Section A-Research paper

Types of Neurological Sleep Disorder and Potential Drug for Their Treatment: A Brief Review

Pratik Prasad[1*], Nishant Thakur[1], Manas Ranjan Kar[2], Ashutosh Tripathi[3]

University Institute of Pharma Sciences, Chandigarh University.

[1*] PG Research Scholar, University Institute of Pharma Sciences, Chandigarh University.

[1] Associate Professor, University Institute of Pharma Sciences, Chandigarh University.

[2] General Manager, Product Development lab, Alkem Laboratories, Baddi

[3] Manager, Product Development lab, Alkem Laboratories, Baddi

Corresponding Author: **Pratik Prasad**

PG research Scholar, Dept of Pharmaceutics,UIPS, Chandigarh University.Mohali 140413

Mobile Number- +919934885622

Email- propratikp@gmail.com

College Email- 21mph1003@cuchd.in

ABSTRACT

In the present investigation an attempt has been made to categorize the Neurological Sleep Disorder with its etiology and clinical management. Different type of sleep disorders like were studied. The metabolism of Dopamine and Noradrenaline/Norepinephrine, mutation of DAT_1 and D_4 receptor in the patients of ADHD was investigated from the literature sources. Study of the Rapid Eye Moment (REM) during sleep cycle and lack of secretion of Hypocretin from hypothalamus of the brain is majorly considered reason for narcolepsy. CPAP therapy, electrocardiography during sleep studies of patients, heart rate monetarization in Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) during sleep cycle are the major modern techniques we use for diagnosis of sleep apnea. These techniques have zero side effect as compared to other drugs we involve for the treatment of a particular disorder.

Keywords: DAT1, D4 receptor, Noradrenaline, Dopamine, Hypocretin, NREM, REM, CPAP Therapy.

INTRODUCTION

National Library of Medicine has published a report in 2020 indicating the soar in the cases of attention deficit hyperactivity disorder(ADHD). Report on ADHD shows that more than 500 million people are affected with ADHD while Sleep Apnea follows the number of patients more than 425 Million and in Narcolepsy more than 3 Million people all over the globe[1].

A common drug which shows enhancement in the patient's condition in all three mentioned neurological disorder is Solriamfetol HCl which is a recently discovered DNRI (Dopamine Norepinephrine Reuptake Inhibitor) class of drug, which is approved in 2019 by USFDA[2,3] The drug was patented by Jazz Pharmaceutical and sold this drug under the brand name of 'Sunosi".

Three main types of Neurological Sleep Disorder, their potential drugs and ways to diagnose the particular disorder are discussed in this review.

1. **ADHD (Attention Deficit Hyperactivity Disorder)**: It's a neurological disorder in which, we majorly see the mutations of gene in dopamine transporter i.e. (DAT_1) and dopamine D_4 receptor. Affected portion of brain due to ADHD is prefrontal cortex, frontal lobe, sensory-motor and cerebellum. We also mark a mutation of Dopamine and Noradrenaline/Norepinephrine. It is chronic disorder which last around more than a year or till life time. Person suffering from ADHD usually face difficulty in pay attention, difficulty in continuous listening to a matter, easy distraction[4].

2. **Narcolepsy**: It is a type of Neurological Sleep Disorder, in which caused due to lack of chemical hypocretin in brain which is also known by orexin. Affected portion of brain due to Narcolepsy is hypothalamus, which mainly responsible for orexin secretion. In this particular disorder patient feel uncontrollable Excessive Daytime Sleep and change in Rapid Eye Moment (REM). In extreme case it also causes Sleep paralysis. Again, it is also a type of chronic disorder which can't be cured but controllable with medicine, diagnosis and management[5].

3. **Sleep Apnea**: It's one of the serious Neurological Sleep Disorder, in which brain becomes unable to convey signals to receptors which controls the heart rate and breathing during the sleep time of the body. Due to this, patient may face starvation of oxygen in the brain, heart attack due to low oxygen level and air blockage during sleep may take place. Sleep studies, heart rate monetarization, REM and other methods give great outcome to detect this disorder. Again, it is also a type of chronic disorder which can't be cured but controllable with medicine, diagnosis and management[6].

Types of ADHD

ADHD can be classified into three types based on the severity of the individual's symptoms:

I. **Predominantly Inattentive Presentation:** The person has difficulty managing or overcoming an activity. To consider spending or adhering to a reference or exchange. The individual is frequently anxious or forgets particular daily tasks[7].

II. **Hyperactive-Impulsive Presentation:** The individual gets agitated and chatty. It is tough to remain squat for an extended period of time. Lower youngsters may able to incessantly jump or run. The person is agitated and prone to hasty behaviour[8].

III. **Combined Presentation:** In this, the combined form of predominantly Inattentive Presentation and Hyperactive-Impulsive Presentation has been seen or present in patient[9].

Pathophysiology and Symptoms[10]:

ADHD is associated with cognitive and functional issues that are associated with generalised brain abnormalities. ADHD patients have a small anterior cingulate gyrus and a dorsolateral prefrontal cortex (DLFPC). These changes are thought to account for the shortcomings in goal-directed behaviour. Furthermore, fMRI shows that activity in the front striatal region is reduced in these persons. Understanding these pathophysiological pathways is crucial in order to address them with therapy. It is crucial to recognise ADHD as a clinical diagnosis. In ADHD individuals, there are no standard laboratory or imaging data.

Symptoms:

- Anxiety
- Depression
- Specific types of learning difficulties
- Analogous signs
- Day dreams
- Epilepsy
- Insomnia
- Alzheimer's disease
- Too much talk
- Difficulty getting along with others

Diagnosis and Management[11]:

When there are attention problems, it may be too easy to attach the label attention deficit hyperactivity disorder, but to identify the nature of attention difficulties and to identify physical, psychological, and social components that impact attention is a more challenging process. Diagnosis is difficult here, and the evaluation should be as detailed as feasible. Interviews during the diagnosis, the following questions could be asked:

- A parent interview to ascertain the student ’s educational background, family medical history, presenting issues, and other pertinent facts, including management measures on the existence or lack of diagnostic manual.

- Teacher records and conversations, as well as comprehensive data on The existence or lack of diagnostic criteria, as well as unique educational requirements.
- Clinicians' use the checklists and diagnostic index to strength and increase challenges
- The children's perception.
- A medical examination to rule out physical reasons of attentiveness or physical difficulties.
- Although intellectual assessment is still not frequently used, it can be useful in analysing particular issues. Because of the difficulties in evaluation and treatment, several organisations have developed multidisciplinary or even different organisations collaborate to assist the procedure.

