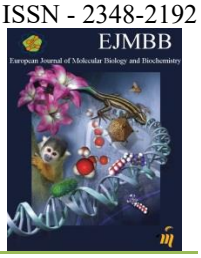
e - ISSN - 2348-2206
Print ISSN - 2348-2192

European Journal of Molecular Biology and Biochemistry

Research article

Journal homepage: www.mcmed.us/journal/ejmbb



CENTRAL NERVOUS SYSTEM (CNS) SEDATING, STIMULATING, OR ANALGESIC DRUGS

Varun R[1]*, Srinivas K[1], Naga Lokesh G[1], Ekamsh P[1], Dr. Pravallika V[2]

[1]Pharm.D, V Year Student, Department of Pharmacy Practice, KLR Pharmacy College, Paloncha, Telangana, India.
[2]Assistant Professor, Department of Pharmacy Practice, KLR Pharmacy College, Paloncha, Telangana, India.

Article Info

Received 23/01/2026
Revised 16/02/2026
Accepted 19/03/2026

Key words: -
CNS drug interactions; anesthesia; tranquilizers; stimulant and painkillers; benzodiazepines; narcotics; non-steroidal antiinflammatory drugs; Gaba neurotransmission; catecholamine neurotransmission.

ABSTRACT

The central nervous system (CNS) sedating, stimulating, and analgesic medications are important pharmacological groups that are employed to regulate neuronal activity, deal with pain, improve alertness, and manage various neurological and psychiatric problems. Benzodiazepines, barbiturates, and Z-drugs are sedative agents that work mostly by enhancing GABAergic inhibition to control anxiety, induce sleep, and achieve procedural sedation. The CNS stimulants include amphetamines, methylphenidate, modafinil and xanthines which enhance catecholaminergic neurotransmission and in turn enhance attention, wakefulness and cognitive functioning in diseases like ADHD and narcolepsy. An analgesic drugs include opioids, NSAIDs, acetaminophen, and adjuvant drugs which modulate nociceptive pathways at peripheral, spinal, and central locations to inhibit acute and chronic pain. These classes of drugs vary widely with respect to their effects of action, usage benefit, safety, and misuse possibilities. The latest developments including orexin antagonists, non-opioid analgesics, psychedelics, and nanocarrier-based CNS delivery exemplify the current development of CNS therapeutics. Their pharmacodynamic diversity is important to understand and maximize their therapeutic effects, reduce their adverse events, and respond to social issues with addiction like dependence, tolerance, and opioid crisis.

INTRODUCTION

The central nervous system (CNS) is the main control centre of the incorporation of sensory data and coordination of physiological reactions at the same time, as well as homeostasis. [1] The CNS acting drugs influence the body by regulating neuronal communication, and this is mainly by altering neurotransmitter release, receptor activation or inhibation, ion channel modulation, and intracellular signallingpathways. These interactions affect some of the vital processes including cognition, mood, perception, motor control and autonomic regulation. The drugs that have CNS-active properties can stimulate neuronal activity or inhibit it, and have a therapeutic effect in such disorders as epilepsy, anxiety, depression, and neurodegenerative diseases. [2]

Corresponding Author
Varun R

Email: varunraavi39@gmail.com

Due to the sophistication and strong connectivity of CNS pathways, a subtle change in synaptic activity can result in extensive behavioural or physiological consequences, and it is in this regard that the targeted and specific pharmacological intervention becomes critical.

Classification of CNS Pharmacological Agents

The pharmacological agents of CNS are widely classified according to their major actions of action and clinical suggestions. Key classes are CNS depressants (e.g. sedatives, hypnotics, anxiolytics, and general anaesthetics), which slow neuronal excitability, and relax or put the patient to sleep; CNS stimulants (e.g. amphetamines, methylxanthines), which accelerates neuronal alertness, attention, and movement; antiepileptic (preventing or reducing seizures) drugs; and psychotropic (e.g. antidepressants, antipsychotics and mood stabilizers) agents, which treat neurochem Other classes are analgesics, especially opioid and non-opioid agents, and

neurodegenerative therapeutics applied in the treatment of such diseases as Parkinson and Alzheimer diseases. This taxonomy gives a logical insight into the effect of various classes of drugs on particular circuits and clinical performance.[3].

