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The Common Items Involved in Substance Use Disorder and their Pharmacology

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Abstract

People with substance use and addiction (SUD) is characterized as uncontrollable useof the substance even they known it is harmful with using the substance, and then getaddictive. Once these substances have been addictive, they are able to change mentalcondition, develop severe psychiatric problems and induce other chronic diseasessubsequently. Due to this kind of mental change, patients will not only hurtthemselves but also jeopardize other people or stuff uncontrollably. Consequently, it develops a major social problem. These phenomena have become more and morecommon worldwide.

According to the announcement by the Food and DrugAdministration of Taiwan, the case numbers of SUD were increasing year by year.Besides, the user's age is younger than before. Report from the [Analysis of the 112Annual Report on DrugAbuse Cases and Inspection Statistics] shows that the priorityof abused substances are central stimulants, sedative, cannabis, tobacco, and alcohol.In this paper, the neurotransmitters triggered by these substances will be discussed,followed by the mechanisms and physiological responses induced by these substances. Information from this paper may provide more knowledge for clinical diagnosis andmanagement.

Keywords: Substance Abuse, Addictive, Central Stimulant, Central Depressant, and Sedative

Introduction

Substance use and addiction (SUD) has become a global problem. One of itscharacteristics of SUD is uncontrollable use even the patients have known the harmcaused by the substance [1]. According to the announcement by the Food and DrugAdministration of Taiwan, the case numbers was increasing year by year. It was overthree million in 2023, and increase in 3.1% reaching the total case number to 329885in 2024. According to the [Analysis of the 112 Annual Report on Drug Abuse Casesand Inspection Statistics] cases of student population was 483, which was elevated20.8% comparing to that in the previous year. However, it still kept elevating up to18.9% in 2024. The major substances used in this population were claimed as thethird-level drugs including ketamine, FM2 and nitrometrazepam.

The total consumption had an increase up to nearly 30% compared with 2022. The followingwas the Class II drugs such as amphetamines, MDMA and cannabis, which wasreported as the number of 100 cases, an increase of 5.3% comparing to that in the2022. The priority of the abused substances was as follows, heroin (33.9% of the totalnumber of claimed reports), followed by methamphetamine (30.7%) andbenzodiazepines (11.3%). Compared with those investigated in 2022, theconsumption of those of heroin, 3,4-methylenedioxymethamphetamine (ecstasy),zopiclone, pethidine, codeine and cocaine decreased in 2023. However, consumptionof those of methamphetamines, benzodiazepines, ketamine, marijuana, zopemian andmorphine raised in 2023.

On the other hand, the most popular substance wasmarijuana in Europe, followed by central stimulants such as cocaine. Although theproportion of opium users is not the largest, the problem of disease transmissionthrough the injection of cocaine cannot be ignored. However, in recent years the SUDpopulation has been shifted to the young age, and the categories of abused substanceswere also much different than before. Combined administrating of more than oneaddictive substance leads to non-specific symptoms of users, which increases thedifficulty of accurately determining which drugs cause toxicity in clinical practice.Therefore, the purpose of this paper is to focus on the neurotransmitters

affected bythese substances, then we can get more understanding about their mechanisms andphysiological responses. Information from this paper may provide more knowledgefor clinical diagnosis and management.

The main neurotransmitters affected by the above drugs/substances include:epinephrine, dopamine, glutamine, serotonin, opiates, etc., which are discussedfollowing.