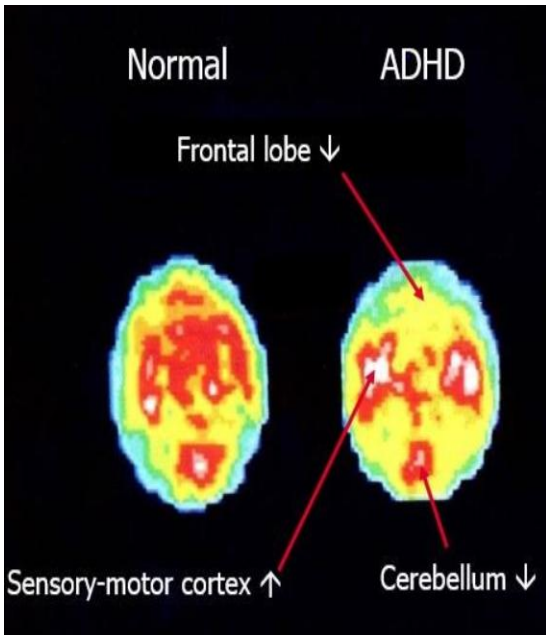


Figure-1
Scanned Image of Brain Showing Affected Portion due to ADHD[12].

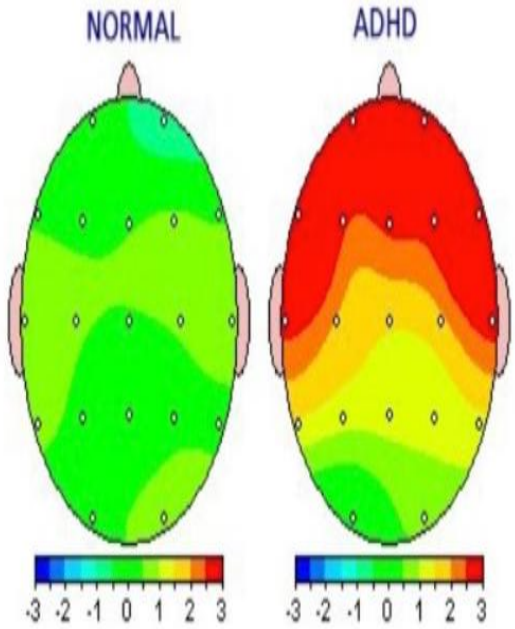


Figure-2
Animated Image of Brain Showing Majorly Affected Portion due to ADHD on Scale of -3 to +3

Types of Narcolepsy:

Narcolepsy are differentiated into two types by the existence or lack of cataplexy in a clinical area.

Type I/ Primary Narcolepsy[13]-

Patients with Approximately 90% of the hypocretin neurons located in the hypothalamus are absent in people with type 1 narcolepsy, resulting in suppression of hormones responsible for wakefulness-promotion as well as a lack of REM sleep regulation.

Due to the disruption of the regular sleeping and wake-up cycle, the patient has excessive daytime drowsiness and struggles to stay awake and attentive throughout the day. Another indication of orexin neuron deficiency is cataplexy.

Type II/ Secondary Narcolepsy[14]-

Both cataplexy and significant hypocretin loss in the brain are absent in people with narcolepsy type 2 patients. Although the specific origin of primary narcolepsy is uncertain and only considered as the lack of orexin, current research has led experts to suspect that this autoimmune disease, which attacks these hypocretin neurons, is T-cell-mediated. Family medical background is also a reason: up to 10 percentage of cataplexy patients have a presence of narcolepsy in family medical background. Furthermore, the presence of gene HLA-DQB1*06:02 is found in more than 98 percentage of individuals with primary narcolepsy and around 50 percentage of patients with secondary narcolepsy. An injury in head or a brain tumour which cause damage to the hypothalamus, which is responsible for production of orexin.

Pathophysiology and Symptoms: -

Excessive daytime drowsiness is the most evident symptom of narcolepsy types 1 and 2. Sleep attacks, characterised as periods of acute, severe weariness that can happen at any time and with no prior notice, may be included.

A significant emotional stimulation, such as crying, laughing, or worry, is frequently experienced together with cataplexy, a defining symptom of primary narcolepsy. Slurred speech is an example of a mild case of cataplexy, while a severe case might include collapsing to the ground. The patient is conscious throughout each episode, which can last anywhere from a few seconds to many minutes[15].

Narcolepsy symptoms include sleep paralysis and hypnagogic/hypnopompic hallucinations. The inability to move during the transition from or into a sleep state is known as sleep paralysis. The frequency of recurrence varies across narcoleptic patients; these episodes can last anywhere from a few seconds to several minutes. Because sleep paralysis commonly occurs in association with hallucinations, patients may describe it as a terrible experience. Hypnagogic hallucinations come in between the little change in sleep, whereas

hypnopompic hallucinations come during the wake-up transition. In any setting, hallucinations might be visual, auditory, or tactile[16].

Amnesia, Narcolepsy is known to cause vivid nightmares, weight gain, disturbed sleep habits, depression/anxiety, and automatic behaviour, however all patients don't experience them all. Only about half of narcolepsy patients, for example, exhibit automatic behaviour, which happens while the body keeps continuing to conduct familiar acts while the brain is sleeping, resulting in total retrograde amnesia[17].

Narcolepsy symptoms can fluctuate, and there is no solid evidence that ageing either makes the problem worse or better. The symptoms first appear is generally between the age of 10 to 25 years old, and the duration between initial symptom onset and formal diagnosis might be many years. If cataplexy occur in advance to additional signs of narcolepsy, it may be falsely believed to be a neurological problem. Likewise, if facial muscle tone is impaired, cataplexy may be mistaken as a transient ischemic stroke. Excessive daily sleepiness may first be misdiagnosed as depression. Obese persons may be detected with (OSA) episodes to explain their fatigue on a daily basis[18].

The diagnosis of narcolepsy is complicated by psychiatric comorbidities. It is sometimes unclear if symptoms like as sorrow and worry are caused by narcolepsy's debilitating nature or whether there is a shared aetiology. Narcolepsy can have a substantial influence on Limiting a patient's capacity to drive or operate large equipment or to be awake and cognizant while taking care of children or other family members might negatively impact a patient's quality of life. Patients frequently feel as though they are "missing out" on events because of sleep episodes on a regular basis or because they have to control certain emotions like anger or laughing to prevent cataplexy symptoms[19].

General Symptoms[20]: -

- Hallucinations: hypnagogic hallucinations or hypnopompic hallucinations
- Disrupted night-time sleep
- Excessive daytime sleepiness (EDS)
- Sleep paralysis
- Cataplexy
- Automatic behaviour: This symptom is described as falling asleep for several seconds

Diagnosis and Management:

To make the American Academy of Sleep Medicine's clinical criteria for the diagnosis narcolepsy are utilised, and the examination should involve a comprehensive investigation of all other potential causes of excessive daytime drowsiness. Genetic testing for HLA-DQB1*06:02 is not advised because up to 30 percentage of the healthy overall population has this gene. A well-known subjective screening tool is the Epworth Drowsiness Scale used to measure patients' level of daytime drowsiness. On total scale of 11 or above necessitates upcoming research could perhaps treat a sleep issue. Other prominent The Swiss Narcolepsy Scale is a screening instrument. Five tests on different factors of sleep-wake cycles as well as symptoms are included in this survey, with the goal of providing a more thorough clinical assessment[21].

