar cortex (**Figures 19** and **20**, **Table 5**). The obtained results indicate a heterogeneous change in the properties of BzDR of selective ligands in the human brain under the influence of chronic alcoholization, which confirms the hypothesis of adaptive receptor neuroplasticity and the heterogeneity of the physiological response in various brain regions to the effect of chronic alcohol exposure [54].

The results we obtained are consistent with data from other studies showing a decrease in the function of $GABA_A$/BzDR in the cerebral cortex in patients with alcohol dependence [36, 55]. These data confirm that the low affinity of BzDR can be a neuronal marker of the development of anxiety and conditions associated with chronic alcohol use and AAS. The study of BzDR carried out by us in various areas of the human brain (on postmortal material) showed that the properties of synaptosomal and mitochondrial receptors differ in the brain structures studied: the prefrontal cortex, the caudate nucleus and the cerebellar cortex. CBR are the sites of specific binding of ligands of benzodiazepine series, neurosteroids and alcohol to the GABA receptor, modulating its function allosteric and regulating the processes of inhibition in brain structures that affect the activity of various neurotransmitter systems, including the activity in the structures of the brain associated with the process of natural reinforcement. The higher affinity and

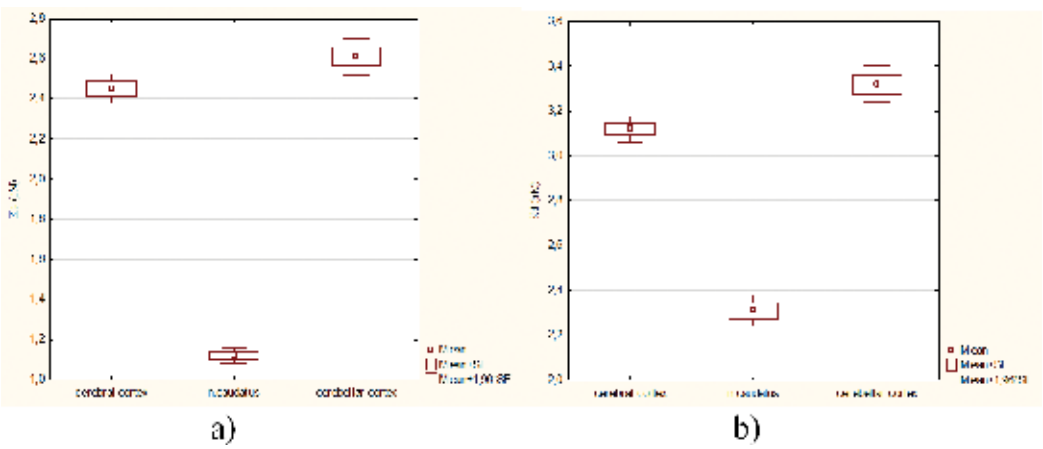


Figure 19. Statistical analysis of [^{3}H]PK-11195 binding parameters [K_d (nM) – constant of dissociation ligand-receptor complex] with mitochondrial membranes in different areas of the human brain in control group (a) and study group (b) (alcoholic patients).

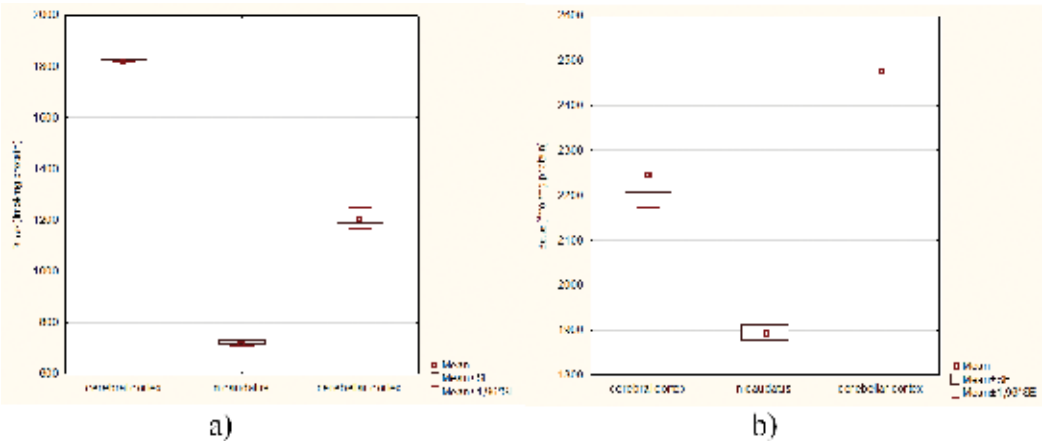


Figure 20. Statistical analysis of [^{3}H]PK-11195 binding parameters [B_{max} (fmol/mg of protein) – density of binding sites] with mitochondrial membranes in different areas of the human brain in control group (a) and study group (b) (alcoholic patients).

density of CBR in the caudate nucleus and the prefrontal cortex are related to their functional activity in the regulation of emotions and motivated human behavior.

The effect of ethanol causes a change in PBR not associated with $GABA_AR$, localized in the mitochondrial membrane, predominantly in glial cells of the brain, and providing cholesterol transfer into the mitochondria [46], thus affecting the regulation of the synthesis of neurosteroids, which are endogenous modulators of $GABA_A$/BzDR in the CNS [42]. Alcohol carries out some of their effects through PBR, regulating the production of neurosteroids and their metabolites, which are critical components of normal brain function [46]. Thus, PBR indirectly affects GABAergic function in the brain, mainly reacting to neurotoxic effects and various brain damage [36, 55, 56].

The data obtained by us confirm the existence of regulatory mechanisms mediating the relationship between the properties of $GABA_A$/BzDR caused by receptor neuroplasticity and alcohol addiction.

3. Conclusion

An important factor that can influence addiction liability is exposure of alcohol and other psychoactive substances during the early life period. Exposure to ethanol, early in life, can have long-lasting implications on brain function and drugs of abuse response later in life.

One of the mechanisms of action of alcohol is the ability to induce vascular spasm, which leads to hypoxia of the developing embryo and affects the retardation of development and growth of the fetus with prenatal effects of alcohol. These changes can lead to the development of fetal alcohol syndrome. Compensatory mechanism in the conditions of this pathology, leading to a decrease in the perimeter of the vessel and the area of the vessel in the cross section, is an

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increase in the number of vessels in the brain [57]. Alcoholization of the mother, leading to prenatal effects of alcohol on the developing fetus, affects the dynamics of embryonic development of the circulatory system in the human brain, which manifests itself in a change in the vascularization of the growing human brain [23].

The effects of ethanol in the early stages of development can disrupt the signaling mechanisms that regulate synaptogenesis. The result was "dilution" of the structure of elementary membranes and damaged membranes are less able to establish strong contact with each other, which is probably due also to a reduced ability of cells that are in constant contact with ethanol, synthesized mediators filling synaptic vesicles. This significantly violated the formation of neuronal mechanisms underlying the susceptibility and processing of information, which in turn could adversely affect a person's mental activity.

The data obtained by us showed a structured picture of synaptogenesis as one of the most significant periods in the formation and development of the brain, providing its functions and determining the adaptive potential in prenatal alcohol influences. The influence of prenatal ethanol on the development of synaptic structures was expressed in reduction of morphometric parameters, namely slowing the formation of synaptic contacts and reducing their formation in the brain of the embryo and fetus in the early stages of development, in contrast to the normally developing brain, which affects synaptogenesis in the developing brain of a person and can underlie fetal death or serious disorders the child in the future [23, 49, 52–54].

On the background of the decrease in the formation of synaptic structures seen here in the fetal brain during gestation under the influence of maternal alcoholism and the simultaneous decrease in the affinity of synaptosomal BzDR, the tendency to an increase in receptor density can be evaluated as neuroplastic features and compensatory reaction directed to adapting the embryo and fetus nervous system to conditions of functional insufficiency of GABAergic neurotransmission. These new data can broaden the understanding of the molecular basis of predisposition not only to alcoholism but also to various disorders associated with PAE. Children and adolescents who were under the influence of alcohol during the period of prenatal development noted functional disorders of neurocognition, self-regulation and adaptive functioning and various neurobehavioral disorders associated with PAE [58]. Plasticity of ion channels and receptors linked to ion channels regulated by neurotransmitters is significant for the realization of adaptive processes in the brain, providing synaptic plasticity for the formation and development of neural network, physiological and pathophysiological processes. Prenatal alcohol exposure (PAE) can cause irreversible physical, neurological and psychiatric impairments that are present at birth and can have lifelong implications [14, 59]. The relationship between prenatal exposure to alcohol and the frequency of behavioral disorders in children and adolescents is established. [60]. The effect remained significant compared to other variables, including environment, maternal psychopathology and some others, and can cause a different mental dysfunction associated with a violation of brain metabolism in children and adolescents in the future [61].