Epinephrineand Norepinephrine

Epinephrine and norepinephrine belong to the group of monoamine neruotransmiters. They activate adrenergic receptors, which consist of five subtypes:α1, α2, β1, β2 and β3. Activation of these receptors can induce excitation of sympathetic nerve system, including the cardiovascular system, pulmonary function, and metabolism [2]. Activation of each subtype of receptor mentioned above will lead to the followingeffect:

- Activating α1 receptors will enhance myocardial contractility, improve motorsystem, and induce glycolysis in fat tissue and liver, and glycogenesis.
- Since the activation of α2 receptor is to inhibit the release of adrenaline, it causeseffects of sedation, inhibiting lipolysis of adipose tissue, reducing intraocular pressure, attenuating renin and insulin secretion.
- Activation of β1 receptor causes increases the myocardial contractility, as well asthe rate of spontaneous depolarization and conduction. In addition, it also induces therelease of renin, antidiuretic hormone from the posterior pituitary gland, and amylasefrom the salivary gland.
- Activation ofβ2 receptors lead to relaxation of the smooth muscle in blood vessels, uterus, bladder, lungs, digestive tract etc. Besides, it makes increases in skeletalmuscle contractility, liver glycolysis and the permeability of potassium.
- Effects ofβ3 receptors in the periphery are similar to those of β2 receptors. While in the central, β3 receptors activating is able to affects mental stability, which, in turn, leads to some phenomena such as headaches, palpitations, tremors, cramps etc. [2,3].

Dopamine

Dopamine is another member of the monoamine neurotransmitters. Its receptors aredistributed in the nervous system. The function of dopamine includes modulating ofcognition, motivation, endocrine, reward system, memory, attention, impulse control,movement, learning, and sleep [4]. The mesolimbic dopamine system plays animportant role in substance abuse. DA receptors in peripheral nerves regulate bloodflow to the glomeruli, inhibiting sodium resorption and vasopressin release. One ofthe common features of schizophrenia found clinically is an abnormal concentrationof dopamine in brain.

Glutamine

The effect of glutamine is to regulate the function of N-Methy-D-as partate (NMDA),□-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite, etc., whichin turn is related to nerve inflammation and degeneration [5].

Serotonin

Serotonin is associated with the change of mood and behavior such as depression,mania, autism, schizophrenia, anxiety, obesity and pain. There are many types ofserotonin receptors in the limbic system, and their functions are related to sensation,autonomic neurocognition, memory, sexual behavior, etc. [6].

GABA(-AminobutyricAcid)

GABA is an inhibitory neurotransmitter that is involved in chloride regulation in neurons. GABA affects not only ion channel regulation but also the metabolic activity. Consequently, causes kinds of mental disorders. Benzodiazepines possess a calmingeffect by activating GABAand inhibiting adenosine reabsorption. GABAA1 receptoractivation induces sedative, forgetful and antiepileptic effects, while GABAA2 receptor is associated with anti-anxiety and muscle relaxant effects.

Cannabinoids

Cannabinoid-related effects are all generated through activating the cannabinoidreceptors/CB receptors, which have a wide variety of receptors, including metabolicreceptors that bind to G proteins, and intranuclear receptors, which are widelydistributed in the brain, skeletal muscle, liver, pancreas and other organs. CB1receptors are distributed in the brain, skeletal muscle, liver, pancreas, etc.

When theCB1receptors activate, the metabolism of human body gets altering. Another one, CB2receptors, is distributed in the testicles and brain. Cannabinoid receptors have beenimplicated in responses to learning, memory, neurodegeneration, addiction, epilepsy,appetite, etc.

Opium Receptors

Opium receptors are divided into μ, κ, and δ receptors, which can be activated by avariety of endogenous molecules, such as endorphins, enkephalins, dynorphins, andalkaloids. In addition, they are also affected by some synthetic molecules, and theactivation of these receptors is related to substance abuse, tolerance and addiction.

Brain and Behavior Changes in Drug Abuse and Addicts

Drug abuse can affect the concentration of several biochemical substances in blood,such as dopamine, serotonin, GABA, etc. Because these drugs affect cognition,judgment, mood, etc., it is related to the compulsion of seeking more drugs duringdrug abuse. Long-term abuse can cause structural and functional damage to the brain.