Therapeutic and Societal Importance

The therapeutic significance of CNS pharmacological agents is immense because it finds application in the treatment of a broad range of neurological as well as psychiatric disorders that have a significant effect on quality of life. [4,5]The conditions of depression, schizophrenia, epilepsy, chronic pain, and neurodegenerative diseases constitute extensive disabling conditions and CNS-targeted therapies are necessary to patients. In addition to personal therapy, CNS medications have significant social effects, affecting the health of the population, their labor efficiency and economic impact. Although they are critically beneficial, certain classes, especially opioids, sedatives, and stimulants, present the threat of dependence, abuse, and social detriment, which requires the establishment of strong regulatory measures and rational prescription habits. Accordingly, CNS pharmacology represents an important point of convergence between medical treatment, social health policy, and professional ethics, and as such further investigation and clinical usage are warranted.[6,7]

General Principles of CNS Pharmacology

Blood–Brain Barrier and Drug Penetration

The blood-brain barrier (BBB) is a very specialized physiological barrier which surrounds the central nervous system by limiting the penetration of potentially harmful substances through systemic circulation. The BBB is created by the tight junction of the endothelial cells, which is supported by the astrocytic end-feet as well as pericytes and there the BBB contributes to the maintenance of the constant transport of the nutrients and also restriction of the diffusion of drugs. [8,9]The BBB can only penetrate small non-ionized compounds that are lipophilic or agents that have some form of special means of entry. The barrier, therefore, has a huge effect on designing drugs, dose and therapeutic effects of CNS disorders. Pharmacological agents cannot reach appropriate brain levels because of active efflux transporters including P-glycoproteins. Knowledge of BBB biology is thus fundamental to creating CNS-active drugs, formulations, bypassing pharmacoresistance with such strategies as prodrugs, nanoparticles, and receptor-mediated transcytosis.[10]

Neurotransmitter Systems in CNS Drug Action

CNS-active drugs have neurotransmitters systems as the primary targets since they mediate the synaptic communication, neuronal excitation, intelligence and behaviour. CNS drugs influence neurotransmission in their effect on synthesis, storage, release, activation of receptors, reuptake, or metabolism of neurotransmitters. [11,12]The neurotransmitter systems, GABA, glutamate, dopamine, noradrenaline, and serotonin each have their own niche in neuronal functioning, and thereby become the key pharmacological targets in the treatment of psychiatry and neurology. The knowledge of these systems has enabled the accurate control of neural circuits, which are useful in treating anxiety, depression, schizophrenia, Parkinson disease, and epilepsy.[13]

GABAergic System

The main inhibitory network of the CNS is the GABAergic system of which the main inhibitory neurotransmitter is 2-deoxy-L-glutamic acid (GABA). GABA A receptors Drugs that act on receivers, including benzodiazepines, barbiturates and some anaesthetics, enhance chloride influx and elevate neuronal hyperpolarization, inhibiting excitability. This system plays a very important role in treatment of anxiety, seizures, insomnia and muscle spasms. GABA transmission is dysregulated and has led to the development of epilepsy and anxiety disorders. [14]Modulation pharmacologically increases the inhibitory tone, restoring an imbalanced neural circuit and creating the effect of calming, anticonvulsant, or sedation.

Glutamatergic System

Glutamatergic system mediated by glutamate, the most important excitatory neurotransmitter, is crucial in learning, memory and synaptic plasticity. The use of drugs acting on NMDA, AMPA, and kainate receptors alters excitatory signalling and NMDA receptor antagonists like ketamine have an anaesthetic and rapid-acting anti-depressant effect. Uncontrolled glutamate causes excitotoxicity, which is one of the major causes of neurodegenerative diseases, stroke, and traumatic brain injury. [15,16]Drugs that work on this system are designed to inhibit pathologic excitatory transmission and leave normal physiological functions intact. Therefore, glutamatergic pathways modulation is potentially useful in the treatment of depression, epilepsy, and neurodegeneration.

Dopaminergic System

Dopaminergic system controls the reward, motivation, motor control, and endocrine functions. It is arranged in pathways which include nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular tracts, each of which is associated with certain physiological and behavioural results. Antipsychotics (D 2 antagonist), antiparkinson agents (L-DOPA, dopamine agonist) and stimulants (amphetamine, cocaine) are dopamine-targeting drugs.[17] The asymmetries between dopaminergic transmission are the core of the problems of schizophrenia, Parkinson, attention deficit hyperactivity disorder (ADHD), and addiction. Dopamine receptor or reuptake

transporter pharmacological modulation permits pathway-specific dysfunctional targeted therapy.

Noradrenergic and Serotonergic Systems.

Noradrenergic and serotonergic systems play a critical role in regulating mood, arousal stress responses and autonomic regulation. Noradrenaline which is a product of locus coeruleus affects attention, memory and sympathetic activity. The serotonin synthesized in raphe nuclei adjusts mood, sleep, appetite and emotional processing. The disorders that are highly linked with the dysregulation of these systems include stress related disorders, anxiety disorders and depression. Such drugs include SSRIs, SNRI, and MAO inhibitors and tricyclic antidepressants that involve these pathways to improve monoaminergic transmission. These agents have therapeutic effects in a broad understanding of psychiatric disorders by restoring neurotransmitter balance.[18,19]

CNS Tolerance, Dependence and Withdrawal.