Similar changes in the benzodiazepine receptor binding were identified by us in the brains of patients with alcoholism also. A decrease in the ability of receptors to bind agonist ligands impairs the ligand:receptor protein ratio, leading to decreased binding of the major neurotransmitter

GABA and impairment to synaptic transmission. Our results are consistent with other studies that showed a reduction in the function of $GABA_A$/BzDR in the prefrontal cortex in patients with alcohol dependence [36, 55]. Alcohol causes neuroplastic changes in BzDR associated with a decrease in the affinity of the receptors, a change in the conformational state of the $GABA_A$/BzD rector complex, as a result of inhibition of the binding kinetics of BzDR by the polypeptide DBI (Diazepam Binding Inhibitor), as well as its metabolites. The endogenous peptide DBI possesses anxiogenic action and is the inverse agonist of BzDR [62]. Chronic alcohol exposure induces the expression of endogenous DBI interacting with receptors and suppresses binding affinity to [^{3}H]-flunitrazepam.

Neuroplastic changes of $GABA_AR$, caused by the influence of ethanol, are associated with a change in the composition of subunits of the receptor complex and change in the pharmacological sensitivity and receptor function associated with the development of tolerance to ethanol and alcohol dependence. High heterogeneity of different isoforms of subunits of the $GABA_A$ receptor (α1-α6; β2,β3) in various regions of the brain: nuclei of the basal ganglia, prefrontal cortex and limbic regions of the brain, underlies the functional differentiation of the $GABA_A$ receptor complex and provides a varying degree of modulation functions of $GABA_AR$ by ethanol in various brain structures [63]. Changes in the expression of neuronal elements induced by alcohol, leading to changes in neurotransmitter function adaptation systems in the brain associated with neuroplasticity [64].

Benzodiazepines, anxiolytics, anesthetics and alcohol are implementing some of its effects through the BzDR "central" and "peripheral" types regulating the synthesis of neurosteroids, which are critical for the provision of brain functions. Ethanol modulates $GABA_A$/BzD receptor complex function by affecting synthesis neurosteroids *de novo* in the brain, stimulating the mitochondrial receptors of the "peripheral type"—PBR, providing the transfer of cholesterol to mitochondria and synthesizing neurosteroids, independent of the functions of the HPA axis. This mechanism can play a principal role in the central effects of alcohol. Thus, the functional activity of PBR has a modulating effect on GABAergic function in the structures of the brain, reacting to various neurotoxic effects and damage [65].

Alcohol does not have specific receptors in the brain; however, the receptor proteins are exposed to ethanol. The research of a number of authors is aimed at studying long-lasting adaptive changes (neuroplasticity), which contribute to the development of alcohol dependence. Our studies aimed at studying neuroadaptation under the influence of chronic alcohol effects on the benzodiazepine receptor system of the brain have revealed that a low affinity of BzDR can be a marker of disorders of synaptogenesis and regulatory mechanisms mediating the $GABA_A$/BzDR bond that induces receptor neuroplasticity and alcohol addiction [41, 54, 65, 66].

BzDR "central" and "peripheral" types can be a key link to the discovery of new promising therapy for the treatment of compulsive craving for alcohol, alcohol abuse and dependence. The integration of current data and our data is necessary to define the role of $GABA_AR$ in modulating the rewarding and aversive effects of ethanol and may lead to the development of pharmacotherapy that targets $GABA_A$/BzD receptors to treat alcoholism in human beings [65–68].

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Chapter 6

Investigation of Emotion Characters of Internet Abusers Using Psychophysiological Signals

Dai-Ling Hsieh and Tzu-Chien Hsiao

Additional information is available at the end of the chapter

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Abstract

Because of ubiquitous Internet and devices, the numbers of the Internet users rapidly increase. Internet addiction (IA) is also a fast growing, serious, and unavoidable problem around the world. The fifth version of Diagnostic and Statistical Manual for Mental Disorders suggested that IA should be studied in a scientific manner, and more related data must be acquired. Emotion was one important character of IA, and emotion-related syndrome was also reported in these years. IA contains psychological and physiological features and usually is assessed by IA scales. However, self-reporting scale is a subjective measurement tool that may be biased. Furthermore, scales or questionnaires assess the long-term developed states of IA rather than the developing states of IA or short-term change. The physiological signals of IA abusers can provide objective, short-term, dynamic change information instead. Therefore, the dynamic physiological regulation and the psychological and physiological responses to emotion of IA abusers, particularly respiration and respiratory sinus arrhythmia, were studied. IA abusers tended to perform thoracic movement for emotion regulation, whereas people without IA tended to perform abdominal movement. IA abusers exhibited stronger RSA reactivity following negative emotion, but exhibited weaker RSA reactivity following positive emotion.

Keywords: Internet addiction, Internet gaming disorder, emotion, physiological signal, respiration, respiratory sinus arrhythmia, heart rate variability, complementary ensemble empirical mode decomposition

1. Introduction

Internet has fast developed over these 2 decades and is widely used worldwide. The population of Internet users has reached 3.8 billion in 2017 [1], and the Internet is now an integral

part of life. In UK, USA, South Korea, and Taiwan, the Internet users are over 80% of the population [2], and in Asia, the Internet users of the world total are 49.7% [1]. Some users, however, excessively use, rely on, and even addict to the Internet, and suffer from negative consequences on physical and mental functions, social and occupational problems [2, 3]. Such excessive Internet use is called Internet addiction (IA). IA, first proposed in 1995 by Goldberg, was regarded as a behavioral addiction, and the widely used definitions of IA include preoccupation with online activities, withdrawal, craving, tolerance, mood modification, conflict, relapse, and negative consequences [2, 4, 5]. If users used computer or the Internet over 10 h/day and 6 days/week [6], they have difficulty in finance and in family relationship, poor performance of school or work, etc. [2, 3]. Such users might be potential IA abusers. The definitions of IA given by several researchers are listed in **Table 1**.

The prevalence rate of IA investigated by several countries, such as Norway 0.7%, the US 1%, Europe 1.0–9.0%, and Asia 2.0–18.0%. The rate varied from different countries (0.7–26.8%) [2].

Authors and Years	Proposed definition
Goldberg [7]	A mal-adaptive pattern of Internet use, leading to clinically significant impairment or distress.
Young [8]	1) Reported the very first case of Internet addiction, 2) Defined addictive use of the Internet.
Young [9]	1) Proposed the Internet Addiction Scale, 2) Proposed two definitions: first definition: behavioral addiction, second definition: Internet-related disorders.
Young [10]	1) An uncontrollable urge, 2) Often accompanied by a loss of control, 3) A preoccupation with use, 4) Continued use despite problems caused by the behavior.
Leung [11]	Internet addiction has been used to describe problematic, excessive, or mal-adaptive use of the Internet.
Shaw and Black [12]	1) Time consuming, 2) Causes distress or impairs one's functioning in important life domains.
Block [13]	1) Excessive Internet use, 2) Withdrawal, 3) Tolerance, 4) Adverse consequences.
Spada [2]	An addictive behavior An impulse-control disorder
Brand et al. [14]	1) Internet use disorder, 2) Specific Internet-use disorders

Table 1. Definitions of IA in literatures.

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Asian countries have higher prevalence rate (e.g., Hong Kong 17–26.8%, Taiwan approximately 20%) [15, 16]. Young reported five types of IA, namely cybersexual addiction, cyber-relationship addiction, net compulsions, information overload, and obsessive computer game playing [17]. The population of computer game players has over one billion in 2012 [18], and the situation that people addicted to the Internet game is called Internet Gaming Disorder (IGD) [19]. IGD is a large population of Internet addicts, and the related research results were the most reported.

The fifth version of Diagnostic and Statistical Manual for Mental Disorders (DSM-5) suggested that IGD/IA should be further studied and more related data must be acquired [13, 20]. DSM-5 addresses and suggests nine criteria for IGD in 2013 [21], including preoccupation, withdrawal, tolerance, reduce/stop, give up other activities, continue despite problems, deceive/cover up, escape adverse moods, and risk/lose relationship/opportunities. The psychological syndromes of IA usually are assessed by IA scales [3, 4, 9]. However, self-reporting is a subjective measurement tool that may be biased, even unintentionally, by a reporter's feelings or forgotten details. Furthermore, scales or questionnaires assess the long-term developed states of IA rather than the developing states of IA or short-term change. Nevertheless, the physiological signals of people with IA can provide objective and short-term information on the condition. In recent years, although a few physiological features of IA were studied [22], the psychological and physiological features rarely investigated together, and the regulation of physiological reactions was little discussed. Both the features can be acquired through emotions, and the physiological regulation can be observed using noninvasive physiological signals. Furthermore, noninvasive physiological signals can provide short-term, dynamic changes of IA, and is a biofeedback means.

1.1. Psychological and physiological syndrome, emotion character of Internet addiction abusers

The behavior, psychological characters, and physiological features of IA abusers were reported, such as mood-altering use of the Internet, guilt, emotional, and social withdrawal from real relationship, craving, and fatigue, and users are vulnerable to disease [3, 23–27]. In clinical contexts, IA has been associated with mental disorders, such as substance use disorder [28] and depressive disorder [29]. IA abusers experienced positive feelings (e.g., pleasure, gratifying sensations, security, calm, and belonging) or negative feelings (e.g., frustrate and lonely) when they are able or unable to use the Internet [2, 3], and they express emotional withdrawal symptoms when offline, such as anxiety and depression [5]. The perceived benefits keep people coming back to the addictive experience [30].