The Behavior of Drug Abusers

Inhibitors

Heroin and opium bind to μ, κ, and δ receptors, which are distributed in thecerebral cortex, optic thalamus, nucleus accumbens, basolateral amygdala, etc. Theactivation of ❍receptors in these areas can produce analgesic effects on the spinalcord and spinal cord, increase prolactin secretion, inhibit peristalsis of the respiratoryand digestive systems, sedation, pupil constriction, immunosuppression and euphoria,and the euphoria in these areas can induce drug dependence in users. Once addictiveeffects develop, poor judgment and cognitive impairment become, leading tocompulsive substance use [7]. When the K-receptors located in the hypothalamus areactivated, individuals experience irritability and decreased dopamine release [7]. Anxiety occurs when D receptors in the basal nucleus are activated [7]. Opium induces feelings of euphoria, sedation, and restlessness when withdrawaloccurs [8].

In addition, activation of central M receptors increases intersynaptic dopamineconcentration, increases the desire to use drugs repeatedly, and leads to an increase indrug addiction, including the left posterior inferior temporal gyrus, hippocampus,amygdala, talar sulcus, precuneus, caudal nucleus, and nucleus accumbens [9]. In addition, lesions in the gray matter structure of the brain can cause neuro adaptations that are associated with substance addiction[10].

Symptoms of acute heroin and opiate intoxication are in a broad spectrum, such assedation, drowsiness, decreased alertness, nausea, vomiting, dizziness, euphoria, etc.[7, 8, 11]. The appearance of euphoria is also one of the trigger factors of substanceaddiction. In addition, itchy skin, flushing, constipation, low body temperature, anddecreased heart rate may occur. Needle pupil can be used as one of the basic clues forthe diagnosis of opium poisoning. In addition, inhibition of the respiratory center canslow down the breathing rate and resulted in shallow breathing, which will be fatal ifnot addressed in time [11]. Immediate identification of the symptoms of opiatepoisoning and administration of appropriate antidote is the best way to prevent deathfrom poisoning [8]. Chronic intoxication from long-term use of cocaine or opium can cause weight loss,pallor, dry skin, rashes, dilated pupils, and antisocial behavior.

Withdrawal symptoms of these CNS inhibitors include agitation, anxiety, palpitations,cramps, high blood pressure, elevated body temperature, headache, insomnia, nausea,vomiting, sweating, abdominal pain, and disorientation. In addition to the above,withdrawal symptoms caused by cessation of cocaine or opium use include runningnose, drooling, watery eyes, dilated pupils, muscle pain, muscle spasms, goose bumps, dehydration, acid-base imbalance, weakness, severe depression, and anxiety, etc. Alcohol is a central nervous system depressant, and at low and medium doses, euphoria occurs, followed by poor judgment, and then dose-related sedative effects [8]. At high doses, the brainstem and cerebellum are depressed, resulting ininhibition,aggression, emotional swings, sadness, and anger.

The inhibitory effect of alcohol is caused by the activation of GABA and the inhibition of NMDA, resulting in a sedative response [9]. Alcohol can also increase the activity of opioid neurotransmitters, followed by increase the dopamine concentration in the nucleus accumbens. For long term alcohol abusers, neuro plasticization reactions are observed, which is the main cause of alcohol withdrawal syndrome development once the patient tries to quit drinking [9]. On the other hand, drinking alcohol will generate pleasant and satisfying sensation, thereby increasing the amount of alcohol drunk and gradually becoming addictive. The effect of alcohol on the periphery is to increase the content of nitric oxide, acetaldehyde, and insulin, causing vasodilatation and lowering blood pressure. Conversely, high doses of alcohol induce 20-hydroxyeicosatetraenoic acid production, which inhibits tubular sodium resorption, resulting in vasoconstriction [13].

In addition, alcohol can increase the nerve activity of the middorsal anterior cingulatecortex, which is closely related to the structural change in gray matter of the braindACC (dorsal anterior cingulate cortex) (10) (10) among long-term alcohol abusersclinically. The white matter volume in the cerebral cingulate gyrus and corpuscallosum is lower in alcohol abusers than that of normal population, and the dendriticintegration is also low, which is related to impaired motor, cognition, emotion, attention and other functions [14].