The recommended diagnostic test is (MSLT[22]). This evaluation of a patient's napping proclivity or aptitude is unbiased. The patient is given five opportunities to sleep during the day under supervised circumstances (usually at a medical sleep facility). The length of each 20-minute timed snooze varies between 1.5 and 3 hours. Narcolepsy is defined by an 8-minute mean sleep-onset delay and during naps, there were two or more sleep-onset REM events (SOREMs). A polysomnogram is performed to check out all other significant secondary reasons of excessive daytime drowsiness, such as OSA or insomnia should be conducted shortly before the MSLT. The polysomnogram is a sleep study that is usually performed overnight at the facility with constant supervision to guarantee accurate data collection. All medications, including those that affect the neurotransmitters serotonin, norepinephrine, and dopamine, must be stopped by the patient. at least two weeks before the test. Benzodiazepines and opioids, which cause sleepiness, should be avoided. If permitted by the doctor, beta-blockers should have been ignored approximately 2 weeks prior to the research since they can make people sleepy and reduce REM sleep. In order to examine their typical sleep/wake cycle, patients must only keep a sleep record for one week prior to testing.

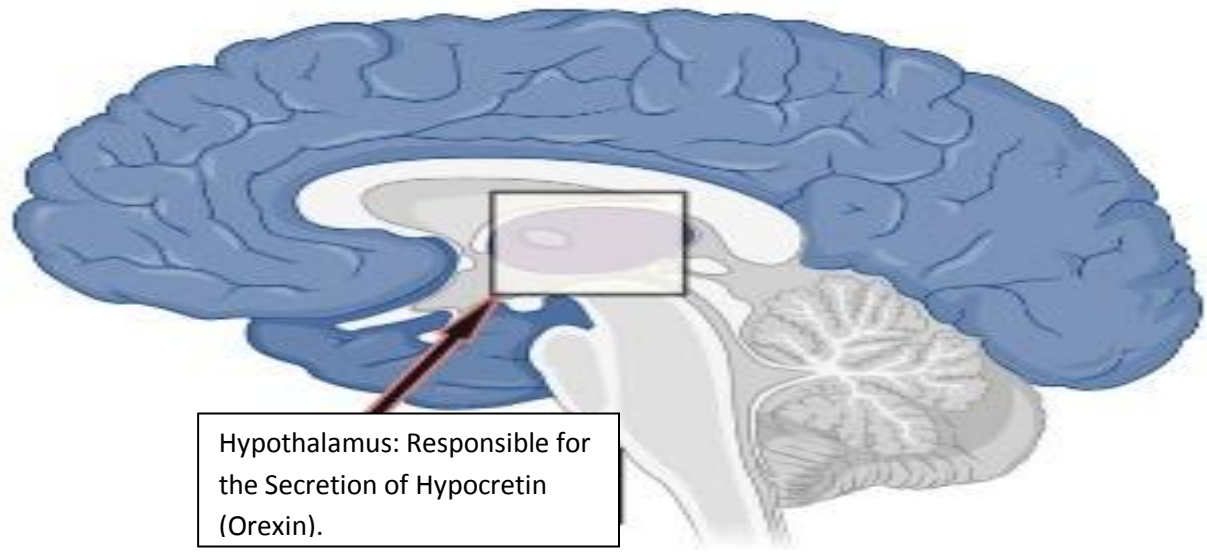


Figure-3

Part of Brain Affected by Narcolepsy.

Types of Sleep Apnea: -

- ***OSA-*** *the more typical variation that appears when tongue muscles loosen.*
- ***CSA-*** *This happens when your brain fails to properly communicate with the respiratory muscles*
- ***CompSAS-*** *sometimes referred to as treatment-emergent central sleep apnea, this condition happens when a person has both CSA and OSA.*

Obstructive sleep apnea (OSA): -

OSA is a neurological problem defined by sporadic and repetitive upper airway stoppage during sleep, which is followed by decreases in arterial blood oxygen saturation and sleep disruptions. Aside from this night medical issue, initially they face symptoms during the daytime for example weariness and reduced cognitive performance. Smoking increases inflammation and fluid retention in the upper side air passage, as well as tiredness during the day. Smokers are more likely than non-smokers or former smokers can suffer to snore during sleep and OSA. The term (OSAS) "Obstructive Sleep Apnea Syndrome" has developed throughout time in accordance to developments in pathology knowledge. OSAS was first described as the overall proportion of apneic episodes (Apnea

Index [AI] > 5/hour) throughout a sleep cycle. The idea of the Apnea/Hypoapnea Index, (which is determined by the sum of the number of apneas and hypopneas for one hour of sleep), a criterion that highlights sleep-physiology alterations and shows the severity, was then substituted for this definition, which was rejected due to a lack of clinical applications. OSAS is classified into three severities Mild (AHI=5–14/hour), moderate (AHI=15–30/hour), and severe (AHI>30/hour) respiratory abnormalities. OSA can be identified if both the RDI and AHI are more than five phases per hour. OSAS intensity can fluctuate from night to night, as can symptoms in the same person[23].

Pathophysiology[24] and Symptoms: -

Nocturnal Symptoms

One of the most usual night-time symptoms of OSA is snoring, and it is caused by a substantial constriction of the upper respiratory path when you sleep, causing turbulence and a blockage in airflow. Sleep apnea does not impact everyone who snores. Snoring affects 25%-30% of all women and 40%-45% of all males on a regular basis in the adult population. Snoring in OSA patients becomes increasingly severe and irregular with time, often as a result of increased body weight, smoking, nasal obstruction, or the use of muscle relaxant medications. Other nocturnal symptoms of OSA include documented apneas (respiratory pauses that disrupt snoring), raised blood pressure, abrupt gasping, choking sensations, night-time perspiration, nycturia, and insomnia[25].

Daytime Symptoms

Daily sleepiness is the most prevalent daytime symptom of OSA, which is caused by sleep fragmentation. It usually occurs during quiet activities. Daytime drowsiness is also linked to weariness, difficulty paying attention, memory loss, mood swings, and decreased libido. Daytime symptoms include getting up with something like a dry mouth or sore throat, as well as morning headaches[26].