Emotion was one important character of IA and IGD. For example, users feel pleasure [23], control, and excitement when online, but feel anxiety and alone when offline [3], and shift emotional states through the Internet or online activities [5]. Emotion can be used to assess pathological Internet use [3]. The relationships among showing emotion, verbal expression of emotions, controlling negative physical reactions, coping, and anger management were examined, and emotion management skill was significant for IA levels. IA abusers exhibited bad emotion management skills [31]. IA and emotional intelligence tests was negatively correlated [32, 33]. Excessive Internet users expressed poorer intimacy, and had worse ability to express positive and negative emotions [34]. The withdrawal symptoms of Internet gaming

disorder (IGD) may indicate an immediate emotional reaction [35]. The possible reasons why people addicted to online game were coping with negative emotions and stress, having entertainment, empowerment, mastery, control, excitement, and challenge [36]. The psychological syndromes regarding emotion of IA are listed in **Table 2**.

Concerning the physiological syndrome of IA, the autonomic nervous responses of high-risk IA (HIA) abusers was studied. The blood volume pulse and respiratory response of HIA abusers would increase, but peripheral temperature and skin conductance would decrease [22]. Heart rate variability (HRV) is one index of autonomic nervous system (ANS) activity. The high frequency percentage acquired from HRV of HIA abusers was lower, but the low frequency percentage of HIA abusers was higher than that of LIA abusers [37]. The results showed that the sympathetic nervous activities of HIA abusers were stronger, and the parasympathetic nervous activities were weaker than that of LIA (low-risk IA) abusers.

Emotion conveys psychological (subjective) and physiological (objective) information, and can be observed and assessed through psychological methods such as self-reports, interviews, questionnaires, and through physiological reactions such as the heart rate, respiration, facial expression, and particularly ANS activities [38]. The ANS which contains the sympathetic nervous system and parasympathetic nervous system, which has antagonistic effects, plays an important role in regulation of physiological reactions and emotions. The emotion-related responses derived from ANS are cardiovascular responses, respiratory responses, and electrodermal responses. These responses usually cannot be manipulated consciously [38–41], and can be measured using noninvasive methods. For example, heart rate variability (HRV) and respiratory sinus arrhythmia (RSA) acquired from electrocardiography (ECG), a noninvasive physiological signal, was a widely adopted index of the regulation of ANS activities. HRV presents the regulation of sympathetic activity and parasympathetic activity, and RSA

Author	Content
Peele (1991) in Young [3]	Emotion and feelings are the psychological hooks of addiction.
Young [3]	Emotion can be used to assess IA.
Oktan [31]	Emotion management skills were meaningful predictors of IA.
Parker et al. [32]	People with IA were reported bad scores on emotional intelligence tests.
Far et al. [33]	
Oktuğ [34]	Excessive internet users were indicated poorer intimacy, and worse ability to express positive and negative emotions than others.
Ko and Yen [35]	Withdrawal symptoms of internet gaming disorder (IGD) may indicate an immediate emotional reaction.
Petry et al. [21]	DSM-V: playing games to escape from or forget about real-life problems or relieve negative emotional states.
Brand et al. [14]	Urge for mood regulation is an important factor within the development of Internet-use disorders

Table 2. Psychological syndrome (emotion) of IA.

presents the parasympathetic activity, the activity of the vagus nerve, and they were related to emotions [42–44]. Lower resting vagally mediated HRV was associated with greater difficulties in emotional regulation, particularly a lack of emotional clarity and impulse control [43]. RSA is rhythmic fluctuations in the heart rate that are associated with respiration and is related to complex emotion responses and social behavior [45, 46]. Therefore, RSA can be utilized to investigate the relationship between emotions and the parasympathetic activity by noninvasive means [27]. People with higher resting RSA expressed less but reported much negative emotion as those with lower resting RSA. People with higher resting RSA tend to express more positive emotions and to suppress negative emotional expressions [47, 48]. RSA values positively link to positive emotions and negatively correlated to negative emotions [27, 44, 49]. People with IA presented lower parasympathetic activity, lower RSA values [50], and People with IGD exhibited higher sympathetic activity than people without IGD [51]. Respiration is vital for mental and physical functions, and is the only autonomic nervous function which can be both automatically and consciously regulated. For example, abdominal breathing can assist people in relaxing and regulating negative emotions. Respiration can be not only the index for emotions, but also a type of biofeedback to regulate or to change emotions. It was noticed that respiratory response and cardiac response importantly affect regulatory functions, and may also be a regulation means to IA.

IA is a serious problem and is worthy to be studied; however, little attention has been paid to its physiological characters of emotion. Emotions were both a response and an influential factor on IA, and were mainly studied using physiological signals. People use the Internet for several online activities; however, different online activities may be variables to affect the physiological responses and the regulation to emotional stimulation. The general IA abusers and specific IA (IGD) abusers should be considered in the further study.

2. Emotional induction experiment

Emotional induction experiments using several emotional induction materials were conducted. The psychological characters were obtained using self-reports and questionnaires, and physiological signals were collected using respiratory belts and ECG. The relationship and differences in respiration between people with IA and people without IA, RSA, and HRV were tested, and the regulation of the parasympathetic activity in emotional states was discussed.

2.1. Emotional induction material and experimental instrument

Materials include emotional induction materials, emotional intensity questionnaire, IA scale (Chen Internet Addiction Scale), and physiological signal acquisition equipment. Emotional pictures selected from International Affective Picture System (IAPS) [52], and emotional film clips selected from Taiwan corpora of Chinese emotions and relevant psychophysiological data [53] were utilized for emotional induction materials. Emotional pictures (anger, disgust, fear, sadness, happiness, and surprise pictures), and emotional film clips (anger, fear, sadness, happiness, and fear films) were adopted. Anger, sadness, and fear are negative emotions, while happiness and surprise are positive emotions. Participants rated their emotional

intensity via questionnaire including happiness, sadness, disgust, surprise, fear, and anger, from 0 (lowest intensity) to 8 (highest intensity). DSM-5 IGD criteria and online game film clips as emotional induction materials were adopted for IGD experiment.

Internet addiction (IA) is usually evaluated using self-reported questionnaires, scales, or interviews. Chen Internet Addiction Scale (CIAS) [4], a well-developed and widely applied scale, was adopted. CIAS consists of 26 items and is a self-assessment scale including five dimensions of Internet-related symptoms and problems, namely symptoms of compulsive use, of withdrawal, and of tolerance, and problems in interpersonal relationship, and in health/time management. People can be classified into high-risk IA (HIA) or low-risk IA (LIA). The nine IGD criteria were used in IGD experiment. The cut-point was five, and people with the score over five were IGD.

Physiological signals including respiratory signals, ECG signals, and facial images were collected. Respiratory signals of thoracic movement (TM), abdominal movement (AM), and thoracoabdominal movement (TAM) were acquired using two respiratory belts with sampling rate at 1000 Hz (SS5LB, BIOPAC Systems, Inc., Goleta, USA). The belts were encircled at the level of armpit (TM, channel 1, C1) and navel (AM, channel 3, C3). Electrocardiography (ECG, with three disposable pregelled Ag/AgCl spot electrodes) was used with electrodes applied to the surface of a participant's skin. ECG signals were sampled at 1000 Hz and acquired using the DAQcard (USB 6218, National Instruments Corp., Austin, USA). Facial images were captured using a webcam (Logitech V-UBK45, USB 2.0, 10 fps, 640 × 480 resolution, Switzerland).

2.2. Experimental setup and procedure

Sixty-eight participants (12 females and 56 males) aged between 20 and of 29 years were recruited from one university in Taiwan for IA experiment. None of the participants had bipolar or related disorders, depressive disorders, anxiety disorders, or agoraphobia. Participants were randomly divided into two groups, group 1: the emotional picture trial group, 34 participants (6 females and 28 males) aged between 19 and 25 years, and group 2: the emotional film trial group, 34 participants (6 females and 28 males) aged between 19 and 27 years. All participants filled out the CIAS, and were divided into the HIA group (n = 15 of group 1, n = 19 of group 2) or the LIA group (n = 19 of group 1, n = 15 of group 2). This study was approved by the Institutional Review Board of the National Taiwan University Hospital Hsinchu Branch (Hsinchu, Taiwan) under the research Project Number 100IRB-32.

Fifty participants (14 females and 36 males) aged between 20 and 36 years were recruited from two universities in Taiwan for IGD experiment. The participants were divided into IGD & HIA group (n = 19, 4 females and 15 males, aged between 20 and 36) and non-IGD & LIA group (n = 21, 9 females and 12 males, aged between 20 and 28) using both CIAS and DSM-5 criteria. This study was approved by Research Ethics Committee for Human Subject Protection of National Chiao Tung University (Hsinchu, Taiwan) under the Project Number NCTU-REC-102-009.

The experimental procedure consisted of three phases. First, in phase 0, participants were seated in a comfortable chair and introduced to the experimental purpose and procedure, and then signed an informed consent form. Second, in phase 1, the physiological baseline including respiratory signals (TAM), ECG signals, and facial images of participants was measured

and recorded [54]. Third, in phase 2, emotional induction experiment was conducted, and participants were elicited by emotional induction materials [50, 51]. All physiological signals during the whole experimental period were acquired and recorded. These data acquired during the psychophysiological signal baseline was the stage of before emotional induction, and during the recording of the emotional induction was the stage of after emotional induction.