Tolerance is common in chronic exposure of the CNS-active drug, whereby increasing doses of the drug are required to produce the same effect over time because neuroadaptative changes occur at the receptors, ion channels or intracellular signalling pathways. Dependence occurs due to the adaptation of the CNS to constant drug availability that results in physiological or psychological dependence. As the levels of drug decline by a rapid margin, there arises the withdrawal symptoms which are an expression of the hyperexcitability of the neural circuits that were suppressed by the drug. These effects can range between mildly uncomfortable to life-threatening depending on the drug category- especially the opioids, benzodiazepines and alcohol. It is very important to comprehend how tolerance and dependence works so as to create safer treatment regimens, inhibit abuse, and treat withdrawal with tapering or substitution therapy.[20]

Sedatives and Hypnotics

Their classification and overview.

Sedative-hypnotic medications are a heterogeneous group of pharmacological substances that can be used to sedate, anxiolise, induce hypnosis or anesthesia depending on the dose. The agents are mostly divided into benzodiazepines, barbiturates, and non-benzodiazepine hypnotics (Z-drugs). Their variations are in chemical structure, receptor-binding mechanism, action duration and safety profile.[21] Although benzodiazepines are the most widely used as they have a wide therapeutic index, barbiturates have been excluded in regular clinical practice owing to increased toxicity, tolerance and dependence. Z-drugs, which are safer derivatives of insomnia, are selective activators of particular subunits of GABA receptors to cause sleep with less cognitive side effects. These classes are vital in understanding in order to select the right therapy on the basis of the clinical sign, the patient factors, and the risk- benefit.[22]

Benzodiazepines

Benzodiazepines are the most frequently prescribed sedative-hypnotic drugs that are characterized by anxiolytic, anticonvulsant, muscle relaxant, and hypnotic effects. They connect to one of the allosteric sites on the GABA A receptor complex, which strengthens the inhibitory effect of GABA and divides the frequency of the opening of chloride channels. Their pharmacokinetic are diverse with short acting drugs like triazolam and long acting drugs like diazepam that can be used to tailor the two across different disorders which include anxiety disorders, insomnia, seizures, and alcohol withdrawal. They are also safer than barbiturates due to their extensive therapeutic index, but there is a risk of tolerance, dependence, and cognitive dysfunction in the long term.

Barbiturates

Barbiturates are hypnotic-sedative drugs with a small therapeutic index, which are used traditionally as anesthetic drugs, in the treatment of seizures, and anxiety. They increase GABAergic inhibition by increasing the duration of chloride channel opening and can directly activate GABA A receptors in high doses, as well as help to produce effective CNS depression.[23] Despite its effectiveness, their tendency to induce respiratory depression, drug-drug interaction, tolerability, and abuse propensity have resulted in reduced clinical use of the drugs. Today Barbiturates such as phenobarbital are still useful in the treatment of refractory seizures and some general anesthetic practice, although they have been largely replaced by safer alternatives.[24]

Z-Drugs (Non-benzodiazepine Hypnotics):

These are non-benzodiazepine drugs that are meant to put one to sleep. Z-drugs such as zolpidem, zaleplon and eszopiclone were invented as being more selective in the treatment of insomnia and less adverse than benzodiazepines. They specifically interact with GABA A receptors that have the alpha one subunit that elicit hypnotic effects with less anxiolysis or muscle relaxation. Their desirable pharmacokinetic characteristics enhance immediate onset and brief action, which minimizes continued residual sedation after use on the next day. Despite being considered less harmful, they may still result in dependence, complicated sleep patterns as well as poor psychomotor performance when abused or combined with alcohol and other CNS depressants

Mechanisms of Action

Sedative-hypnotics have a therapeutic action mainly by changing the GABAergic inhibitory system in the brain. They reduce the excitability of neurons, facilitate sleep, anxiolysis and sedation by improving the GABA-mediated influx of chloride. Although the benzodiazepines and Z-drugs can bind specific allosteric sites of the GABA a receptor, barbiturates have a greater CNS effect because of allosteric action and direct receptor activation at high

doses. These mechanistic variations explain the difference in their clinical profile, side effects, and overdose.[25]

GABA-A Receptor Modulation

GABA A receptors are chloride ion channels that are ligand-gated channels where activation of these channels causes neuronal hyperpolarization. Benzodiazepine enhances the speed of the channel opening and barbiturates enhances the duration of the opening leading to a greater depressing effect. Z-drugs are selective receptors with α1 subunit, which produces mostly the effects of hypnotics. These agents have a dose-dependent CNS depression capability, that is, mild sedation to deep anesthesia by potentiating GABAergic neurotransmission. These differences in efficacy, safety, and clinical use are due to the fact that they modulate receptor subtypes.[26]

Insomnia Effects on Sleep Architecture.