There are many symptoms and complications of alcohol poisoning, and the ability toperceive the surrounding environment is reduced due to blurred vision. Euphoria willmake users relaxed, increase self-confidence and social performance. In addition,alcohol can cause an increase in heart rate and a feeling of palpitations. Itsvasodilating effect, which leads to dilation of superficial blood vessels, heatdissipation, flushing and a sensation of increased body temperature; In addition,alcohol directly irritates the mucosa of the digestive tract, so symptoms of nausea andvomiting often occur, and in some special cases, alcohol poisoning has been found tocause respiratory arrest and heart failure and other fatal effects.

Chronic poisoning caused by long-term alcohol consumption will cause poor memory, convulsions, physiological and psychological dependence, and mental status changes andeven schizophrenia. Long-term intake of medium and high doses of alcohol is easy toincrease the chance of accidents. Moreover, alcohol abuse also leads to a variety ofchronic

diseases, such as hypertension, heart disease, stroke, digestive tract diseasesand even cancer.

Studies have found that the alcohol drinking will inhibit the REM phase of the sleepcycle initially. However, after 3-5 consecutive days, the effect of inhibition of REMdisappears, which is inferred to be a compensatory phenomenon, so withdrawalsymptoms that occur during alcohol withdrawal are often accompanied by deliriumtremens. It is worth mentioning that absorption of alcohol before birth can cause fetalneurodevelopmental defects, facial abnormalities, and growth defects, which is the socalled fetal alcohol syndrome. Neonatal withdrawal symptoms include hallucinations,epilepsy, agitation, anxiety, palpitations, cramps, high blood pressure, increased bodytemperature, insomnia, nausea, vomiting, sweating, abdominal pain, anddisorientation

Inhalers

The vapor of inhalers is used as central anesthetics in clinic. Psychiatric activities arealso revealed. The vapor of inhalers contains aerosols, and nitrites, etc. Those arecommonly found in household products, factory chemicals and pharmaceuticalpreparations. Through inhalation into the lungs, these substances are advanced intothe brain via bloodstream and directly act on GABA and its receptors, resulted incentral inhibition and obstruction of brain function in users.

Inhalers can induce euphoria, euphoria, headache, dizziness, sweating, nausea,vomiting, delirium, drunkenness, tonic episodes, respiratory depression, fatigue,irritability, memory loss, restlessness, sleep disturbance, confusion, loss of appetite,weight loss, conjunctivitis, bronchitis, dermatitis, anemia, and leukopenia [14]. Generally speaking, most of these poisoning symptoms last only for a short time, andrepeated use of these agents will gradually jeopardize the body. Long-term abuse willcause harm to the brain, liver, kidneys, lungs and other organs.

Benzodiazepine Sedatives

The abuse rate of such central inhibitors among substance addiction in Taiwan is morethan 10%, and its acute poisoning symptoms include lethargy, slurred speech, ataxia, coma, apnea, hypereflexia, loss of pupil reflexes, and hypothermia; Chronic poisoning, on the other hand, can impair motor coordination, drunkenness, muscle relaxation,irritability, frustration, limb tremors, muscle twitching, and poor appetite. Amongthem, slurred speech is a special symptom caused by the central inhibition effect ofthis type of drug, which is acting through relaxation of articulation muscles andabnormal joint movement, and these movement disorders also create a comorbiddisorder response. People with severe benzodiazepine poisoning can developcoma and respiratory depression, and the latter one is fatal. Severely symptomatic individuals may fall into coma, fatal respiratory depression, and pupil centering.