2.3. Data analysis and result

Data analysis method included statistics, such as correlation coefficient, T-test, and factorial ANOVA, and signal processing method for ECG and respiratory signals. ECG signals were processed and analyzed using an R-peak detection method. The RR intervals were transformed into an auto power spectrum, and the obtained HRV contained three frequency bands—high frequency (HF, 0.15–0.4 Hz), low frequency (LF, 0.04–0.15 Hz), and very low frequency (VLF, <0.04 Hz, excluding 0.00 HZ). Usually, HF indicates a parasympathetic nervous response and LF indicates a sympathetic nervous response. The RSA value was calculated as HF/((HF + LF)). Complementary Ensemble Empirical Mode Decomposition (CEEMD) which has been validated to be suitable for respiratory signals was applied to decompose respiratory signals [55]. CEEMD can acquire high frequency (HF, muscle contraction frequency), dominant frequency (DF, main respiratory frequency), and power of each respiratory signal. We are curious about the responses or reaction intensity (normalized power difference value) to several emotional stimuli from different time scale materials of IA abusers. The value of normalized power difference upon before and after the emotional inductions indicated the respiratory amplitude (emotional intensity), and the trend of difference implied the positive and negative respiratory responses. The differences in TAM, ECG (RSA) between HIA and LIA were examined.

2.4. Result

No statistical difference in age and gender existed whether in IA experiment or in IGD experiment. The consistency of CIAS scoring, IGD scoring, and emotional intensity among participants was tested, and results (Cronbach's alpha values) were acceptable [56]. Regarding the results of respiratory signals, the normalized power differences of high frequency (HF) and dominant frequency (DF) varied along different emotions. The HIA and the LIA groups also exhibited different normalized power differences among some emotions. Respiratory amplitude and frequency implied the emotional intensity of physiological reaction. In the HIA group, the power differences of DF in positive and negative emotional states were less consistent than those in the LIA group, and the trends of difference were almost opposite. The emotional effects on respiratory amplitude almost positively affected the HIA group but negatively affected the LIA group. The results of trends of respiratory power difference suggested that when HIA group in whether negative or positive emotional states, their thoracic movement was mainly responsible for respiratory regulation, whereas LIA group mainly used abdominal movement to regulate respiration [30]. Concerning the autonomic nervous response, the results of RSA and HRV indicated that the RSA base of the HIA group was lower than that of the LIA group. Hence, the HIA group did not tend to express positive emotions. They may express negative emotions rather than positive emotions, and did not suppress negative

emotions [47, 48]. The RSA reactivity to positive emotions was not varied that much as that of negative emotions. The results of RSA reactivity of before and after emotional inductions were shown in **Table 3**. The summary result of emotional intensity, TAM and RSA reactivity in IA experiment was shown in **Table 4**.

	RSA reactivity		
Emotion	1: Before emotional induction	2: Emotional state	Difference (2–1)
Negative	HIA < LIA	HIA < LIA	HIA(0.029, ↑) > LIA (0.000, −)
Anger			HIA(−0.031, ↓) > LIA (−0.010, ↓)
Fear			HIA(0.107**, ↑) > LIA (−0.004, ↓)
Sadness			HIA(0.017, ↑) = LIA (0.017, ↑)
Positive	HIA < LIA	HIA < LIA	HIA(0.125**, ↑) > LIA (0.016, ↑)
Happiness			HIA(0.126*, ↑) > LIA (0.080, ↑)
Surprise		HIA > LIA	HIA(0.124*↑) > LIA (−0.053, ↓)

HIA: high-risk IA; LIA: low-risk IA; ↑: increase; ↓: decrease; −: no difference; *p < 0.05; **p < 0.01.

Table 3. RSA reactivity before and after emotional inductions.

Group	**1**		**2**	
Stimulation	Picture (static stimulation)		Film (dynamic stimulation)	
Emotion intensity	HIA > LIA (questionnaire)		HIA < LIA (questionnaire)	
Emotional type	Positive	Negative	Positive	Negative
TAM (power difference)	HIA		HIA	
	TM (−0.34, ↓) AM (−1.32, ↑)	TM (0.21, ↑) AM (−0.87, ↑)	TM (−0.19, ↓) AM (−2.22, ↓)	TM (0.20, ↑) AM (0.63, ↑)
	LIA		LIA	
	TM (0.11, ↑) AM (0.44, ↑)	TM (−1.44, ↑) AM (0.27, ↑)	TM (−4.33, ↓) AM (−1.42, ↑)	TM (−2.70, ↓) AM (−4.26, ↑)
	HIA: TM, LIA:AM TM: breathing frequency changed faster AM: breathing frequency changed slower (parasympathetic)			
RSA reactivity			RSA↑ (except surprise) (HIA*↑ < LIA↑)	RSA↓ (except sadness) (HIA*↑ < LIA↓)

HIA: high-risk IA; LIA: low-risk IA; TAM: thoracoabdominal movement; TM: thoracic movement; AM: abdominal movement; RSA: respiratory sinus arrhythmia; ↑: increase; r: decrease; *p < 0.05.

Table 4. Summary table of emotional intensity, TAM, and RSA reactivity in IA experiment.

The experimental result of IGD experiment indicated that the IGD & HIA group felt more positive emotion for online game films than the non-IGD & LIA group, and the IGD & HIA group exhibited weaker physiological activity to online game films than the non-IGD & LIA group. It was interesting that IGD abusers have positive emotion to online game films, but they self-rated not much physiological activity (arousal) than people without IGD. The results of HRV index (LF/HF) in the IGD & HIA group also implied that the IGD abusers exhibited stronger sympathetic nervous activity or weaker parasympathetic nervous activity. The parasympathetic activity of the IGD & HIA group to regulate negative emotions was weaker than the non-IGD & LIA group, which consisted with the RSA results of IA experiment.

It is noticed that the effect of induction material, film and picture, was different. Emotional films induced a single targeted emotion, whereas some emotional pictures (anger and fear) induced multiple emotions. The stimulation type and time interval may cause such difference [57]. For temporal character, picture is a kind of static stimulation which displayed lasting for 12 s, and one frame is regarded as one stimulus. The emotional film clip is a kind of dynamic stimulation which displayed lasting 180 s (1/30 s/frame), and it is total 5400 stimuli for 180 s. Nevertheless, the display time of induction material was different from film and picture, and that may affect the emotional induction effect. For cognitive feature, films convey complex cognitive feature and can catch people's attention [57]. The emotional complexity was observed from the emotional picture trial but the film trial. In the real world, people usually receive dynamic stimulation rather than static stimulation, and therefore, the emotional film inductions are more close to the real world stimulation. In addition, the negative emotional materials induced multiple negative emotions. The stimulation type and property were shown in **Table 5**.

Property			**Film**	**Picture**
Substantial [57]	Temporal	Display time	1/30 s/frame	∞ s/frame
		Stimulation period	180 s	12 s
	Spatial	Resolution	1180 × 800	1024 × 768
	Feature		1. Complex cognitive feature	
			2. Catch attention	
Emotional	Type		Positive/negative	Positive/negative
	Complexity			1. Fear overlaps surprise
				2. Anger overlaps surprise and fear
Stimulation			1. Real world stimulation	Static stimulation
			2. More pure emotional induction	
			3. Dynamic stimulation	
			4. Dynamic physiological regulation	

Table 5. Stimulation properties of film and picture induction materials.

3. Conclusion

IA is a hot and serious issue worldwide, and psychophysiological relationship between emotion and IA using physiological signals was studied. This study was not only a hypothesis testing research, but also a hypothesis generating research. Emotion and physiological signals play important roles in (dynamic) expression and regulation of emotional responses to IA. Emotional induction experiments were conducted to acquire respiratory signals (thoracoabdominal movements), ECG signals, facial images, and self-assessed emotional intensity of IA abusers and IGD abusers. Complementary Ensemble Empirical Mode Decomposition (CEEMD) was also adopted as a feature extraction method for respiratory signals without phase loose or distortion. The power values, respiratory amplitude, of dominant frequency from thoracic movement and the abdominal movement in HIA and LIA groups were analyzed. The HIA group and the LIA group expressed different respiratory response upon positive and negative emotional inductions. The induction effects of emotional picture and film stimulation were also different. The autonomic nervous responses were also considered. RSA and HRV index computed from the ECG signals, reflected autonomic nervous system (ANS) activity, and particularly vagus nerve regulation (RSA reactivity). The results revealed that the HIA group had a lower RSA level than the LIA group. IA abusers (HIA) exhibited stronger RSA reactivity following negative emotion, but exhibited weaker RSA reactivity following positive emotion. The emotional responses of IGD abusers were also examined. IGD abusers had stronger happiness feelings to positive emotional online game films, and felt multiple negative emotions to negative emotional online game films. IGD abusers have more positive emotion, and stronger sympathetic activity, but weaker physiological activity to the online game films than those of people without IGD. This study provides results of respiration, HRV index, and RSA reactivity, the ANS and vagus nerve activity of IA abusers, and assists further study of the emotion regulation of the ANS for IA abusers.