Nasal Obstruction:

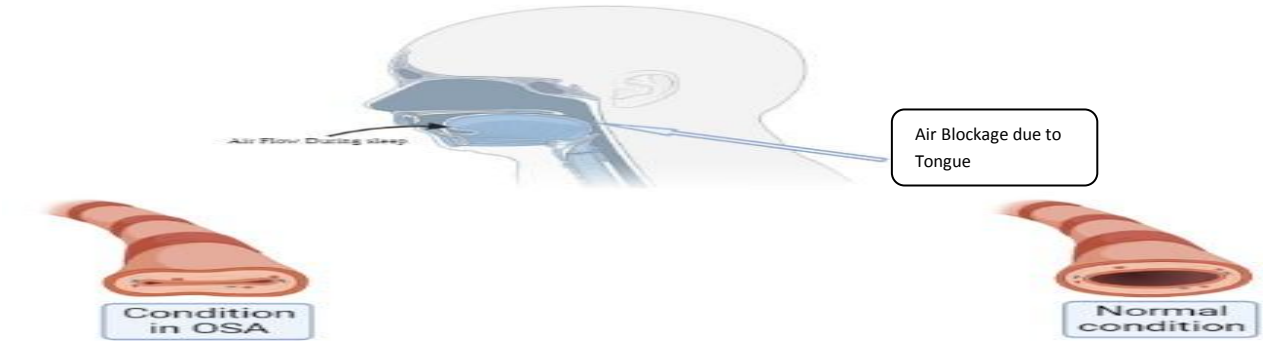
The nasal passages are the most natural way for air to enter our bodies. Any obstruction in these passages reduces airflow, which is particularly visible during sleep, leading in apnea and OSA symptoms[27].

General Symptoms

- Headaches
- Irritability
- Heartburn
- diminished libido and erectile dysfunction
- exhaustion
- restless sleep or sleeplessness
- difficulties focusing
- getting up numerous times during the night to use the restroom
- rising with a dry mouth or scratchy throat

Diagnosis and Management: -

Before the diagnosing OSA, the necessary part to identify the syndrome's typical symptoms, such as daytime drowsiness, which may be measured using both subjective as well as objective assessment measures, regular and lengthy snoring (all night for the 6 months or above), breathing stops while sleeping reported by a person, waking events with the sense of choking in snoring patients, etc. In order to rule out other diseases or disorders, it is crucial to measure the patient's BMI, neck and abdominal circumferences, cranium-facial relationships, oral dentition & tongue, pharynx, pressure of blood, neurologic, cardio - vascular, and respiratory conditions during clinical testing. Instrumental testing is more successful than laboratory tests in making a diagnosis. Despite differences in results from one night to the next in the same patient, studies of sleep cycle remain the gold-standard examination for detecting OSAS is polysomnography, the reference diagnostic techniques, and evaluating treatment success[28].



Central Sleep Apnea (CSA): **Figure-4** Body Condition in OSA during Sleep. -

There's not one cause of central apnea during sleeping. In a number of clinical diseases, it is an indication of central respiratory instability. Despite substantial progress in identifying the particular mechanisms of CSA during the preceding ten years, the pathophysiology at the root of the condition is still unknown. Furthermore, The distinction between the two "silos" is in doubt since CSA and OSA have similar pathophysiologic characteristics. Least expectedly, many current treatment techniques for central sleep apnea (CSA) are based on OSA procedures. This article will check the causes for CSA, symptoms, treatments, and way to detect, as well as area of controversies and misunderstanding. The momentary cessation of ventilatory motor output causes central apnea. The "switching off" of ventilatory motor control and the onset of central apnea can be caused by sleepiness, temporary hypocapnia, an inconsistent ventilatory controller, upper respiratory pathway relaxation, and brain stem rhythm producing depression[29].

Pathophysiology and Symptoms: -

Respiration during N-REM sleep

Understanding the inherent physiological variations in breathing that occur between waking and Non-Rapid Eye Movement (NREM[30]) sleep required for the awareness of CSA. Changing sleep stages and the shift from awake to sleep significantly change respiratory control. Typically, PaCO2 rises from Two to Eight mmHg while Non-REM phase of sleep. Ventilation is entirely under metabolic control while a person is in Non-REM phase of sleep. Lack of alertness while driving has been marked, Upper respiratory pathway resistance has risen while hypoxic as well as hypercapnic impulses have decreased. Some have questioned whether there is a genuine decrease of chemo-responsiveness and drive, while others argue that increased upper respiratory pathway resistance is mostly to blame for the alterations in sleep.

Respiration during REM sleep

REM[31] sleeping is identified by a generalised atonia of the skeletal muscles, with diaphragm functioning as a principal active respiratory muscle. Further we mark decrease in hypercapnic as well as hypoxic impulses. Diaphragmatic movement and muscles of the upper

respiratory pathway are more suppressed during phasic REM, which may result in low tidal volumes as well as CSA.

Apneic threshold (AT)

A CSA occurs when a person's specified amount of PaCO2 is exceeded (apnoea threshold). Every time the PaCO2 level rises over the threshold limit, ventilation will start up again. Sleeping PaCO2 levels are usually 2 to 8 mmHg higher than waking levels. Typically, the AT is 1 to 2 mmHg below the awaken PaCO2. The difference between a person's PaCO2 and AT is an important factor in determining the predisposition to develop apnoea. The larger The greater the difference of PaCO2-AT, the higher probability of CSA development. It's critical for memorization of a person's PaCO2-AT differential might not in continuous form along with it may alter depending on ventilatory control[32].

Loop gain

It is important to understand concept of loop gain for understanding the genesis of CSA. The plant rise or the controller rise conjointly determine overall loop gain. The ability of the lungs as well as respiratory muscles to optimize the ventilation in this situation is known as the plant gain, as well as the variation in ventilation brought on by a difference in PaCO2 is known as the controller gain[33].

General Symptoms: -

- Alzheimer's condition
- Seen instances of sleep-related no-breathing or irregular breathing patterns.
- Encephalitis
- Cheyne-Stokes breathing (CSR)
- Sudden awakenings followed by breathlessness.
- Concentration issues.
- Trouble falling asleep (insomnia)
- Kidney disease
- Lou Gehrig's disease (ALS, commonly known as amyotrophic lateral sclerosis)
- headaches in the morning.
- Snoring.
- Excessive daytime drowsiness (hypersomnia)

- Parkinson's syndrome
- Heart failure
- Brain injury
- Hyperthyroidism
- Mood swings

Diagnosis and Management: -

A physical examination is typically the first step in diagnosing central sleep apnea.

The following tests might be used to identify CSA or rule out other problems:

- A lung function test to rule out other disorders.
- Study during sleep-cycle, or polysomnography.
- An ECG to monitor the heartbeat.
- For examine the structural problems of the spine and brain, MRI is required.

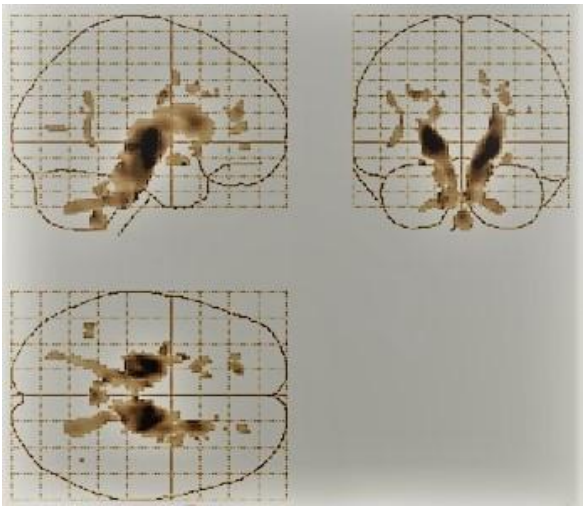


Figure-5
Scanned Brain image of CSA patient.