Sedative-hypnotics distort normal patterns of sleep, which affects the proportion of REM and non-REM sleep. The Benzodiazepines and Z-drugs have the ability to shorten the sleep latency and extend the total sleep duration but decrease the deep slow-wave sleep, which may lead to sleep quality issues in the long run. Barbiturates have a more significant effect of inhibiting REM sleep, which will result in rebound effects during withdrawal. Although Z-drugs are believed to be effective in maintaining the sleep pattern, any sedative should be used in the long term, which disturbs the body sleep patterns and this requires short-term treatment and close observation.[27,28]

Clinical Uses

The anxiolytic, hypnotic, anticonvulsant, and muscle relaxant properties of sedative-hypnotic agents are popular in clinical practice. They have a wide range of use as they are used in the treatment of generalized anxiety, sleep disorders, seizure management, alcohol withdrawal, muscle spasticity and pre-anesthetic sedation. The choice of drug to use will be based on the timing of action, the length, comorbidities in the patient and dependence potential. Z-drugs are used when there is short term insomnia, benzodiazepines in anxiety and acute seizure management and barbiturates in special situations such as refractory epilepsy or even in anesthesia induction.

Anxiety and Insomnia

Benzodiazepines are still the first-line treatment of acute anxiety because their onset is fast and their anxiolytic properties are sure. In the case of insomnia, short acting benzodiazepine and Z-drugs may be employed in order to minimize sleep onset latency and enhance sleep maintenance. Nonetheless, its prophylaxis is not recommended because it may lead to tolerance, dependence, and rebound insomnia. Many non-pharmacological methods like CBT-I are commonly prescribed to be used together or instead of pharmacotherapy.[29]

Pre-anesthetic Medication and seizure Disorders.

The sedative-hypnotics have an important part in the treatment of seizure disorder, through the achievement of GABA-mediated inhibition. Diazepam and lorazepam are the benzodiazepines used as the frontline in the acute seizure control, including status epilepticus. Phenobarbital is still useful in the treatment of refractory epilepsy and in the treatment of neonatal seizures. [30]Benzodiazepines have been applied in the field of anesthesiology as pre-medications in diminishing anxiety, initiating sedation, and bringing about anterograde amnesia prior to surgery.

Unauthorized Effects and Intolerance.

Sedative-hypnotics have adverse effects that are mainly as a result of over-depression of CNS and changes in psychomotor and cognitive functions. The typical effects are drowsiness, lack of coordination, dizziness, memory problems, and lack of concentration. Prolonged use causes pharmacological tolerance caused by receptor desensitization and neuroadaptive modifications. There is the development of cross-tolerance between agents that work with GABA A receptors that are hard to withdraw, and there is a risk of abuse. These risks are critical to know in order to prescribe and educate the patient appropriately.[31]

Dependence and Withdrawal

The use of benzodiazepines, barbiturates, and Z-drugs may cause physical and mental dependency. Depending on the mode of withdrawal, the withdrawal symptoms may be perceived as anxiety, insomnia, shakers or shivers and the severe symptoms that may be experienced include the seizure and delirium particularly when the withdrawal is sudden. [32]Factors that influence dependence risk are drug potency, duration of action and length of treatment. Safe discontinuation requires gradual tapering strategies, monitoring strategies and substitution strategies.[33]

Sedation and Cognitive Disability.

The most frequent adverse effect of sedative-hypnotics is called sedation which may disorient the reaction time, attention and coordination, leading to an increased probability of falls and accidents. Other effects of Benzodiazepines and Z- Drugs include anterograde amnesia, impaired learning capacity and sleepiness during the day. The elderly are quite susceptible to age-related pharmacokinetic alterations.[34] Cognitive impairment and respiratory depression are highly increased when these drugs are combined with alcohol or opioids, and therefore, prescribing such drugs must be cautious. [35]

CNS Stimulants

Major Drug Classes

The CNS stimulants include a wide array of the pharmacological substances that increase alertness, attention, and psychomotor activity by amplifying excitatory neurotransmission in the brain. Such major classes of stimulants are amphetamines, methylphenidate, modafinil, armodafinil, and natural xanthines including caffeine. Even though these agents vary in their chemical make up and receptor selectivity, they can be characterized by a broad commonality of being able to increase the levels of dopamine and norepinephrine in crucial brain circuits. [36]Their clinical uses include attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and cognitive fatigue, as their illicit use has serious issues of dependence, tolerance, and cardiovascular issues. Knowledge of the stimulants classification can help in making rational prescriptions and also help in identifying the risks of non-medical use.