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Chapter 7

Methadone Treatment for Heroin Dependence

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Additional information is available at the end of the chapter

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Abstract

In substitution therapy for treatment of heroin addiction, methadone is the synthetic opioid agonist of first choice. Methadone doses vary depending on addict profile established by repeated evaluation. It studied a group of 82 patients both male and female, aged between 19 and 47 years, residing in Bucharest, with diagnosis of heroin addiction. They were voluntarily submitted in the methadone substitution treatment at a specialized treatment center for addiction in Bucharest. The study group was characterized in detail, taking into account demographic, comorbid and addiction characteristics, heroin use history, treatment history, and clinical and paraclinical evaluation. The outcomes resulting from the study design on 82 heroin addict patients enrolled into a methadone maintenance program highlighted: lowering of the onset age of heroin use, HVC infection comorbidity, and the extension of the treatment period due to the relapses. The results obtained by clinical, laboratory, and psychological complex evaluations in a correlative approach is essential both in initiating methadone treatment and monitoring the detox period but also in the supervision of methadone maintenance treatment.

Keywords: methadone substitution treatment, heroin addiction, addict profile

1. Introduction

The opiates, especially the heroin could be the main problem in the matter of drugs at world level, as statistics on the treatment request show. Heroin use dominates the demand for treatment in Europe (around 80% of new opioid-related treatment demands) [1]. However, the opiates consuming is relatively stable at the world level, with an estimated 33 million users of opiates and prescription opioids, according to the latest world report on drugs [2]. European

statistics show that heroin is the most commonly used illicit opioid in Europe, but synthetic opioids such as methadone, buprenorphine, and fentanyl are also misused. The average prevalence of high-risk opioid use among general EU population (15–64 years) is estimated at 0.4%, the equivalent of 1.3 million high-risk opioid users in Europe in 2015 [1].

In addition, opioids remain major drugs of potential harm and health consequences. There are several complications, which are derived from the illicit opioids consumption, among which there are overdoses, transmissible infections, the increase of criminality, reduction of workforce, and general life quality [3, 4].

The addiction to opioids, a complex disease, necessitates a long-term treatment, which mainly consists in the substitution therapy, also called, according to WHO, "agonist pharmacotherapy," "agonist replacement therapy" or "agonist-assisted therapy"; this is a key component of the treatment resources [5]. WHO defines it as the administration under medical supervision of prescription psychoactive substances, which are pharmacologically related to the one producing dependence, to people with addiction, for achieving defined treatment goals.

Several tries of substitution treatments of the opiates addiction took place at the beginning of the twentieth century and they used the morphine. The morphine did not prove to be a corresponding substance for substitution (tolerance used to rapidly install, the patient needed to have several injections per day). Since 1960s, starting with the discovery of the methadone, the substitution treatment began to be reevaluated.

In 2005, WHO added methadone and buprenorphine in the list of essential drugs for the treatment of opioid dependence [6]. This decision was based on numerous studies that have shown that using these two drugs in substitution therapy bring benefits for physical and mental health, improves quality of life, and reduces injection behaviors associated with high risks. Therefore, international guidelines recommend methadone and buprenorphine as first-line medication treatment for opioid dependence [7]. The studies were conducted in countries with different socio-economic conditions and different treatment systems for drug addiction. These studies have shown that therapy with methadone or buprenorphine is safe and effective [5]. The substitution therapy with methadone or buprenorphine gives addicted people the possibility to function normally within their families, jobs, and communities [8]. However, methadone was shown to have higher treatment retention rates than buprenorphine-naloxone, and it is preferred over buprenorphine-naloxone for patients at higher risk of treatment dropout [9].

A standard terminology for the treatment with methadone, classified into four categories, has been proposed:

- Short-term detoxification: decreasing doses for up to 1 month;
- Long-term detoxification: decreasing doses over more than 1 month;
- Short-term maintenance: stable doses for up to 6 months;
- Long-term maintenance: stable dose for more than 6 months.

Usually, the term "substitution therapy" is utilized as an equivalent to "substitution maintenance therapy" [10].

The methadone maintenance therapy (MMT) is an intervention of harm reduction type, because the patient does not become abstinent (i.e., the patient does not cure, i.e., he/she does not give up any substance consumption); instead, a series of positive changes such as managing opioid withdrawal, reducing craving, returning to a job, education, and a family happens [11]. The methadone is orally administrated and due to its half-life, between 24 and 36 hours, it may be administered once a day. Administered in doses of 80–120 mg/a day (adjustments are possible according to each patient), the methadone blocks the euphoric effects of the heroin, and moreover, eliminates the craving for heroin; they are some of the most important factors in case of relapses. Methadone maintenance programs decrease mortality by approximately 50% among persons with opioid-use disorders, decreased prevalence of significant infections such as HIV and hepatitis, decrease crime, reduces illicit opioid use, improve social functioning, and increase the rate of retention in rehabilitation programs [12].

The use of the methadone in the substitution treatment of the patients addicted to opiates is well-documented and its efficacy is well established but responses vary. Despite successful outcomes, the MMT and the influence of methadone pharmacodynamics and pharmacokinetics on dose requirements continue to remain controversial [13]. A relationship between methadone dose and plasma methadone concentration in addicted patients during substitution therapy has been suggested, the plasma level depends on different factors [14, 15]. However, research conducted so far have demonstrated fully and unequivocally follows: patients receiving inadequate doses of methadone will continue to use heroin; these patients do not respond to behavioral therapies or they need maintenance treatment with methadone for long periods; when doses of methadone are tailored and individualized favorable trends are observed in these patients [16, 17, 18]. Optimal treatment can only be determined if one takes into account the factors that determine differences in drug response and only when the dosage is determined based on diagnosis, severity, and stage of the disease and on the presence of other diseases or concomitant therapy. This allows pre-evaluation of efficacy and acceptable toxicity limits. If these assessments are not done properly before treatment, if patients are not appropriately monitored during treatment, there is a risk that the therapy to be ineffective.

In this context, we conducted a study, on a period of a year, on a group of patients with a diagnosis of heroin addiction, who have voluntarily submitted to an addiction treatment center in Bucharest, for inclusion in the program of methadone substitution treatment. The objective of the study was to define the profile of the patient entering the methadone substitution therapy and to evaluate the adherence to treatment.

2. Study design

The group to be studied consisted of 82 drug addicts, consumers of heroin; these patients were examined from the psychological point of view at the Addiction Section, were hospitalized and monitored during the detoxification which was carried inpatient, under strict medical supervision, for a period of 10–14 days, then in the outpatient treatment (methadone

substitution treatment). The study was approved by the Ethical Committees of the Centre and the informed consent for the participation in the study was obtained from all patients.

The study group was characterized in detail, taking into account demographic, comorbid and addiction characteristics, heroin use history, treatment history, and clinical and paraclinical evaluation.

Indicators/parameters to be followed: age; sex; occupation; comorbidity; the history of heroin consumption (detailed as follows: recognized consumption age, intravenous heroin consumption starting age, way of heroin administration, other tested/consumed drugs); history of treatment (previous abstinence periods, previous hospitalizations, previous treatments, when starting treatment with methadone, which is currently under, psychological counseling; methadone dose); and toxicological analytic screening aiming at both diagnosing the drug consumption as well as checking and confirming the abstinence along the period of substitution therapy with methadone.

During the hospitalization, the psychological investigation of the patients was made. The description of the mental state, together with monitoring the behavior during the psychological interview, aim at filling in the examination file and applying efficiency and personality tests for the psycho-diagnostic purpose.

Qualitative analytical screening and quantitative assays refers to the immunofluorescence method for the quantitative determination of heroin and their metabolites in urine [19]; it is based on a technique of fluorescence polarization immunoassay using an automatic drug analyzer version TDxFLx (Abbott Laboratories). The results can be expressed either in qualitative (presence or absence of opiates) or quantitative (sample concentration in ng/mL) terms. Detection threshold (cut-off) was established at 200 ng/mL (this being the most widely accepted value). Measurements obtained are used for the diagnosis of heroin use and for establishing the substitution therapy.

3. Statistical analysis

To achieve the study, we have used individual medical files, and, for instruments of interpreting data, we have used a series of statistic applications including both the descriptive methods and the analytic ones; the data are centralized in the database EXCEL and SPSS and processed with the available statistic functions, compatible and adequate to the type of the collected data (at nominal, regular and reporting level).

The descriptive statistics, the distribution of the frequencies and the comparisons have been done by means of the program SPSS Statistics, ver. 21; the data of the different parameters are presented as average ± standard deviation (SD). The correlations between the parameters, using the correlation coefficients (Pearson, Spearman, and Kendall) have also been evaluated. The comparisons among the groups under study have been made by means of the Student and Anova tests. All of them have been statistically significant at the level of $p_1 = 0,05$ and $p_2 = 0,01$.

4. Results and discussions

We have taken a group of 82 patients, both males and females, aged between 19 and 47, living in Bucharest and diagnosed with heroin addiction (according to ICD-10), who came voluntarily to get a substitute treatment with methadone in a center of specialized treatment of addiction, placed in Bucharest. The group under study has been described in details, taking into account the demographic, addiction characteristics and comorbidity, the history of the heroin consumption, the history of the treatment, the clinical and laboratory evaluation.

4.1. Demographic, addiction characteristics, and comorbidities

The complex description of the patients group regarding the demographic, addiction, and treatment characteristics, as well as comorbidities is presented in the **Table 1**.

4.1.1. Indicator: sex

In the selected group, males are predominant; so, the group has included 75/82 patients, respectively 91.5% and 7/82 patients, respectively 8.5% females (**Table 2**), leading to a proportion of 10.71 males/females.