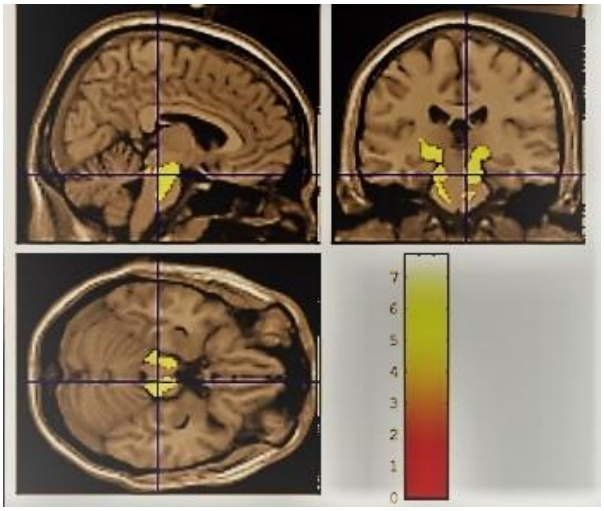


Figure-6
MRI of Brain to detect the change in CSA patient.

Complex sleep apnea syndrome (CompSAS): -

A form of sleep abnormality respiration called CompSAS[34] occurs when CSA continue or start to occur after OSA events have now been treated with CPAP. According to the current official definition, the CSA index (CAI) must be more than five events/hour and central events must report for greater than 50% of such residual sleep abnormality breathing

incidents and the outcome in a routine respiration pattern that takeover and cause obstruction on CPAP therapy. Bilevel-PAP at two levels By boosting ventilation while correspondingly reducing carbon dioxide, spontaneously ventilation may raise the occurrence of CSA. It's still debatable if an individual having narcotic-induced CSA or the individual also having Cheyne-Stokes breathing brought on by systolic heart failure. CompSAS would now only include those whose CSA could not be found anywhere else on the spectrum of CSA disorders[35]. These populations are excluded from our report, for the better understanding of this demography as well as the physiological reason that cause CSA. Although any criterion may be used to diagnose CompSAS, Patients during the treatment-emergent of CSA, in particular anyone whose CSA does not resolve with CPAP therapy, require a diagnostic check-up. CompSAS is also known as CPAP-related periodic breathing, complicated disturbed breathing during sleep, CompSAS while using CPAP, and CSA when utilising CPAP. The incidence of CompSAS has just recently been evaluated. Percentage of CompSAS which was detected till now is 15% of individuals (34/223) who were evaluated for suspected sleep-disordered breathing over a month in a routine clinical check-up that did not exclude the patients of cardiac arrest or use of any narcotic substances. The prevalence for this sickness, however, vary according to the many populations that have been reported on or researched, and it is significantly influenced by traits like drug usage, BMI, and some other medical conditions, particularly cardiac arrest. In a group of patients suffering from chronic heart disease with OSAS and the occurrence of CSA was estimated the range as 0.56% in the German Westhoff research (participants who have BNP l less than 100 pg/mL were removed) to 18%[36].

Pathophysiology and Symptoms: -

The necessity to define the mechanism of this condition and create effective treatment plans drove the requirement to distinguish CompSAS out of both the two i.e., OSA and CSA. Aetiology is still unknown, however numerous variables are thought to interact to determine pathology. Upper respiratory pathway obstruction and host circumstances and features as well as inconsistent central ventilatory control elements, are thought to be important contributors[37]. CompSAS is known to be more common during disrupted sleep periods. CompSAS arises as a result of a mixture of respiratory instability, shifting PaCO2 levels, variations in upper respiratory pathway related airflow resistance, and a fluctuating sleep state according to this theory. A mix of behavioural and physiological factors, as well as

cerebral and peripheral chemoreceptors, govern breathing when awake. Increased variability in PaCO2 levels is caused by the loss of behavioural control of ventilation during sleep, as well as decreased response chemo to variations in relation to the kind of sleep, variations in lung capacities and minute ventilation, as well as alterations in artery CO2 (PaCO2) and O_2 (PaO2) (REM or Non-REM). PaCO2 fluctuation is much greater in the context of frequent upper airway obstructions caused by OSAS. By using CPAP to treat chronic recurring blockages, ventilation stabilises, enhancing gas exchange and facilitating CO2 removal. PaCO2 levels can quickly fall below the apneic threshold if a CSA results from a high ventilation reaction to stimuli[38]. Once the patient is awakened by the CSA events, the ventilator output and air circulation PaCO2 set points may change depending on whether the patient is awake or sleeping. This can lead to a recurrent pattern of CSA, disruption in sleep, rapid sleep, CSA, disturbance in sleep, and so on. Few persons have a low breakpoint (narrower threshold for apnea-hyperpnea), which makes them highly vulnerable to periodic respiration. Furthermore, patients who are most likely to start the treatment-emergent centrals ought to be aware that, in contrast to predominating OSA events, they have a higher chance to encounter CSA events on their polysomnogram in between their diagnostic stage. These major episodes become frequently visible with CPAP therapy. And other possible explanation for CSA development after starting PAP therapy's impact on lung stretch is to boots receptors or in activation of the receptors as a after effect of CPAP, which results in ventilatory changes. The Hering-Breuer response produces central apnea when lung stretch receptors are activated. Inherently leaky nasal covers as well as mouth leaks during PAP treatment have been discovered by Montesi et al. as probable origins of hypocapnia-induced CSA. Finally, frequent stimulation, interrupted sleep, with PaCO2 fluctuation may be brought on by both internal and environmental stimuli, including the patient's health condition and the obtrusiveness of CPAP therapy[39].

General Symptoms: -

- Pain in head
- Mouth Dryness
- Daytime exhaustion
- Insomnia or unable sleep properly
- Sudden wake-up from sleep
- Confusion on rising-up in the morning

Diagnosis and Management: -

Diagnosis of CompSAS is done via PSG. The very first criterion of CompSAS is to check for OSA, which is characterised by a minimum (AHI) i.e., apnoea-hypopnea index, where we check for five episodes of sleep cycle per hour, with the most of events for OSA. CompSAS can be diagnosed if the frequency of obstructive episodes is decreased to five episodes of sleep cycle per hour with CPAP titration and (CAI) i.e. Central Apnoea Index, which is five episodes of sleep cycle per hour. Use of an automated electrocardiography-based method, CompSAS may be distinguished from diagnosis of sleep cycle study in OSAS. According to studies, this application is now not in hand in a routine diagnosis[40].