Methylphenidate and Amphetamines.

Amphetamines and methylphenidate are highly effective psychostimulants, which are commonly used in the management of ADHD and some sleeping disorders. Amphetamines work by stimulating the release of both dopamine and norepinephrine by the neurons of the presynaptic and forbidding their uptake, which leads to an overabundance of these substances in the synapses. Methylphenidate is mainly a reuptake inhibitor of norepinephrine and dopamine, which improves neurotransmitters in the attention-related systems. These agents enhance concentration, impulse control and alertness with the dangers of insomnia, loss of appetite and abuse because of their reinforcing nature[37].

Modafinil and Armodafinil

Modafinil and its R-enantiomer armodafinil are wakefulness-stimulating drugs that have a better safety profile than traditional stimulants. These are highly multifactorial in their specific mechanisms, and they influence dopaminergic, glutamatergic, and orexinergic pathways without the intensive euphoria of amphetamines. [38]They are mainly prescribed due to narcolepsy, sleepiness in case of obstructive sleep apnea and shift-work disorder. They are becoming more popular in situations where long-term alertness is required and the few side effects result in minimal cardiovascular effects.[39]

Caffeine and Xanthines

Xanthines like caffeine and others like theophylline have a mild stimulant effect, which occurs through antagonizing the adenosine receptors, which leads to release of neurotransmitter and an increase in cortical activity. These are stimulants, decrease fatigue and bronchodilatory. Though it is commonly used in the form of coffee, tea and drinks, at high doses it causes palpitations, anxiety and stomach disruption. They are one of the most known classes of stimulants all over the world because of the ubiquitous use.[40].

Mechanisms of Action

Stimulants are believed to have its effects by regulating the monoaminergic neurotransmission, especially the dopamine and norepinephrine, in the prefrontal cortex, basal ganglia, and reward pathways. Stimulants elevate cortical arousal, attention and executive-functional output by augmenting the synaptic levels of these neurotransmitters. The amount of neurotransmitter increase differs among classes of drugs leading to differences in the effects of these agents on therapy, onset of action, and the potential to cause abuse. The knowledge of these mechanisms can be used to explain clinical advantages as well as risks of using stimulants.[41,42]

Monoamine Reuptake Inhibition.

The majority of stimulants such as methylphenidate and modafinil operate by blocking the uptake of dopamine and norepinephrine through blockage of DAT and NET transporters. This enhances monoamine levels in the synapses, which enhance the level of attentional control, wakefulness, and the higher cognitive functions. Reuptake inhibition is dose dependent and both therapeutic and reinforcing at both prescribed and abused doses respectively.[43]

Therapeutic Uses

The CNS stimulants are used in a clinical setting to enhance attention, minimize excessive sleepiness, and impose cognitive functions in targeted groups of patients. Their practice in the treatment of various disorders including ADHD and narcolepsy has changed the outcome of treatment allowing improved academic, occupational and social behavior. Besides this, some of the stimulants are also off-labeled or used in a special clinical application to treat fatigue related to neurological illnesses, depression or shift-work schedules. Therapeutic choice is thoughtfully determined by careful evaluation of patient needs, comorbidities and risk factors.[40,44]

ADHD and Narcolepsy

Amphetamine salts and methylphenidate are mostly used to treat ADHD. These agents enhance sustained attention, impulse control and task performance by increasing the activity of catecholamine in the prefrontal cortex. In narcolepsy, modafinil is a type of stimulant used to increase wakefulness, decrease sleep attacks, and enhance the functioning of the day. They are the first-line therapy in each of the conditions when they are used under the supervision of a professional.

Cognitive Enhancers and Fatigue Control.

Stimulants are also applied to improve cognitive functions or fight fatigue, especially in highly stressful

careers or in school. Although modafinil and caffeine might enhance vigilance, attention and mental stamina, their performance differs among people and reduces with extended use. Cognitive enhancement when used non-medically as a form of enhancement has ethical and safety issues because of misuse, psychological dependence, and impaired judgement when over-used.[45]

Side effects and abuse Potential.

Although CNS stimulants have therapy values, they pose serious dangers, particularly when an individual misuses them or their doses are excessive. The side effects are usually insomnia, anxiety, loss of appetite, tachycardia and gastrointestinal discomfort. More severe risks are hypertension, arrhythmia, and psychiatric symptoms provoked by stimulants. This means that they are capable of raising the quantity of dopamine in reward systems, which makes them add to the abuse potential, especially of amphetamines. The misuse may result in dependence, tolerance, and withdrawal syndromes in the long-term, which is why the controlled prescribing and monitoring of the patient are crucial.[46,47]

Cardiovascular Risks

Stimulants enhance the activity of sympathetic nervous system leading to the increase of heart rate, blood pressure, and myocardial oxygen demand. This has the potential to trigger arrhythmias, hypertension or ischemic events in vulnerable individuals. There are also higher-risk groups with the underlying cardiovascular disease, congenital heart defects, or uncontrolled hypertension. Frequent observation and a careful dose is required in order to decrease cardiac complications.