4.1.2. Indicator: age

In the general hypothesis of the study, we have anticipated that, when speaking about the drug consumers, there are clear differences between the average age of the drug consumers who are registered and the onset average age of the drug consumers within the same population, and the results lead to the confirmation and acceptance of the general hypothesis.

Thus, the average age of the patients registered at the beginning of the study was 31.28 ± 5.15 years and varied between 19 and 47 years (**Figure 1**), being significantly higher than the average age at the onset of drug use, which was 19.52 ± 4.35 years and varied between 11 and 33 years (**Figure 2**) ($p < 0.001$, t-Student). The statistic significant difference was also noticed when the Anova Test was applied ($p < 0.001$).

As regards the age at the onset of heroin use, there is a dramatic remark which says that many of the patients declared their onset under the age of 20, respectively, the most frequent interval, between the age of 15 and 20 (40/82 patients, 48.8%). The study points out the growth of the drug consumption among young people and the decrease of the onset age. Thus, the history of the opiates consumption is a long term one, an average of 11.73 ± 4.52 years varies between 3 and 25 years (**Figure 3**). We have pursued, on the other hand, the duration of the drug consumption, previous to the first requirement of treatment. The obtained results, using some specific statistic methods, have shown that the total period of the drug consumption is significantly different, from the statistic point of view ($p < 0.001$; t-Student, ANOVA**),** from the period of the drug consumption until the first methadone substitution treatment, with an age average 6.51 ± 3.45 years, varying in the area 1–18 years (**Figure 4**).

Proportion according to the sex	91.5% males; 8.5% females
The male/female ratio	10.71
Age (years) (mean ± SD)	31.28 ± 5.15 (range:19–47)
Age at the onset of the consumption (years) (mean ± SD)	19.52 ± 4.35 (range: 11–33)
Age category	≤ 20 years old (1.22%); 21–25 years old (9.75%); 26–30 years old (37.8%); 31–35 years old (32.92%); 36–40 years old (14.63%); > 40 years old (3.66%)
Age category at the onset of the consumption	< 15 years old (12.2%); 15–20 years old (48.78%); 21–25 years old (31.7%); 26–30 years old (4.87%); >30 years old (2.44%)
Length of consumption (years) (mean ± SD)	11.73 ± 4.52 (range: 3–25)
Length of consumption previous Methadone maintenance treatments (MMT) (years)	6.51 ± 3.45 (range: 1–18)
Occupation (% of the patients)	Unemployed 58.83; Employed 41.7
Problems with the law (damnation) (% of the patients)	17
Daily dose of heroine (g) (mean ± SD)	1.04 ± 0.74 (range: 0.3–3.3)
Way of consuming (i.v. since the onset) (% of the patients)	78
Concentration of heroine metabolites in the urine (ng/mL)	1000–30,000
Patients with poly-drug consumption (%)	52.5 (new psychoactive substances consumption, NPS in 58.14% of cases)
Methadone dose (mg) (mean ± SD)	55.91 ± 26.71 (range: 15–125)
Previous MMT (number of treatments)	5.45 ± 2.14 (range 1–10) (40/82 of the patients)
Previous hospitalizations (number of periods)	8.31 ± 6.06 (range: 1–30) (58/82 of the patients)
Psychological counseling (number of meetings)	9.48 ± 10.48 (range 1–46)(33/82 of the patients)
Patients with previous periods of abstinence (%)	24.4
Patients with comorbidities (Hepatitis C, Hepatitis B, human immunodeficiency virus) (%)	70.7% (58/82)

Table 1. Characterization of the group under study.

These aspects, together with the typical profile of the drug addict, are set up in essential data, because they contribute to the accurate identification and peculiarity of the target groups, who should be hinted at when starting a prevention or therapeutic program within the drug addiction phenomenon.

The data are in accordance with the official statistics at the national level, which show that the duration of the consumption previous to the first requirement of assistance is longer for the opiates, with an average of 7.4 years and a frequent value of 4 years [20]. The official reports also show that, even though there are beneficiaries who require some medical assistance after

Parameter	Parameter	Correlation coefficient, statistic significance
Age	Length of consumption	r = 0.461**; p < 0.001
Age	Length of consumption previous to MMT	r = 0.354**; p = 0.001
Length of consumption	Length of consumption previous to MMT	r = 0.611**; p < 0.001
Length of consumption previous to MMT	Comorbidities	r = 0.409*; p = 0.025
Length of consumption previous to MMT	Methadone dose	r = 0.526**; p = 0.007
MMT numbers	Previous hospitalizations periods	r = 0.655**; p < 0.001
MMT numbers	Number of psychological counseling meetings	r = 0.501*; p = 0.02

*Statistically significant correlation.

**Statistically highly significant correlation.

Table 2. Pearson correlations among the analyzed parameters in the study.

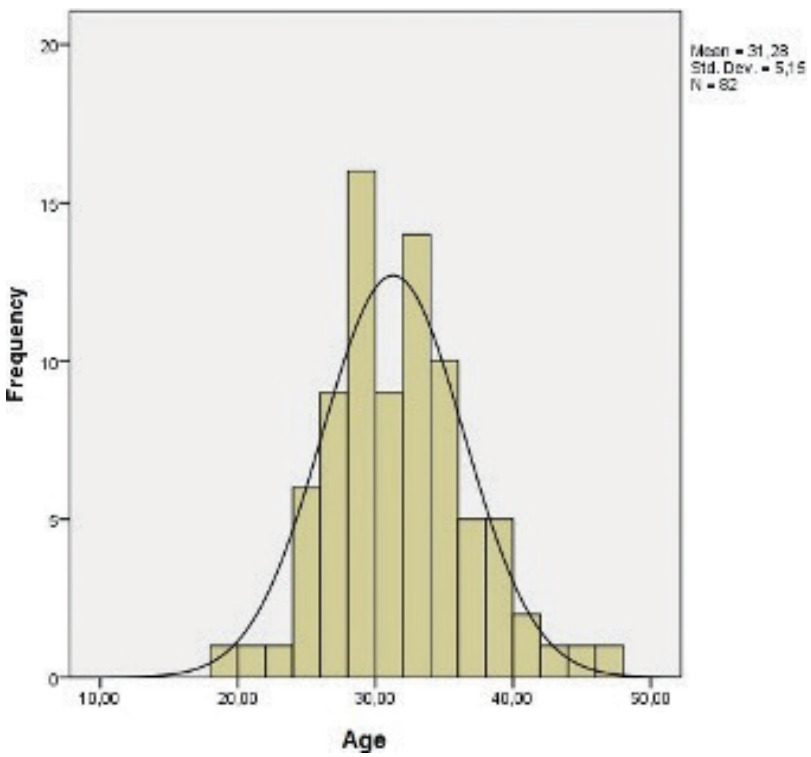

Figure 1. Proportion of the patients according to the age.

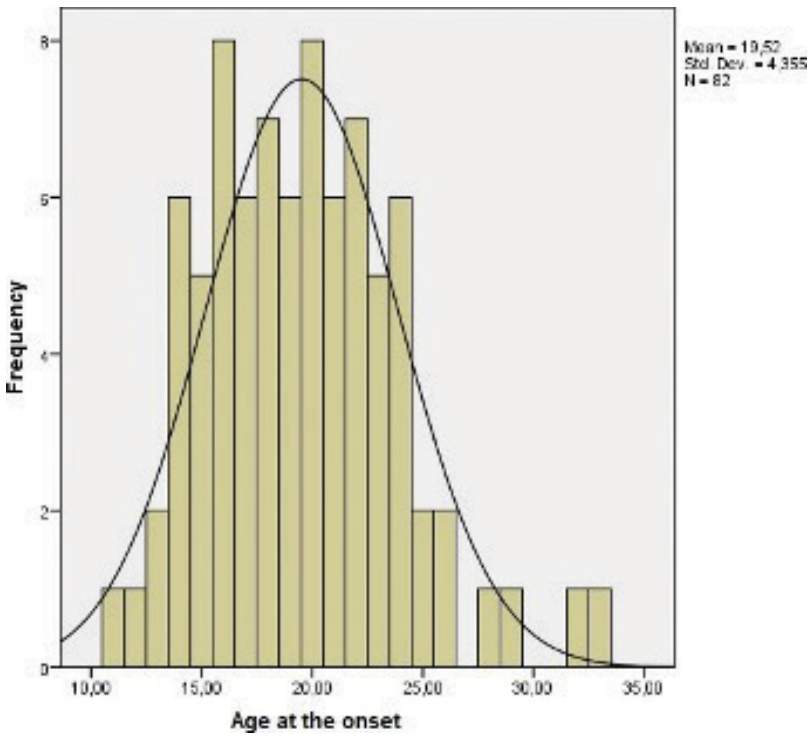

Figure 2. Proportion of the patients according to the age at the beginning of the drug consumption.

less than a year, there is a slight growth of the period of demand of the specialized services: most of the beneficiaries who have never been admitted in the treatment, have required medical assistance after 3 years of drug consumption, comparative to the cases of relapse, in which most of the patients have demanded medical assistance after 2 years of drug consumption [20].

Regarding the category of age, the groups of ages between 26 and 30 years and 31–35 years are pinpointed as follows. We can notice that these groups of ages are distinctly different from the most frequent categories in case of the age at the onset of heroin use (15–20 years and 21–26 years.