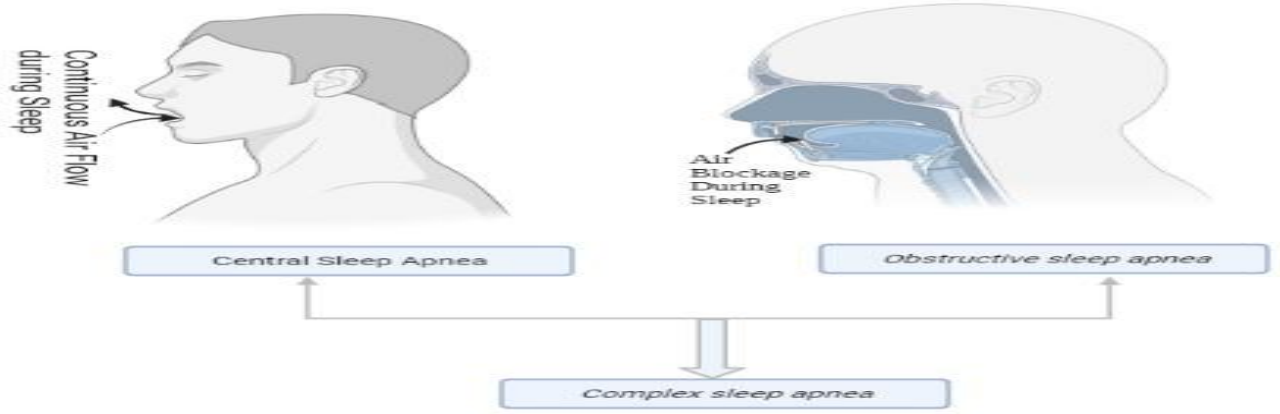


Figure-6
Complex sleep apnea syndrome (Combination of OSA and CSA).

The following table shows the drugs which are used in the treatment of all the three diseases.

Drug Category	Name Of the Drug	Effect Of Wakefulness	Clinical Use	Route of Administration	Year of Approval/Stage by US FDA
Dopamine Norepinephrine Reuptake Inhibitor (DNRIs)	Solriamfetol[41]	Eugeroics	Narcolepsy, OSA, ADHD	Oral	2019
	Armodafinil[42]	Eugeroics	ADHD	Oral	2007

	Modafinil[43]	Eugeroics	Narcolepsy Sleep Apnea	Oral	1998
Serotonin and norepinephrine reuptake inhibitors (SNRIs)*	Venlafaxine[44]	Eugeroics	Mild ADHD	Oral	2008
	Duloxetine[45]	Eugeroics	Mild ADHD	Oral	2004
Aminoketones	Bupropion[46]	No Effect on Wakefulness	Mild ADHD	Oral	1985
Stimulants	Methyl-phenidate[47]	Eugeroics	ADHD Narcolepsy	Oral	2002
	Dextro-amphetamine[48]	Eugeroics	ADHD	Oral	2001
	Amphetamine[49]	Eugeroics	ADHD	Oral	2002
Selective norepinephrine reuptake inhibitor(SNRIs)	Atomoxetine[50]	Eugeroics	ADHD	Oral	2002
Antipsychotics (first-generation)	Haloperidol[51]	Less Effective	ADHD, Bipolar Disorder	Oral/ IV,IM (Injectables)	2000
	Chlorpromazine[52]	Less Effective	ADHD, Bipolar Disorder, Acute Psychosis	Oral, Rectal, Intramuscular, Intravenous infusion	1999
	Thioridazine[53]	Less Effective	Psychotic disorders, ADHD	Oral	1985 2005 (Discontinued)
Alpha-2 agonists	Clonidine[54]	No Effect on Wakefulness	Hypertension, ADHD	Oral, Transdermal. Tropical, Epidural	1961
	Methyldopa[55]	No Effect on Wakefulness	Hyper-tension	Oral, Injectables	1962
Glucocorticoids	Dexamethasone[56]	Less Effective	Asthma, ADHD, Sleep Apnea	Oral	1958
Antihistamines/ H_1 Blocker	Loratadine[57]	Eugeroics	allergic rhinitis	Oral	1988

(second-generation)	Cetirizine[58]	Eugeroics	dermatitis, urticaria, ADHD	Oral	2004
Decongestants	Phenylephrine[59]	Less Effective	ADHD, Narcolepsy Allergies	Oral, Nasal, IV/IM	2012
	Pseudoephedrine[60]	Eugeroics	ADHD, Sleep Apnea, Narcolepsy	Oral	2002
Antiseizure drugs	Lamotrigine[61]	Eugeroics	Bipolar Disorder. Depression Mania	Oral	2003
	Levetiracetam[62]	Eugeroics	Epilepsy	Oral	2000
	Felbamate[63]	Eugeroics	Epilepsy	Oral	1993
	Tiagabine[64]	Eugeroics	Epilepsy	Oral	1997
Selective - Orexin 2 Receptor Agonist	Ciproxifan[65]	Eugeroics	Sleep-wake disorders, Alzheimer's disease, ADHD	Oral	--
	Clobenpropit[66]	Eugeroics	Sleep-wake disorders, Alzheimer's disease, ADHD	Oral	Under Clinical trails
	Pitolisant[67]	Eugeroics	Narcolepsy	Oral	2019
Tricyclic antidepressant (TCA)	Acetazolamide[68]	Eugeroics	Complex Sleep Apnea, OSA, ADHD	Oral	1966
H3 blockers/Histamine Blocker	Danavorexton(TAK-925)[69]	Eugeroics	Sleep Apnea (OSA)	IV(Injectables)	Under Phase-1 Trails
Carbonic Anhydrase Inhibitors	Acetazolamide[70]	Eugeroics	Complex Sleep Apnea,	Oral, IV/IM (Injectable)	1952

			OSA, Epilepsy		
Progestin	Medroxy-progesterone[71]	Less Effective	Sleep Apnea, OSA, Breathing Effect	Oral Subcutaneous, IM(Injectable)	2004

Conclusion-

From the above detailing, all the widely spread neurodevelopment sleep disorder are majorly linked with DAT1 and D4 receptor i.e., ADHD. Where the progress and development in the particular field is at peak, new drugs are getting approved day by day for the management, which show a wide range in the field of Research and Development in Neurological Sleep Disorder. Whereas, founding show us, catalepsy and lack of orexin to be the main cause of Narcolepsy. Which can be controlled by medications. New drug category is coming in light for the treatment of Narcolepsy, Examples- H3 blockers/Histamine Blocker, DNRIs, Antiseizure, etc. But in case of Sleep Apnea, It show the Medical Device Advancement with zero side effect and medication with high efficacy. Where CPAP Therapy and Heart Rate Monetarization is life saver application for the patients suffering from Sleep Apnea.

