

Review Article:**CNS Stimulants Currently Available for Treatments in Patients Suffering with Worldwide Pandemic of Coronavirus Disease**Khatija Aslam¹, Somia Gul²**Abstract:**

Outbreak of Coronavirus disease is worldwide pandemic declared by WHO. Patients either suffered from coronavirus infection or not both are physically and mentally disturbed. Patient whom suffered with such pandemic diseases or infections, have a greater risk of mental illnesses such as depression, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), schizophrenia and mania. CNS stimulants are psychoactive drugs available from resources like from nature (herbal/crude drugs) or from synthetic routes, are used to treat such diseases. In current research, extensive research review is done to find the best CNS stimulants currently available for treatments for such diseases. It is concluded from this research that stimulants that prescribed more frequently are amphetamine, methylphenidate and lisdexamfetamine. Moreover, stimulants that are not prescribed or illicit are like cocaine as such agents caused highly dependency, tolerance and addiction.

Keywords : CNS Stimulants, amphetamine, methylphenidate, lisdexamfetamine, Coronavirus.

International Journal of Human and Health Sciences Vol. 05 No. 02 April'21 Page : 148-153
DOI: <http://dx.doi.org/10.31344/ijhhs.v5i2.251>

Introduction

Mr. Zia, 50 years old businessman, lived in Karachi. After the death of his wife, his son became addicted to drugs and also suffered from COVID-19, then committed suicide. His daughter noticed that he was suffering from depression. She took appointment and treatment started with counselling by then medicines such as antidepressants, CNS Stimulants and multivitamins to subside the adverse effects. After a while, he recovered from depression and returned back to life.

Outbreak of Coronavirus disease is worldwide pandemic declared by WHO. Patients either suffered from coronavirus infection or not both are physically and mentally disturbed.¹ According to a recent research published 11 May, 2020, in Pakistan 29 suicide cases were reported.² Patient whom suffered with such pandemic diseases or infections, have a greater risk of mental illnesses such as depression, attention deficit hyperactivity

disorder (ADHD), obsessive compulsive disorder (OCD), schizophrenia and mania.³ Moreover, in Pakistan cases were increased day by day (Figure 1 and Figure 2).

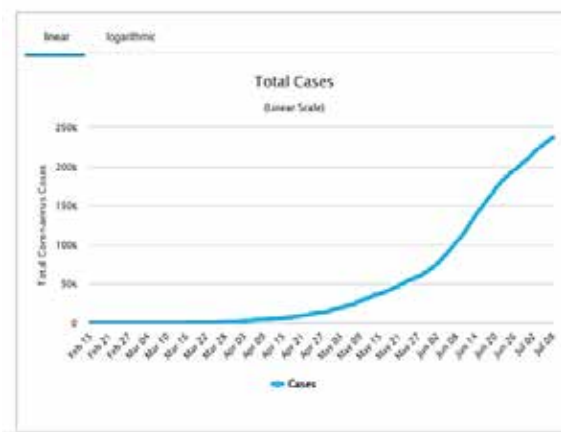


Figure 1: Total coronavirus cases in Pakistan from February 15–July 08, 2020. (Source: <https://www.worldometers.info/coronavirus/country/pakistan/>)

1. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan.
2. Associate Professor, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan.

Correspondence to: Somia Gul, Department of Pharmaceutical Chemistry, Faculty of Pharmacy Jinnah University for Women, Karachi, 74600, Pakistan. E-mail: drsomi1983@yahoo.com

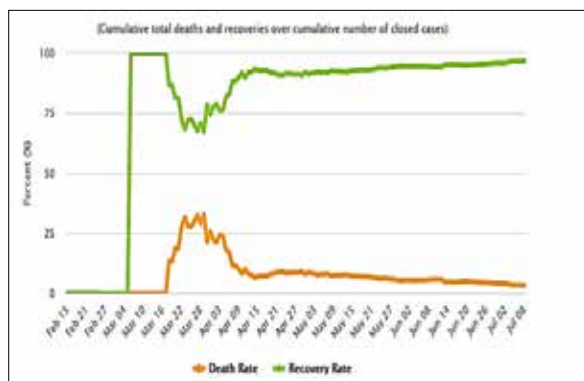


Figure 2: Outcome of cases (Recovery or Death) in Pakistan from February 15 – July 08. (Source: <https://www.worldometers.info/coronavirus/country/pakistan/>)