4.1.3. Indicator: occupation

More than half of the patients (58.83%, 48/82) do not have an occupation, and the others have only a temporary occupation. Only one patient of the group has graduated a private faculty; all the others have graduated high or secondary school. Around 17% of the patients have legal antecedents, respectively detention, because they stole in order to get money for drugs.

Psychologically, the drug addicts have problems because they do not have a permanent job; on the other hand, they are not able to keep a permanent job, because the withdrawal and the relapses prevented them from doing it; it is a vicious circle with no break.

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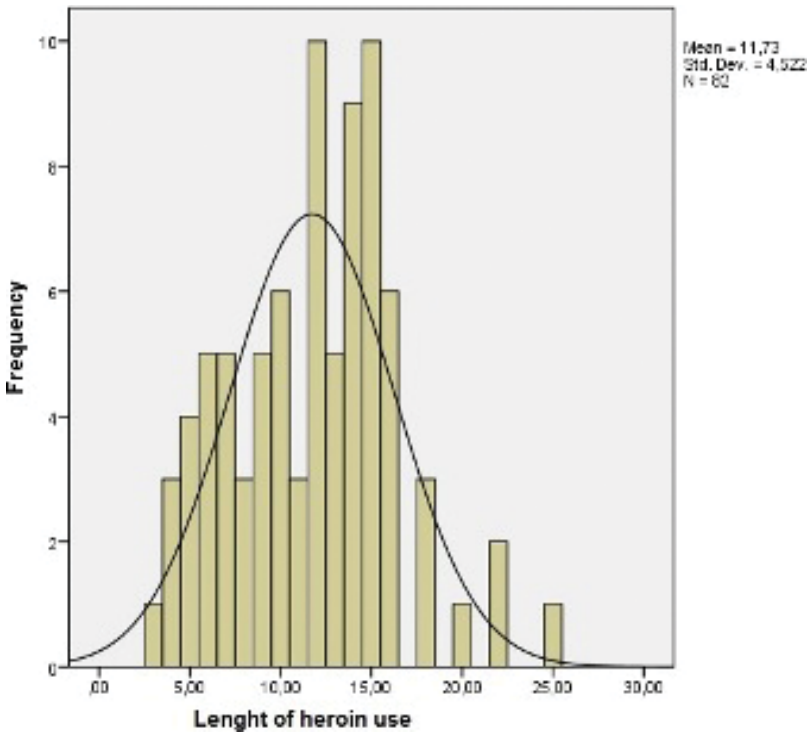

Figure 3. Proportion of the patients according to the duration of the consumption.

4.1.4. Indicator: comorbidity

A proportion of 70.7% of the target patients are proven to have the virus of the hepatitis C (HCV), hepatitis B (HBV), or HIV. Some of the patients have declared the common use of the syringes, this being the explanation of their infection. Two of the patients have got cardiac arrhythmia and are under adequate treatment. Four of the patients have got post-injection thrombophlebitis. Two of them have received a recommendation of treatment with acenocoumarole. Some of the patients had different forms of psychic disturbances, ranging from anxious depression to personality disturbance of mixed type; three of these patients were previously hospitalized in Psychiatric Hospitals.

4.1.5. Indicator: type of drug addiction

More than half of the patients of the target group are poly-drugaddicts (52.5%, 43/82), because they consume heroin and, occasionally, other types of drugs (frequently NPS, Cannabis or Ecstasy). Thus, the statistics on drug consumption show an important proportion of new psychoactive substances ("ethnobotanicals," like PUR, MAGIC, SPICE), marijuana and hashish in a context of chronic use of heroin. The consumption of ethno-botanicals is the most frequent, being reported by 58% of the patients with poly-drug consumption. It is also noted a relatively high incidence (nearly 20–30%) of psychostimulants use, for example types of

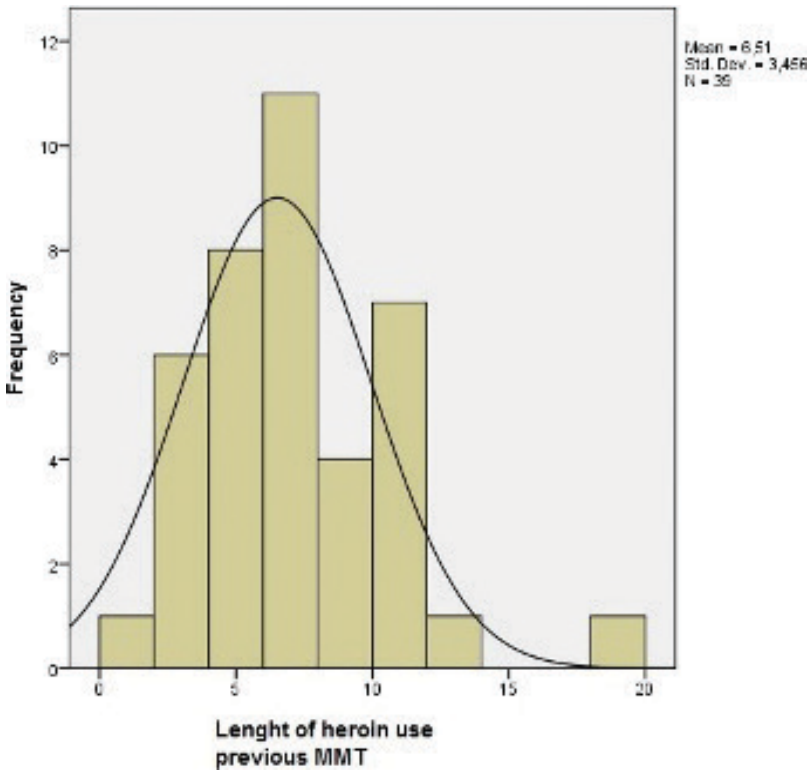

Figure 4. Proportion of the patients according to the duration of the consumption, previous to MMT.

cocaine or designer amphetamines with a hallucinogen component (ex. Ecstasy). Other different hallucinogens (ex. L.S.D., ketamine) have occasionally been reported.

4.1.6. Indicator: way of administration of the heroin

The most frequent way of the heroin administration is the i.v. (all the patients have declared the intravenous use of the heroin, in most cases, even at the onset use of the heroin (78% of the patients). The other patients have used it differently: smoking or nose sniffing.

The study shows that most of the patients had previous hospitalizations (70.7%, 58/82), an average number of 8.31 periods and previous periods of MMT (48.78%, 40/82 patients), an average number of 5.45 treatments, previous to the presented study. Also, 40.24% of the patients (33/82) have benefited from psychological counseling, an average of 9.48 meetings. Referring to the abstinence length, only a little percentage (24.4%, 20/82) had abstinence on relatively short length of time, up to 1 year.

These results show that, among the confirmed drugaddicts, the opiates consumers present the most invalidating, with the longest duration and frequency of drug consumption, with a lower compliance to treatment and high resistance as regards the initiation and the maintenance of the abstinence. These present a high frequency of relapses as well as long term and high intensity of drug consumption.

The data in terms of demographic characteristics, addiction, and comorbidity are in accordance with the official statistics and reports. Thus according to the annual report with respect to the situation of drugs in Europe, in 2012, the number of the male patients, consumers of opiates, exceeds three times the number of female consumers. Most of the opiates consumers report that they have first started using the drug before the age of 30, and nearly half (46%) of all the opiates consumers confess that they started before the age of 20. Generally, the opiates consumers frequently report their lack of a dwelling, unemployment, as well as a more reduced level of education than the primary consumers of other drugs [21].

The national report as regards the situation of drugs [20] shows that, at national level, the profile of the consumers of injection drugs, no matter the provided assistance (program of changing the syringes, admission to treatment, and emergency assistance), reveals a 30 year old man, who lives in Bucharest and has a long period of drug consumption, the main drug used belonging to the opiates category. Out of 1529 persons who received medical assistance in 2013, for illegal drugs consumption and NPS, nearly half of them were consumers of opiates, and among them 328 had previous episodes of substitute treatment with methadone or other opiates.

On the other hand, according to the official data, the heroin (42.7%) and NPS represent the most important types of substances which was the reason why consumers called medical assistance for; however, although heroin is the main drug for which were most treatment demands, significant differences have also been reported among beneficiaries who received previous medical assistance and the new cases, which outlines a possible change in the pattern of drug consumption.

4.2. Statistic correlations among the evaluated indicators

Applying some specific statistic methods (the SPSS program, Pearson, Spearman, Kendal correlations), we have evaluated the possible correlations among the analyzed indicators/parameters. Thus, we have obtained positive correlations which are statistically significant among the parameters (**Table 2**): age-length of consumption; age-length of consumption previous to the first MMT; length of the consumption – length of consumption previous to the first MMT; comorbidities – length of consumption previous to the first MMT (suggesting the positive influence of the treatment on the morbidity); the methadone dose - length of consumption previous to the first MMT; MMT number- number of previous hospitalizations. The MMT numbers previous to the presented study has correlated with the number of psychological counseling meetings and this underlines the importance of the psychological intervention, along with the pharmaceutical treatment with methadone.

4.3. Toxicological analysis

4.3.1. Indicator: the urine concentration of heroin and metabolites

The methodology of the quantitative and qualitative toxicological analysis provides with a support, useful in order to analytically diagnose of the drug abuse and to initiate and supervise the substitution treatment.