Dependence and Tolerance

The chronic use of stimulants may result in tolerance, where the person involved has to be administered increasing amounts of the drug to maintain the desired therapeutic effect. The dependence is caused by neuroadaptative modifications in the dopaminergic reward systems, and these alterations complicate withdrawal and appear with the withdrawal symptoms, which include exhaustion, depression, and insomnia. Amphetamines have a high potential of abuse especially because of their high reinforcing effects hence the need to ensure controlled usage and following the prescribed regimens.

Side Effects and Abuse Potential.

Although the CNS stimulants are effective in therapy, they have serious risks, particularly when administered wrongly or in large quantities. The negative effects commonly reported are insomnia, anxiety, reduction in appetite, tachycardia and gastrointestinal discomfort. More severe risk factors are high blood pressure, heart rhythm disorder and psychiatric symptoms that are caused by stimulants. They are capable of increasing the levels of dopamine in the reward systems, which increases their potential to be abused especially in the case of amphetamines.[48] Misuse in the long term may result in dependence and tolerance as well as withdrawal syndromes, and thus, should be prescribed carefully and monitored in patients.

Cardiovascular Risks

Stimulants stimulate the work of the sympathetic nervous system, it may raise the heart rate, blood pressure, and the demand of myocardial oxygen. This could trigger arrhythmias, hypertension or ischemic events in vulnerable people. The increased risk groups are individuals who have underlying cardiovascular diseases or cardiac abnormalities and those with uncontrolled high blood pressure. Close balancing and frequent observation are necessary to reduce cardiac complications.[49]

Dependence and Tolerance

Long term use of stimulants may result in tolerance whereby a person needs to take a higher amount to achieve the same therapeutic effect. Dependence is because of neuroadaptive processes in dopaminergic rewards circuits, which result in dependence and withdrawal symptoms, including fatigue, depression, and sleep disturbances. Amphetamines have a high potential of abuse especially because they are highly reinforcing, something that has made it essential to exercise control and follow of regimens.[50]

Analgesics and CNS Pain Modulation

Categorization of Analgesics.

Analgesics refer to medications that help the process of relieving pain by acting on several elements of the nociceptive pathway. They can be categorized into 3 great groups: opioid analgesics, non-opioid analgesics, and adjuvant analgesics. Opioids are known to affect the central opioid receptors and control the sensation of pain, especially in moderate to severe pain. The non-opioid analgesics including NSAIDs and acetaminophen have peripheral or centrally acting mechanisms to inhibit pain mediators such as prostaglandins. Neuropathic or chronic pain may be treated with adjuvant analgesics, firstly meant to treat other conditions, including depression or epilepsy. Knowledge of these classifications will enable clinicians to design pain management approaches according to etiology, intensity of pain and patient profile.[51]

Opioid Analgesics

Opioid analgesics (such as morphine, fentanyl, and oxycodone) are strong medications which are more likely to interact with μ-, 8-, and 9-opioid receptors found in the central nervous system and peripheral receptors. They reduce neuronal excitability, prevent release of neurotransmitters and affect the emotional reaction to pain. Opioids are very effective in acute and cancer pain but have the risks of tolerance, dependence, respiratory depression and misuse. They must be used with caution on

the selection and monitoring of patients to ensure therapeutic advantages are balanced with any harm they cause.[52]

Non-opioid Analgesics (NSAIDs, Acetaminophen).

Some of the non-opioid analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen used in mild to moderate pain. NSAIDs are effective in the treatment of inflammation and pain by inhibiting the enzymes cyclooxygenase (COX) which are involved in the production of prostaglandins. Low anti-inflammatory effects of acetaminophen are accompanied by central analgesic and anti-pyretic effects and can be used in place of NSAIDs in patients who do not tolerate it. The two classes of drugs are safe, and with proper use, but can lead to gastrointestinal, renal or hepatic adverse effects at high dosage.[53]

Analgesics (Antidepressants, Anticonvulsants)

Antidepressants, anticonvulsants, corticosteroids and some muscle relaxants are adjuvant analgesics that are used in the treatment of neuropathic and chronic pain syndromes. Antidepressants (tricyclic and SNRI) and anticonvulsants (gabapentin and pregabalin) increase the activity of the descending inhibitory route, and decrease hyperexcitability in neurons via calcium channels, respectively. These medications are critical where standard painkillers are ineffective in giving relief particularly in neuropathic pain, fibromyalgia and chronic musculoskeletal pains.[54]

Mechanism of Pain Sensation and Medication.