Naturally a type of stimulant presents in our body to maintain and regulates the normal mechanism. Dopamine, serotonin and noradrenaline are the three main chemical agents present in body. Dopamine a neurotransmitter, its high levels may lead to enhance mood and increase motor activity. If too many dopamine presents then its lead to schizophrenia, nervousness and irritability whereas too little levels may lead to paralysis and tremors. According to past researches it is thought that dopamine is a master molecule of addiction.⁴ 5HT Serotonin is a natural mood stabilizer present in central nervous system, digestive track and blood platelets help to reduce anxiety, depression, digestion, sleeping, healing of wound and control nausea.⁵

Noradrenaline also known as norepinephrine, act as neurotransmitter and hormone. It consists of catecholamine and phenethylamine. Norepinephrine is a mediator to responsible for

fight and flight, produced by adrenal glands. It increases heart rate, anxiety, alertness, restlessness and improve memory.⁶

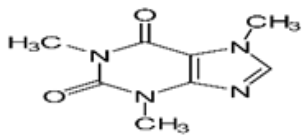
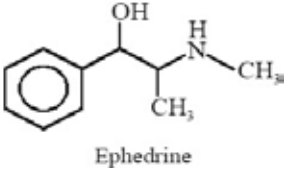
These chemical substances regulate normal physiological function in body, but sometimes too-much or too-little levels may lead to pathological condition which are prevented or/and treated by medication either natural or synthetic drugs (Table 1 and Table 2). Caution may be taken by the use medication agents such as amphetamine, cocaine, caffeine and methylphenidate caused addiction and dependency in patient if they use long term., usually these medications are used by sport players for anaerobic exercise.⁷

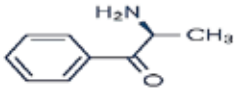
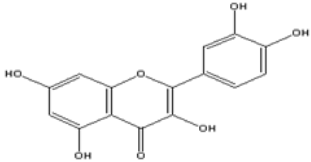
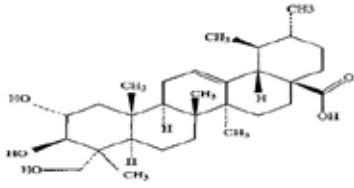
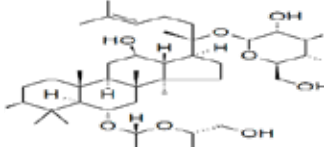
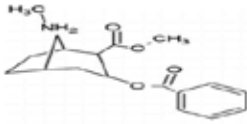
On the other hand, new generation also suffered from addiction of drugs, such as cocaine, khat, ecstasy, alcohol, smoking, also with substance use disorder (SUB) reported recently.⁸ Variety of drugs are now available to treat or prevent such type of illness and disorders.

CNS Stimulants are psychoactive drugs available from resources like from nature (herbal/crude drugs) or from synthetic routes, are used in number of diseases such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), depression, narcolepsy, neonatal apnea and sleep disorder.⁹

Nature has provided countless blessings for human mankind including number of herbs, plants, animals and marine creatures as resources for treatment of different diseases and ailments. Naturally a vast number of CNS Stimulants¹⁰⁻¹³ are present as herbal or crude form of drug such as caffeine, khat, and cocaine etc. as some most common and advanced herbs are summarized in Table 1.

Table 1. Brief Summary of Naturally Available CNS Stimulants.