In the present study, the quantitative toxicological analysis aimed at determining the levels of the heroin and the metabolites in the urine of the heroin consumers, applying the technique of the fluorescent antibody, and using an automatic analyzer. The heroin and metabolite levels in their urine tests have been placed to a large extent, from approximately 700 to over 30,000 ng/mL (**Figure 5**).

During the treatment, not only the initial one, they do tests (which are marked as follows: negative, slightly positive, positive), no matter the patients' declarations. At the assumption or the declaration of relapses, tests grow in number, especially when we speak about the combinations of opiates and heroin or other medicines. The maximum number of tests along a whole year for a single patient has been 27.

4.4. Substitution treatment

All the patients in the group have been administered a substitute treatment with methadone. A single patient with a 15-year drug consumption has been changed on Suboxone instead of Methadone.

The analysis of the group of patients reveals that the average dose of methadone is approximately 56 mg, varying between 15 and 125 mg, enough for the stabilization and avoidance of the abstinence syndrome (**Figure 6**). This is in accordance with the data in the literature, which recommends a test dose of methadone of 20 mg, at the beginning of the substitute treatment. Till the end of the hospitalization, the doses of methadone were generally increased with approximately 10 mg in 2 days; for the outpatients, the level of methadone was increased to 125 mg/methadone/day in some patients.

Some patients have required the reduction or the increase of the doses, but this depended on the symptomatology.

Our study shows that the patients' stabilizing is done with moderate methadone doses (approx. 50–60 mg/zi), compared to those reported in the literature (approx. 90–100 mg); this is an advantage, taking into account the possible interactions with other medicines, under the circumstances of the associations of the necessary medicines during the substitute treatment, as well as the somatic comorbidities of the patients (mainly the liver chronical problems caused by HCV infection).

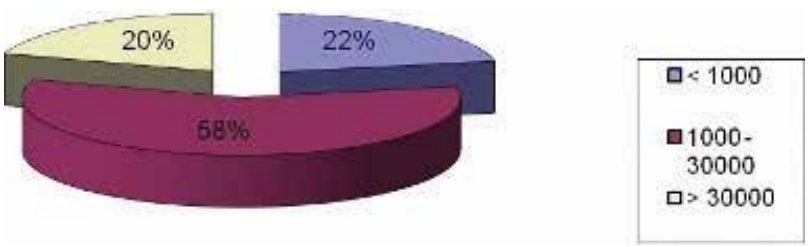

Figure 5. Proportions in the patient group according to the concentration of heroin and metabolites (ng/mL) in the urine tests.

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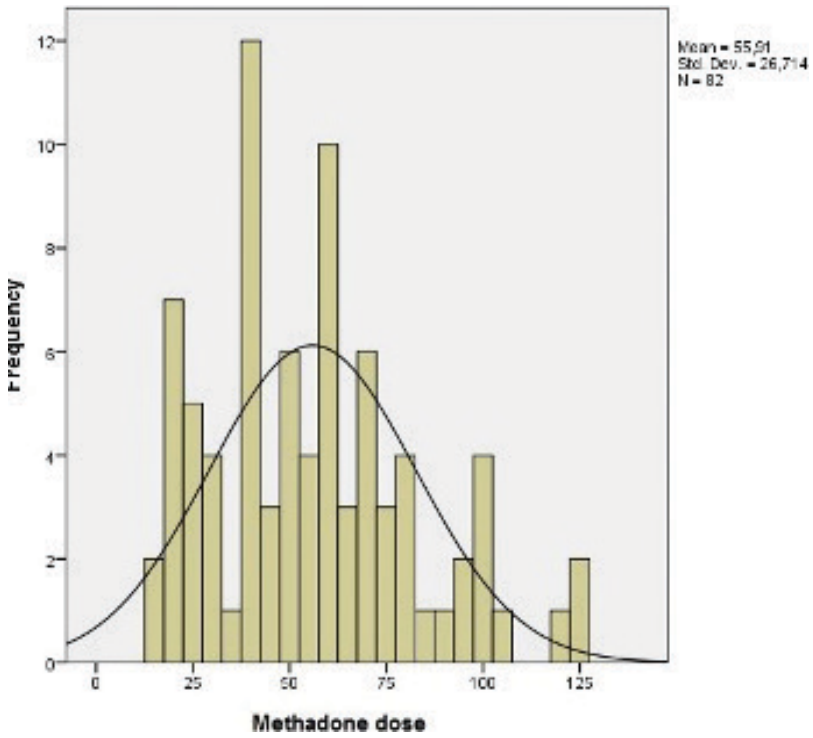

Figure 6. Proportion of the patients according to the methadone dose.

During the methadone substitution treatment, they often prescribe different medicines to improve anxiety, agitation, and severe muscular contractions; generally, phenothiazines and benzodiazepines are used to treat agitation, to stabilize the patients' sleep and muscular contractions. They also take into account the somatic and psychic comorbidities of the patients. The co-medication makes possible different medical interactions. Thus, the data in the literature suggest that the benzodiazepines (they themselves being medicines with potential of abuse consumption), especially for the fact that the diazepam interferes with the normal metabolization of the methadone. To be more precised, the individual treatment has a different graphic according to: the test results, symptomatology, and comorbidities. At the beginning of the treatment, patients are informed on the condition to remain under treatment, notably the negative tests of the heroin and combinations. Otherwise, they are removed from the program.

Together with the treatment with methadone, over 80% of the patients have accepted the individual or group psychological therapy. We consider that, without this type of therapy, the situation of the patients would be more dramatic. The study shows that 40% of the patients have confessed their relapses, because of their bad company or some dramatic events in their family. For this reason, the methadone doses have been adjusted and the treatment has been extended. The relapses have been confessed and marked out at the heroin presence in the tests. The rehospitalizations have been done out of the patients own initiatives, because of their syndrome of withdrawal. Their motivation of the relapse was depression, the lack of

a positive emotional support on behalf of the people close to them and inability to prevent from not using drugs. Even if they have not restarted all of a sudden (with heroin) they have used NPS (such as Magic/Supergold, Pure). Three patients who gave up the substitution treatment were hospitalized at Psychiatric Hospitals. The evaluations which maintain or change the methadone doses are made in accordance with the clinical behavior, psychological and paraclinical monitoring. We state that, an important proportion of the patients have confessed self-medication with methadone, before their onset in the program. The methadone was used in order to stop the state of withdrawal with heroin (a short term detoxification), and also, as an agent for long term substitution.

All the patients in the group have been included in the program for years, because of their relapses. Their periods of abstinence have lasted for only several days, months, but not years. For instance, one patient had repeated attempts of abstinence during a year, as follows: four times of 1–7 days, two times of about 1 month, and one time (but interrupted) of approximately 4 months.

In spite of monitoring the treatment carefully, there are relapses which impede the personal and social reintegration. Current literature data indicate that sustained remission occurs in a significant minority of heroin users and the treatment does not cure this addiction, but it can contribute to prevent the heroin use and reduce its adverse effects [22].

The results of the study show that the complex correlative, clinical, laboratory, and psychological evaluation is essential to start and supervise the methadone substitution maintenance. This is in line with the recent data from the literature emphasizing the need for multidisciplinary evaluation of candidates for opioid agonist therapy, including a careful medical history, physical and psychiatric examination, psychosocial evaluation, as well as the determination of the patient's readiness to change [23].

5. Conclusions

The study has revealed the following aspects:

- Most of the population using the medical assistance with MMT is represented by male persons, with low level of education, predominantly without any occupation or with a temporary one. The average age of the patients is approximately 30 years; they have a long history of consumption of opiates (approximately 11 years); they predominantly use heroin injections, in most cases associated with other drugs (polyconsumption, i.e., high frequency of association with NPS); most of the patients present somatic comorbidities (HCV or HIV infections), and have several previous hospitalizations and lengths of treatment. The average age of the patients at the onset of the study is significantly different from the age of the patients at the onset of their drug consumption. The total duration of the consumption is statistically different from the duration of the consumption, previous to the first MMT.

- These aspects, together with the typical profile of the drug addicts, represent essential data, as they contribute to the accurate identification of the target groups who would have to be targeted at the beginning of a prevention or therapeutic program within the phenomenon of drug addiction.
- The methodology of the toxicological analysis provides with a useful support to initiate a substitution treatment as well as to detect the relapses during the treatment.
- The integrated care programs of assistance should involve both therapeutic programs and psychological ones in order to prevent relapses.
- The results of the study contribute to the extension of information area in terms of consumption phenomenon and its breadth; the identification of the onset ages in the case of heroin consumption; establishing the prevalence and types of comorbidities with drug addicts; the identification and description of the multiple facts involved in the consumption (biological, emotional, psychological, familial, interpersonal, educational, social, environmental, and within the community) including the precursors, associated with or favorable to the drug consumption; the identification of the determinant elements to enroll in the treatment program.
- In spite of monitoring the treatment carefully, there are relapses, which impede the personal and social reintegration. They point out the necessity to increase the patients' awareness, in terms of their health, and to enroll them in a substitution program, and they also highlight the complicated situation in case of a dual diagnosis (emotional and personality disturbance).

Conflict of interest

The authors declare no conflict of interest.

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