The process of perception of pain is a complex process that involves a series of physiological activities, which include transduction, transmission, modulation and perception. The peripheral tissues have nociceptors that sense harmful stimuli and pass the signal to the brain and spinal cord. Analgesic drugs have various levels of action along this path: at the periphery, they prevent the release of inflammatory mediators, at the spinal cord, they prevent neurotransmission, and at the central centres, they change the perception of pain. Knowledge of these mechanisms assists in rational choice of drug to use in various types and levels of pains.[55]

Spinal cord and Brainstem Pathways.

Nociceptive signals are observed in the dorsal horn where they are inhibited by the activity of inhibitory interneurons on ascending pain pathways. The pathways leading down to the brainstem, including the ones that start in the periaqueductal grey and the rostral ventromedial medulla, also control the sensation of pain by either activating or inhibiting the transmission through the spinal system. Most analgesic medications, such as opioids and antidepressants, stimulate or suppress some of these inhibitory routes or facilitation loops, respectively, which minimize the intensity of pain.[56]

Table 1: Classification of CNS Pharmacological Agents.

Class	Examples	Primary Action	Clinical Use
CNS Depressants	Benzodiazepines, Barbiturates, Z-drugs	Enhance GABAergic inhibition	Sedation, anxiety, insomnia
CNS Stimulants	Amphetamines, Methylphenidate,	Increase catecholamine levels	ADHD, narcolepsy
Antiepileptic Drugs	Valproate, Carbamazepine	Stabilize neuronal membranes	Seizure disorders
Psychotropics	SSRIs, Antipsychotics, Mood stabilizers	Modulate monoamine systems	Depression, schizophrenia, bipolar disorder
Analgesics	Opioids, NSAIDs, Acetaminophen	Inhibit nociceptive transmission	Acute and chronic pain
Neurodegenerative Therapies	L-DOPA,	Enhance dopaminergic/cholinergic function	Parkinson's, Alzheimer's

Table 2: Comparison of Sedative-Hypnotic Drugs

Drug Class	Mechanism of Action	Duration	Clinical Use	Side Effects / Risks
Benzodiazepines	GABA-A receptor positive allosteric modulator	Short to long	Anxiety, insomnia, seizures	Tolerance, dependence, sedation
Barbiturates	Prolong GABA-A Cl^- channel opening	Long	Anesthesia	Respiratory depression, overdose risk
Z-drugs	Selective α1 subunit of GABA-A receptor	Short	Short-term insomnia	Complex sleep

Table 3: CNS Stimulants – Mechanisms and Clinical Uses

Drug	Mechanism of Action	Main Use	Abuse Potential
Amphetamines	Increase release of dopamine/norepinephrine	ADHD, narcolepsy	High
Methylphenidate	Inhibits reuptake of dopamine and norepinephrine	ADHD	Moderate

Modafinil	Weak dopamine reuptake inhibitor, affects orexin system	Narcolepsy, shift work disorder	Low
Caffeine (Xanthine)	Adenosine receptor antagonist, increases neuronal firing	Alertness, fatigue relief	Low–Moderate