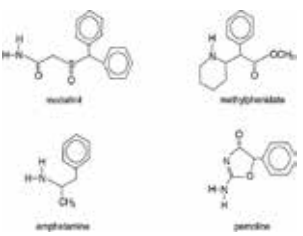
S.NO	HERBAL DRUGS	DESCRIPTION	STRUCTURE
1	<i>Caffeine</i>	It had been used ancient as CNS stimulant in China. Pseudoephedrine and ephedrine are the main constituents which increases the heart rate, and stimulates the brain. Ephedra also used in weight loss therapy, but having severe side effects. ^{10,11}	
2	<i>Ephedra</i>	Khat is a Psychoanalaptic found in leaves and plants shoots. Khat contain cathinone as a main constituent responsible for its activity. Cathinone is structurally resembling to amphetamine. It reduces the appetite by increasing the feeling of fullness. ¹¹	 Ephedrine

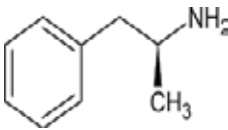
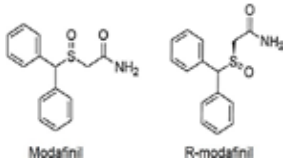
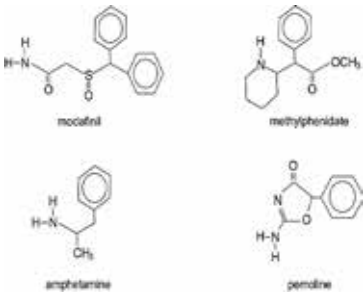
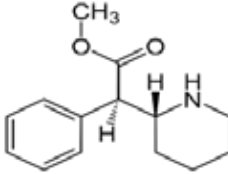
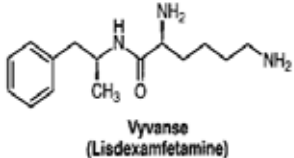
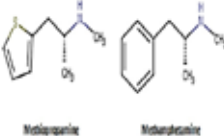
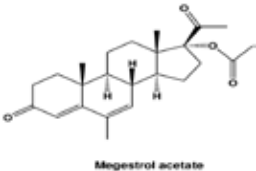
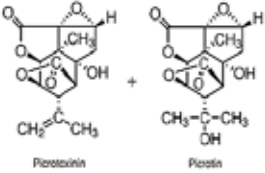
S.NO	HERBAL DRUGS	DESCRIPTION	STRUCTURE
3	<i>Khat</i>	Ginkgo is a cognitive enhancer, used for the treatment of lack of attention, vertigo, cerebral vascular diseases and loss of short-term memory. ¹²	 cathinone
4	<i>Ginkgo</i>	Centella asiatica is a medicinal herbal plant used to improve cognitive functions, having anti-anxiety properties also improves memory. Gotukola used traditionally by Chinese, its roots and leaves are used to support the healthy tissues of skin and hairs. ¹²	
5	<i>Gotukola</i>	Panax ginseng dried roots are used in the treatment of Alzheimer's disease. It reduces fatigue, cholesterol and stress also maintains high blood pressure, heart rate and boosts the immune system. ¹²	
6	<i>Ginseng</i>	Alkaloidal Extract Derived from the coca plant. It produces a local anesthetic effect by blocking sodium channels and also produces convulsant effects by blocking NMDA receptors. Cocaine long-term use may produce cardiotoxicity. ¹³	
7	<i>Cocaine</i>	It has been used anciently as a CNS stimulant in China. Pseudoephedrine and ephedrine are the main constituents which increase the heart rate, and stimulate the brain. Ephedra also used in weight loss therapy, but having severe side effects. ^{10, 11}	 Cocaine