Stimulants (Amphetamines, Methamphetamines, MDMA)

Anandamide and Methamphetamine and other Central Stimulants

Amphetamine administering produces intense euphoria, and as a result, it is oftenused illegally in order to create alertness and reduce feelings of exhaustion. Amphetamines are often used as a stimulant. In amphetamine addiction, the doseneeds to be increased with time to maintain the same degree of pleasure. However,with the increasing dose, kinds of delusions occur, including persecution, auditoryhallucinations, and paranoia. Therefore, amphetamines can aggravate the symptomsof schizophrenia, which is presumably related to the increase in dopamineconcentration in the brain, and it is in turn related to the reward response which feedsback into the addiction phenomenon. Schizophrenia and inattention after the use ofamphetamines are mostly generated through dopamine pathways; Alertness iscontributed by adrenaline; Interference with the action of serotonin can lead toschizophrenia and delusions.

Methamphetamine increases monoamine neurotransmitters in synapses, includingepinephrine, dopamine, and serotonin. Anandamide disrupts the active transport ofintrasynaptic monoamine neurotransmitters to empty neural messages. At the sametime, it will also slow down the metabolism of catecholamines and inhibit therecovery of dopamine. MDMA (methylenedioxymethamphetamine) is structurallysimilar to methamphetamine and therefore possess a central excitation effect. MDMAalso increases the concentration of dopamine and adrenaline, resulted inhallucinations, which is thought to be induced by affecting the function of serotonicneurons projected into the occipital lobe by the nuclei raphe [10]. Since amphetamine inhibits REM during sleep, it has been observed that the time ofREMwhen the drug is stopped will rebound by up to 75%, and thetimeofoccurrenceis much earlier, which may be related to the user's tendency to have nightmares whenthe drug is stopped.

Acute reactions to amphetamines include unconsciousness, anxiety, restlessness, headache, anorexia, confusion, teeth grinding, agitation, convulsions, coma, palpitations, arrhythmia, hypertension, shortness of breath, chest pain, pulmonary edema, night sweats, nausea, vomiting, etc. Chronic poisoning is characterized by delirium, weight loss, and thirst and personality changes due to long-term loss of appetite. Withdrawal symptoms of anandamide include severe depression, suicidal tendencies, unusual agitation, exhaustion, lethargy, polyphagia, abdominal cramps, and gastroenteritis.

Phenethylamines

phenethylamines will act on the cardiovascular system, lead torising of blood pressure, palpitations, arrhythmia, individual nervousness, irritability,restlessness and other emotional changes. Delusional psychosis, persecution,threatening delusions, dissociation, headaches, seizures, hallucinations, and panicattacks may also occur when using phenylethylamine.

Among these side effects,insomnia will aggravate other adverse effect.

Ethylenediamine (Piperazines)

The structure of this kind of central stimulant canpromote the release of dopamine and adrenaline, resulting in hallucinations, so it isusually abused by substance addicts. Users will experience convulsions, hallucinations, and increased body temperature. Hallucinations maylead tochanges invision, hearing, and taste. Hyperthermia will be developed and even lead to death.

Synthetic cathinone, or named as benzoylethanamine, is a central nerve system stimulant based on the structure of amphetamine. It is able to induce the effectssimilar to epinephrine, dopamine and serotonin. The active components extractedfrom the leaves and buds of Catha edulis are used against starvation and lethargy in ancient time.Initially,ingestionof cathinone will induce euphoria, increase awareness so it was frequently be abused. Acute intoxication will develop severe psychological symptoms such as anxiety in somnia psychological disorder, depression, self-harm, suicide, agitation, restless, and even panic oppressiveness tachycardiatachypnea chest pain□ tremor□ irritation. Besides, some peculiar behavior such as disoriented limb movement, provocative and aggressive behavior, loss or orientation, hallucinations will also be presented. Discontinuation of cathinone sometimes will induce severe depression and headache.

Cocaine

Using cocaine can cause intense euphoria, increased alertness and confidence, all of which are related to the effects of dopamine. Its high euphoria, accompanied by confusion and hallucinations, is related to the increase of dopamine, while a sudden decrease in dopamine can cause feelings of irritability. Cocaine reduces the amount of monoamine neuro transmitters reabsorbed in the presynapse, thereby increases the effects of adrenaline, dopamine, and serotonin on postsynaptic receptors, and also increases the concentration of catecholamines in the blood. For me assuring dopamine concentration in rat striatum by using micro-dialysis; the result showed young rat striatum generated more dopamine than adult rat after administering cocaine [15].