REFERENCES-:

1. Ronnebaum S, Bron M, Patel D, Menno D, Bujanover S, Kratochvil D, et al. Indirect treatment comparison of solriamfetol, modafinil, and armodafinil for excessive daytime sleepiness in obstructive sleep apnea. Vol. 17, Journal of Clinical Sleep Medicine. 2021.
2. Powell J, Piszczatoski C, Garland S. Solriamfetol for Excessive Sleepiness in Narcolepsy and Obstructive Sleep Apnea. Annals of Pharmacotherapy. 2020;54(10).
3. Abad VC. Profile of solriamfetol in the management of excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea: Focus on patient selection and perspectives. Nat Sci Sleep. 2021;13.
4. Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Stevenson J, Danckaerts M, Van der Oord S, Döpfner M, Dittmann RW. Nonpharmacological

interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. American journal of psychiatry. 2013 Mar;170(3):275-89.

5. Kornum BR, Knudsen S, Ollila HM, Pizza F, Jennum PJ, Dauvilliers Y, Overeem S. Narcolepsy. Nature reviews Disease primers. 2017 Feb 9;3(1):1-9.
6. White DP. Sleep apnea. Proceedings of the American Thoracic Society. 2006 Mar;3(1):124-8.
7. Custodio RJ, Kim M, Chung YC, Kim BN, Kim HJ, Cheong JH. Thrsp gene and the ADHD predominantly inattentive presentation. ACS chemical neuroscience. 2023 Jan 30;14(4):573-89.
8. Gibbins C, Weiss MD, Goodman DW, Hodgkins PS, Landgraf JM, Faraone SV. ADHD-hyperactive/impulsive subtype in adults. Mental Illness. 2010 Jan 25;2(1):41-5.
9. Ghaderi AH, Nazari MA, Shahrokhi H, Darooneh AH. Functional brain connectivity differences between different ADHD presentations: impaired functional segregation in ADHD-combined presentation but not in ADHD-inattentive presentation. Basic and Clinical Neuroscience. 2017 Jul;8(4):267.
10. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Annals of Pharmacotherapy. 2014 Feb;48(2):209-25.
11. National Collaborating Centre for Mental Health (UK. Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults.
12. Epstein JN, Casey BJ, Tonev ST, Davidson MC, Reiss AL, Garrett A, Hinshaw SP, Greenhill LL, Glover G, Shafritz KM, Vitolo A. ADHD- and medication- related brain activation effects in concordantly affected parent–child dyads with ADHD. Journal of Child Psychology and Psychiatry. 2007 Sep;48(9):899-913.
13. Cavaliere C, Longarzo M, Fogel S, Engström M, Soddu A. Neuroimaging of narcolepsy and primary hypersomnias. The Neuroscientist. 2020 Aug;26(4):310-27.
14. Madan R, Pitts J, Patterson MC, Lloyd R, Keating G, Kotagal S. Secondary narcolepsy in children. Journal of Child Neurology. 2021 Feb;36(2):123-7.
15. Dauvilliers Y, Billiard M, Montplaisir J. Clinical aspects and pathophysiology of narcolepsy. Clinical Neurophysiology. 2003 Nov 1;114(11):2000-17.
16. Dauvilliers Y, Beziat S, Pesenti C, Lopez R, Barateau L, Carlander B, Luca G, Tafti M, Morin CM, Billiard M, Jaussent I. Measurement of narcolepsy symptoms: the narcolepsy severity scale. Neurology. 2017 Apr 4;88(14):1358-65.
17. Goswami M. The influence of clinical symptoms on quality of life in patients with narcolepsy. Neurology. 1998 Feb 1;50(2 Suppl 1):S31-6.
18. Fortuyn HA, Lappenschaar GA, Nienhuis FJ, Furer JW, Hodiamont PP, Rijnders CA, Lammers GJ, Renier WO, Buitelaar JK, Overeem S. Psychotic symptoms in narcolepsy: phenomenology and a comparison with schizophrenia. General hospital psychiatry. 2009 Mar 1;31(2):146-54.
19. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. Sleep medicine. 2014 May 1;15(5):502-7.

20. Kim J, Lee GH, Sung SM, Jung DS, Pak K. Prevalence of attention deficit hyperactivity disorder symptoms in narcolepsy: a systematic review. Sleep Medicine. 2020 Jan 1;65:84-8.
21. Barateau L, Lopez R, Dauvilliers Y. Management of narcolepsy. Current treatment options in neurology. 2016 Oct;18:1-3.
22. Aldrich MS, Chervin RD, Malow BA. Value of the multiple sleep latency test (MSLT) for the diagnosis of narcolepsy. Sleep. 1997 Aug 1;20(8):620-9.
23. Strollo Jr PJ, Rogers RM. Obstructive sleep apnea. New England Journal of Medicine. 1996 Jan 11;334(2):99-104.
24. Horner RL. Pathophysiology of obstructive sleep apnea. Journal of cardiopulmonary rehabilitation and prevention. 2008 Sep 1;28(5):289-98.
25. Krieger J, Petiau C, Sforza E, Delanoë C, Hecht MT, Chamouard V. Nocturnal pollakiuria is a symptom of obstructive sleep apnea. Urologia internationalis. 1993 Feb 3;50(2):93-7.
26. Guilleminault C, Partinen M, Antonia QS, Hayes B, Dement WC, Nino-Murcia G. Determinants of daytime sleepiness in obstructive sleep apnea. Chest. 1988 Jul 1;94(1):32-7.
27. Series F, St Pierre S, Carrier G. Effects of surgical correction of nasal obstruction in the treatment of obstructive sleep apnea. Am Rev Respir Dis. 1992 Nov 1;146(5 Pt 1):1261-5.
28. McNicholas WT. Diagnosis of obstructive sleep apnea in adults. Proceedings of the American thoracic society. 2008 Feb 15;5(2):154-60.
29. Javaheri S, Dempsey JA. Central sleep apnea. Comprehensive Physiology. 2013 Jan;3(1):141-63.
30. McCarley RW. Neurobiology of REM and NREM sleep. Sleep medicine. 2007 Jun 1;8(4):302-30.
31. Blumberg MS, Lesku JA, Libourel PA, Schmidt MH, Rattenborg NC. What is REM sleep?. Current biology. 2020 Jan 6;30(1):R38-49.
32. Dempsey JA, Skatrud JB. A sleep-induced apneic threshold and its consequences. American Review of Respiratory Disease. 1986 Jun;133(6):1163-70.
33. Deacon-Diaz N, Malhotra A. Inherent vs. induced loop gain abnormalities in obstructive sleep apnea. Frontiers in Neurology. 2018 Nov 2;9:896.
34. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex sleep apnea syndrome: is it a unique clinical syndrome?. Sleep. 2006 Sep 1;29(9):1203-9.
35. Wang J, Wang Y, Feng J, Chen BY, Cao J. Complex sleep apnea syndrome. Patient preference and adherence. 2013 Jul 3:633-41.
36. Khan MT, Franco RA. Complex sleep apnea syndrome. Sleep disorders. 2014 Feb 16;2014.
37. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. Chest. 2007 Feb 1;131(2):595-607.
38. Baillieul S, Revol B, Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Pépin JL. Diagnosis and management of central sleep apnea syndrome. Expert review of respiratory medicine. 2019 Jun 3;13(6):545-57.