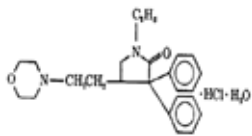
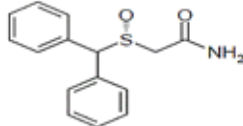
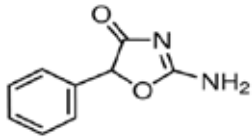
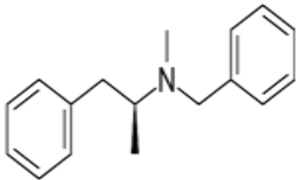
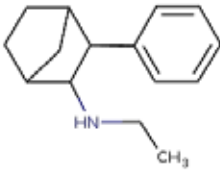
Advance research in the field of medicine and new technologies made our lives easier. CNS stimulants are easily available as synthetic form to treat numerous diseases for example; ADHD, OCD, depression, narcolepsy, neonatal apnea and sleep disorder. Caffeine,¹⁰ amphetamine, benzphetamine, modafinil, methylphenidate, lisdexamfetamine, dextroamphetamine, metamfetamine, megestrol

acetate, pemoline, benzphetamine, minaprine, armodafinil and fencamfamin are currently available for treatment of such types of diseases. They are available in oral, injectable and also in inhaled form (Table 2). Stimulants that are prescribed more frequently are amphetamine, lisdexamfetamine, caffeine, methylphenidate and benzphetamine are commercially available.¹⁴

Table 2. Brief Summary of Currently Available Synthetic CNS Stimulants.

S.no	CNS stimulants	Description	Structure	Different renowned brands available worldwide	Available dosage form
1	<i>Amphetamine</i>	CNS Stimulant currently available, used to treat ADHD and also used as a recreational purpose, highly addicted and also causes weight loss because it suppresses appetite. ¹⁴		Adzenys XR-ODT, Dyanavel XR, Evekeo.	Extended release oral disintegrating tablets (<i>Adzenys XR-ODT</i>) Extended release oral suspension (<i>Dyanavel XR</i>)

S.no	CNS stimulants	Description	Structure	Different renowned brands available worldwide	Available dosage form
2	Dextroamphetamine	Sympathomimetic agent used to treat narcolepsy and attention deficit hyperactivity disorder. ¹⁴		1. Dexedrine 2. Dexedrine spansules 3. Dextrostat 4. Liquadd 5. Procentra 6. Zenedi	Extended release capules (Dexedrine) Oral Solution (Procentra) Immediate release tablets (Zenedi)
3	Modafinil	Used to treat narcolepsy, sleep disorder and promote wakefulness. Sometimes causes allergy or skin rashes. ¹⁵		Provigil	Tablets are available.
4	Methylphenidate	CNS Stimulant agent used to treat attention deficit disorder ADD and narcolepsy by increasing dopamine and norepinephrine levels in brain. Methylphenidate are controlled release drugs available in capsule, tablets, oral solution and oral suspension form. Methylphenidate long term may cause addiction and dependency in patient. ¹⁶		Ritalin Aptensio XR Ritalin LA Metadate CD Adhansia XR Jornay PM Methylin Ritalin SR QuilliChew ER Generics	Tablet (Ritalin) Extended release capules (Aptensio XR) Ritalin LA Metadate CD Adhansia XR Extended/delayed release capules (Jornay PM) Extended release tablets (Methylin, Ritalin SR, Generics) Extended release chewable tablets (QuilliChew ER) and transdermal patches are also available.
5	Dexmethylphenidate	It is a nor epinephrine dopamine reuptake inhibitor used in conjugation with other therapies in the treatment of ADHD. ¹⁶		Focalin, Focalin XR	Tablets and extended release capsules are available.
6	Lisdexamfetamine	CNS Stimulant drug used to treat ADHD, severely eating disorder, decrease restlessness in children and also used to improve hyperactivity. ¹⁷		Vyvanse	Available in capsule and chewable tablets.
7	Metamfetamine	Sympathomimetic agents used in the treatment of exogenous obesity and attention deficit hyperactivity disorder. ¹⁸		Desoxyn	Tablets
8	Megastrol acetate	Megastrol acetate is a progestin used in the treatment of cachexia, anorexia, weight loss and as an antineoplastic agent. ¹⁹		Megace, Megace ES.	Tablets Oral suspension.
9	Picrotoxin	An analeptic class of drug used for relieving respiratory distress. It is also used as an antidote for barbiturate poisoning and GABA receptor antagonist. ²⁰		Cocculin, Coques du levant, Cocculine, Cocculus, Fish berry, Oriental berry	currently not available