The mechanism of cocaine addiction is related to the activity of dopamine in the cortical pathwayat mid brain, especially the ventral tegmental projectingpathwayandnucleus accumbens, anditisrelatedto thereward pathway ofdrugaddiction. On the other hand, cocaine can act directly on the receptors of adrenalin, NMDA and also opioid receptors. Among them, opoid receptor is related to the reward path way mechanism of cocaine [16,17].

Cannabis

Cannabis will alter attention, cognition, and the ability of exercise, memory and learning. Long term addition will cause serous psychiatric diseases. Cannabis will induce organic lesions of brain, and the severity is related to the degree of addition. For young patient who use cannabis once a week, the volume of right amigdala and bilateral hippocanpus are tend to be decreased [15, 18]. Repeating use of cannabis affects the reward pathway of CB1 receptor in GABA neuropathway. The dopamine concentration between synaps increases, resulted in addiction.

Once the cannabis receptors have been activated, the adenosin cyclase activity will be reduced, also attenuate the neural excitability and the release amount neurotransmitters. Otherwise, GABA release also be reduced, which in turn toincrease the concentration of dopamine between the synapes.

The effects of cannabis are through the cannabinoid system, indicating activation of CB receptors.The CB1 cannabinoid receptors islocated inthe neural system, bones, heart, lever, lungs, vascular endothelium, and reproductive system. The CB2 cannabinoid receptors is expressed in the immune system and nerve system.Activation of the CB1 cannabinoid receptors significantly decrease the amount of cyclic adenosine monophosphate (cAMP), which elicit the responses including irritability, confusion, delusions, agitation, hallucination, and even psychosis [19,20].

Besides the responsesmention above, the phenomenon ofacuteintoxication isincluded vomiting, convulsion, slurred speech, restless euphoria conjunctival injection mydriasis fine tremor panic schizophrenia impaired thinking and attention, loss of orientation, loss of logicality, disorganized thinking orthostatic hypotensionand loss of consciousness in severe condition. Slurred speech is causebythecentralactivityofcannabinoidsaffectingthecoordinationofthemusclesand joints involved in articulation. The severity of symptoms is related to the route of intake, so intravenous injection yields more severe symptoms than inhalation.

For long term cannabinoid addictors, symptoms of schizophrenia will be revealed. Presenting of cognition deficiency, memory loss, pharyngitis, pharyngeal cancer, periodontitis, dental caries, chronic bronchitis, endocrine disorders, immonodeficiency, leukocytopenia, tachycardia, heart disease, impaired of neural development, insomnia, disorientation, hallucination, gastrointestinal tract symptoms such as nausea and vomiting, anorexia nervosa, cachexia with low body weight will also be observed. It can also cause testicular lesions, cancer, sex hormone imbalance, and sexual dysfunction Cannabis withdraw will induce convulsion, nystagmus, diaphoresis, nausea, vomiting, diarrhea, irritable, anorexia nervosa and sleep disorder, and depression.

Conclusions

According to the Analysis of drug abuse cases and inspection statistics– Annual Report Year [2023], total cases of drug abuse reported by all official agencies is 20159, among them, 82.4% are males. The largest number of occupations is "workers" and unemployed, about 64.5%. Analyzing by marriage status, most are single, about 73.3%. Analyzing by education level, junior high school graduate accounting for the largest numbers (47.8%). It is obviously to show that drug abuse and addiction are closely related to social pressures such as occupation, education and family conditions. Understanding the physical hazard of drug abuse and addiction and effectively promoting it should increase people's vigilance against addictive substances and reduce the number of abuse cases on the other hand, government should improve the environment of working and studying in order to decrease the social pressure upon our nationals, so that it will provide effective control to drug abuse and addiction.

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