39. Bounhoure JP, Galinier M, Didier A, Leophonte P. Sleep apnea syndromes and cardiovascular disease. Bulletin de l'Academie nationale de medecine. 2005 Mar 1;189(3):445-59.
40. McLaren AT, Bin-Hasan S, Narang I. Diagnosis, management and pathophysiology of central sleep apnea in children. Paediatric respiratory reviews. 2019 Apr 1;30:49-57.
41. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3).
42. Hirshkowitz M, Black JE, Wesnes K, Niebler G, Arora S, Roth T. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respir Med. 2007;101(3).
43. Gerrard P, Malcolm R. Mechanisms of modafinil: a review of current research. Neuropsychiatric disease and treatment. 2007 Jun 1;3(3):349-64.
44. Aiyer R, Barkin RL, Bhatia A. Treatment of neuropathic pain with venlafaxine: A systematic review. Vol. 18, Pain Medicine (United States). 2017.
45. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: A systematic review and meta-analysis. Vol. 34, Korean Journal of Internal Medicine. 2019.
46. Bae S, Hong JS, Kim SM, Han DH. Bupropion shows different effects on brain functional connectivity in patients with Internet-based gambling disorder and internet gaming disorder. Front Psychiatry. 2018;9(APR).
47. Tagaya H, Murayama N, Fukase Y. Methylphenidate. Vol. 73, Nihon rinsho. Japanese journal of clinical medicine. 2015.
48. Denzer C, Denzer F, Lennerz BS, Vollbach H, Lustig RH, Wabitsch M. Treatment of Hypothalamic Obesity with Dextroamphetamine: A Case Series. Obes Facts. 2019;12(1).
49. Reyes-Parada M, Iturriaga-Vasquez P, Cassels BK. Amphetamine derivatives as monoamine oxidase inhibitors. Front Pharmacol. 2020;10.
50. Rae CL, Nombela C, Rodríguez PV, Ye Z, Hughes LE, Jones PS, et al. Atomoxetine restores the response inhibition network in Parkinson's disease. Brain. 2016;139(8).
51. Shen YZ, Peng K, Zhang J, Meng XW, Ji FH. Effects of Haloperidol on Delirium in Adult Patients: A Systematic Review and Meta-Analysis. Vol. 27, Medical Principles and Practice. 2018.
52. Ahmed R, Maroney M, Fahim G, Ghin HL, Mathis AS. Evaluation of the use of chlorpromazine for agitation in pediatric patients. Mental Health Clinician. 2021;11(2).
53. Yin T, He S, Shen G, Ye T, Guo F, Wang Y. Dopamine receptor antagonist thioridazine inhibits tumor growth in a murine breast cancer model. Mol Med Rep. 2015;12(3).
54. Wang JG, Belley-Coté E, Burry L, Duffett M, Karachi T, Perri D, et al. Clonidine for sedation in the critically ill: A systematic review and meta-analysis. Crit Care. 2017;21(1).

55. Mah GT, Tejani AM, Musini VM. Methyldopa for primary hypertension. Cochrane Database of Systematic Reviews. 2009.
56. Giles AJ, Hutchinson MKND, Sonnemann HM, Jung J, Fecci PE, Ratnam NM, et al. Dexamethasone-induced immunosuppression: Mechanisms and implications for immunotherapy. J Immunother Cancer. 2018;6(1).
57. Rodriguez Amado JR, Prada AL, Duarte JL, Keita H, da Silva HR, Ferreira AM, et al. Development, stability and in vitro delivery profile of new loratadine-loaded nanoparticles. Saudi Pharmaceutical Journal. 2017;25(8).
58. Blaiss MS, Bernstein JA, Kessler A, Pines JM, Camargo CA, Fulgham P, et al. The Role of Cetirizine in the Changing Landscape of IV Antihistamines: A Narrative Review. Vol. 39, Advances in Therapy. 2022.
59. Biricik E, Karacaer F, Ünal İ, Sucu M, Ünlügenç H. The effect of epinephrine for the treatment of spinal- hypotension: comparison with norepinephrine and phenylephrine, clinical trial. Brazilian Journal of Anesthesiology. 2020;70(5).
60. Gagliano A, Aricò I, Calarese T, Condurso R, Germanò E, Cedro C, et al. Restless Leg Syndrome in ADHD children: Levetiracetam as a reasonable therapeutic option. Brain Dev. 2011;33(6).
61. Han SA, Yang EJ, Song MK, Kim SJ. Effects of lamotrigine on attention-deficit hyperactivity disorder in pediatric epilepsy patients. Korean J Pediatr. 2017;60(6).
62. Gagliano A, Aricò I, Calarese T, Condurso R, Germanò E, Cedro C, et al. Restless Leg Syndrome in ADHD children: Levetiracetam as a reasonable therapeutic option. Brain Dev. 2011;33(6).
63. Graves NM. Felbamate. Annals of Pharmacotherapy. 1993 Sep;27(9):1073-81.
64. Leach JP, Brodie MJ. Tiagabine. The Lancet. 1998 Jan 17;351(9097):203-7.
65. Day M, Pan JB, Buckley MJ, Cronin E, Hollingsworth PR, Hirst WD, et al. Differential effects of ciproxifan and nicotine on impulsivity and attention measures in the 5-choice serial reaction time test. Biochem Pharmacol. 2007;73(8).
66. Meng F, Han Y, Staloch D, Francis T, Stokes A, Francis H. The H4 histamine receptor agonist, clobenpropit, suppresses human cholangiocarcinoma progression by disruption of epithelial mesenchymal transition and tumor metastasis. Hepatology. 2011;54(5).
67. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, Lehert P, Ding CL, Lecomte JM, Schwartz JC. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. The Lancet Neurology. 2013 Nov 1;12(11):1068-75.
68. Schmickl CN, Landry SA, Orr JE, Chin K, Murase K, Verbraecken J, et al. Acetazolamide for OSA and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis. Chest. 2020;158(6).
69. Evans R, Kimura H, Nakashima M, Ishikawa T, Yukitake H, Suzuki M, Hazel J, Faessel H, Wu J, Hang Y, Alexander R. Orexin 2 receptor- selective agonist danavorexton (TAK- 925) promotes wakefulness in non- human primates and healthy individuals. Journal of Sleep Research. 2023 Mar 19:e13878.

70. Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. Annals of Pharmacotherapy. 1996 May;30(5):514-9.
71. Mishell Jr DR. Pharmacokinetics of depot medroxyprogesterone acetate contraception. The Journal of reproductive medicine. 1996 May;41(5 Suppl):381-90.