S.no	CNS stimulants	Description	Structure	Different renowned brands available worldwide	Available dosage form
10	<i>Doxapram</i>	An analeptic class of drug act as short acting respiratory Stimulant available as injectable solution. ²¹		Dopram	Injectable solution
11	<i>Armodafinil</i>	Used in the treatment of narcolepsy, improve wakefulness, sleep disorders, shift work disorders and sleep apnea available for orally administration ²²		Nuvigil	Available in tablets form.
12	<i>Pemoline</i>	CNS Stimulant used in the treatment of narcolepsy and attention deficit hyperactivity disorder but it may cause severe hepatic failure in patient so that not be used as first line agent. ²³		Cylert	Available in tablets and chewable tablets.
13	<i>Benzphetamine</i>	Sympathomimetic short-term agent similar to amphetamine used in the treatment of obesity but not indicating under 17 years of age. ²⁴		Didrex	Available as tablet form.
14	<i>Fencamfamin</i>	Psychostimulant class of drug used to treat lack of concentration, depressive fatigue and lethargy. ²⁵		Reactivan	Available in syrup and tablet form.

Investigation and research in the field of CNS stimulants reported that, to improve ADHD, JORNAY PM was the only medication dosing in evening to control the symptoms in morning, day and also in evening time (in phase 3 trail). In August 2018, CNS stimulant drug methylphenidate HCL was approved by FDA used for treating ADHD in children 6 years or greater.²⁶

Conclusion:

From among the above mention both natural and synthetic central nervous system stimulants, it is found that stimulants that prescribed more frequently are amphetamine, methylphenidate and lisdexamfetamine. These agents are used for the treatment of attention deficit hyperactivity disorder, depression, and narcolepsy and sleep disorder. Methylphenidate (*Ritalin*) is used as first line agent in attention deficit hyperactivity

disorder. Amphetamine (*Addrella*, *Addrella XR*) is a most potent CNS stimulant and potential for abused was discovered hundreds of years ago and still it is used for ADHD. Lisdexamfetamine (*Jyvanse*) is a prodrug of amphetamine used for the treatment of ADHD and narcolepsy. Stimulants that are not prescribed or illicit are like cocaine as such agents caused highly dependency, tolerance and addiction.

Conflict of Interest: No conflict of interest exists.

Funding: No funding exists.

Ethical Approval Issue: Not applicable.

Authors' contribution: Data gathering and idea owner of this study: Somia Gul and Khatija Aslam; Study design: Somia Gul; Data gathering: Khatija Aslam and Somia Gul; Writing and submitting manuscript: Khatija Aslam and Somia Gul; Editing and approval of final draft: Somia Gul.

References:

- World Health Organization. Critical preparedness, readiness and response actions for covid-19: interim guidance, 24 June 2020. No. Who/covid-19/community actions/2020.4. World Health Organization, 2020.
- Mamun MA, Ullah I. COVID-19 suicides in Pakistan, dying off not COVID-19 fear but poverty? - The forthcoming economic challenges for a developing country. *Brain, Behavior, and Immunity*, 2020;87:163-6.
- ThakurV, Jain A. COVID 2019-suicides: A global psychological pandemic. *Brain, Behavior, and Immunity*, 2020;88:952-3.
- BerkeJD. What does dopamine mean? *Nature Neuroscience*, 2018;21(6):787-93.
- BergerM, Gray JA, Roth BL. The expanded biology of serotonin. *Annual Review of Medicine*, 2009;60:355-66.
- O'DonnellJ, Zeppenfeld D, McConnel E, et al. Norepinephrine: a neuromodulator that boosts the function of multiple cell types to optimize CNS performance. *Neurochemical Research*, 2012;37(11):2496-512.
- George AJ. Central nervous system stimulants. *Bailliere's Best Practice & research. Clinical Endocrinology & Metabolism*. 2000;14(1):79-88.
- Dubey MJ, Ghosh R, Chatterjee S, Biswas P, Chatterjee S, Dubey S. COVID-19 and addiction. *Diabetes MetabSyndr*. 2020;14(5):817-23. doi: 10.1016/j.dsx.2020.06.008
- Kumar V. Potential medicinal plants for CNS disorders: An overview. *Phytother Res*. 2006;20(12):1023-35. doi:10.1002/ptr.1970
- DurrantKL. Known and hidden sources of caffeine in drug, food, and natural products. *Journal of the American Pharmaceutical Association (Washington, D.C. : 1996)*, 2002;42(4):625-37. doi:10.1331/108658002763029607
- GriffithsP, Lopez D, et al. Khat use and monitoring drug use in Europe: the current situation and issues for the future. *Journal of Ethnopharmacology*, 2010;132(3):578-83. doi: 10.1016/j.jep.2010.04.046
- GyllenhaalC, Merritt SL, et al. Efficacy and safety of herbal stimulants and sedatives in sleep disorders. *Sleep Medicine Reviews*. 2000;4(3):229-251.
- ParrottAC, HayleyAC, Downey, LA. Recreational stimulants, herbal, and spice cannabis: The core psychobiological processes that underlie their damaging effects. *Hum Psychopharmacol Clin Exp*. 2017;32(3):e2594.
- HealDJ, Smith SL, et al. Amphetamine, past and present--a pharmacological and clinical perspective. *Journal of Psychopharmacology*, 2013;27(6):479-96.
- HashemianSM, FarhadiT. A review on modafinil: the characteristics, function, and use in critical care. *Journal of Drug Assessment*, 2020;9(1):82-6.
- StorebøOJ, Pedersen N, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies. *The Cochrane Database of Systematic Reviews*, 2018;5(5):CD012069.
- NajibJ, Wimer D, et al. Review of Lisdexamfetamine Dimesylate in Adults with Attention-Deficit/Hyperactivity Disorder. *Journal of Central Nervous System Disease* 2017;9:1179573517728090.
- RadfarSR, Richard RA. Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. *Addiction & Health*, 2014;6(3-4):146-54.
- Yeh SS, Michael WS. Megestrol acetate in cachexia and anorexia. *International Journal of Nanomedicine*, 2006;1(4):411-6.
- CraigCR. Stimulants. In *Kirk-Othmer Encyclopedia of Chemical Technology*, (Ed.). doi: 10.1002/0471238961.1920091303180109.a01.pub2, 2007.
- CunninghamKP, MacIntyre DE, et al. Effects of the ventilatory stimulant, doxapram on human TASK-3 (KCNK9, K2P9.1) channels and TASK-1 (KCNK3, K2P3.1) channels. *Acta Physiologica (Oxford, England)*, 2020;228(2):e13361.
- LolandCJ, Mereu M, et al. R-modafinil (armodafinil): a unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. *Biological Psychiatry*, 2012; 72(5):405-13.
- CorteseS, et al. Safety of Methylphenidate and Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): Data from the Italian National ADHD Registry. *CNS Drugs*, 2015;29(10):865-77.
- De SousaA, Gurvinder K. Drug therapy of attention deficit hyperactivity disorder: current trends. *MensSana Monographs*, 2012;10(1):45-69.
- Garcia-MijaresM, DeLucia R, Silva MTA. Fencamfamine-induced changes in the parameters of the matching law and the effect of previous exposure to the drug. *Behavioural Pharmacology*, 2004;15(8):577-584.
- Gomeni R, Komolova M, Incledon B, Faraone SV. Model-Based Approach for Establishing the Predicted Clinical Response of a Delayed-Release and Extended-Release Methylphenidate for the Treatment of Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*, 2020;40(4):350-8.