Figure 1: General Principles of CNS Pharmacology

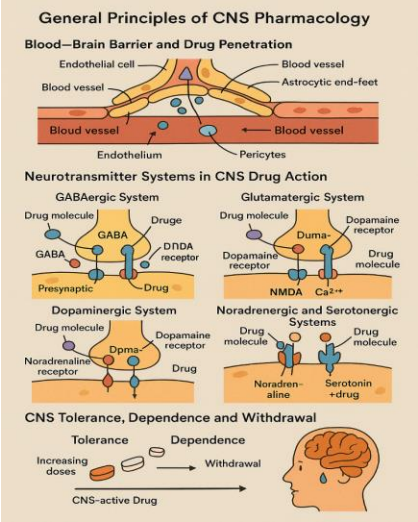


Figure 2: Analgesics and CNS Pain Modulation

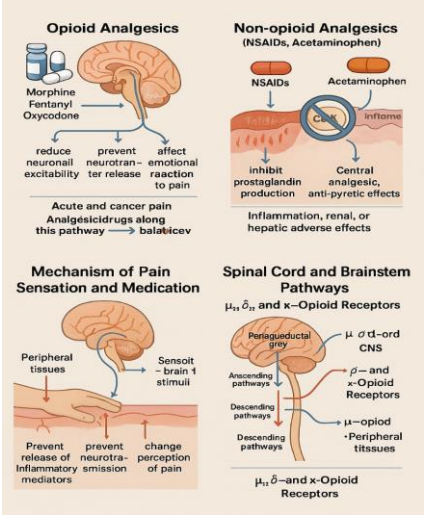


Figure 3: Clinical Applications and Guidelines

CONCLUSION

Sedative, stimulant, and analgesic drugs remain fundamental components of modern CNS pharmacotherapy, playing crucial roles in managing anxiety, sleep disorders, attention deficits, and pain. While these agents provide significant therapeutic benefits, their use requires careful consideration of safety issues such as tolerance, dependence, misuse, and adverse neurological effects. Advances in neuroscience have led to the development of novel therapies including orexin receptor antagonists, non-opioid analgesics, and psychedelic-assisted treatments, offering promising alternatives to traditional medications. Additionally, emerging drug-delivery technologies such as nanocarriers are improving the ability of drugs to cross the blood–brain barrier and target specific brain regions. Despite these innovations, challenges such as polypharmacy, long-term safety, and patient adherence remain important concerns. Future CNS pharmacotherapy will increasingly rely on personalized medicine, pharmacogenomics, and improved therapeutic monitoring to enhance efficacy, safety, and patient quality of life.

REFERENCES:

1. Cheng T, Xu Z, Ma X. The role of astrocytes in neuropathic pain. *Front Mol Neurosci*. 15, 2022.
2. Zhang Y, Wang Z, Xu F, Liu Z, Zhao Y, Yang LZ, et al. Progress of astrocyte-neuron crosstalk in central nervous system diseases. *Neurochem Res*. 49, 2024, 3187-3207.
3. Tateiwa H, Evers AS. Neurosteroids and their potential as a safer class of general anesthetics. *J Anesth*. 38, 2024, 261-274.
4. Alrouji M, Al-Kuraishy HM, Al-Gareeb AI, Alshammari MS, Alexiou A, Papadakis M, et al. Role of uric acid in neurodegenerative diseases, focusing on Alzheimer and Parkinson disease: a new perspective. *Neuropsychopharmacol Rep*. 44, 2024, 639-649.
5. Ferrillo M, Giudice A, Marotta N, Fortunato F, Di Venere D, Ammendolia A, et al. Pain management and rehabilitation for central sensitization in temporomandibular disorders: a comprehensive review. *Int J Mol Sci*. 23, 2022, 12164.
6. Nath A, Choudhari SG, Dakhode SU, Rannaware A, Gaidhane AM. Substance abuse amongst adolescents: an issue of public health significance. *Cureus*. 14, 2022.
7. Vishwas S, Gulati M, Baishnab S, Awasthi A, Kapoor B, Kumar A, et al. Expanding the arsenal against Huntington's disease-herbal drugs and their nanoformulations. *Curr Neuropharmacol*. 19, 2021, 957-989.
8. Halder SK, Sapkota A, Milner R. The importance of laminin at the blood-brain barrier. *Neural Regen Res*. 18, 2023, 2557-2563.
9. Halder SK, Sapkota A, Milner R. The impact of genetic manipulation of laminin and integrins at the blood-brain barrier. *Fluids Barriers CNS*. 19, 2022.
10. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation and drug delivery. *Signal Transduct Target Ther*. 8, 2023.

11. Raiteri L. Interactions involving glycine and other amino acid neurotransmitters: focus on transporter-mediated regulation of release and glycine-glutamate crosstalk. *Biomedicines*. 12, 2024, 1518.
12. Ali DN, Ali HM, Lopez MR, Kang S, Choi DS. Astrocytic GABAergic regulation in alcohol use and major depressive disorders. *Cells*. 13, 2024, 318.
13. Lozano J, Fabius S, Fernández-Ciganda S, Urbanavicius J, Piccini C, Scorza C, et al. Beneficial effect of GABA-producing Lactiplantibacillus strain LPB145 isolated from cheese starters evaluated in anxiety- and depression-like behaviours in rats. *Benef Microbes*. 15, 2024, 465-479.
14. Doyno CR, White CM. Sedative-hypnotic agents that impact gamma-aminobutyric acid receptors: focus on flunitrazepam, gamma-hydroxybutyric acid, phenibut, and selank. *J Clin Pharmacol*. 61 Suppl 2, 2021.
15. Rana V, Ghosh S, Bhatt A, Bisht D, Joshi G, Purohit P. N-methyl-D-aspartate receptor antagonists and their pharmacological implication: a medicinal chemistry-oriented perspective outline. *Curr Med Chem*. 31, 2024, 4725-4744.
16. Ladagu AD, Olopade FE, Adejare A, Olopade JO. GluN2A and GluN2B N-methyl-D-aspartate receptor subunits: their roles and therapeutic antagonists in neurological diseases. *Pharmaceuticals*. 16, 2023, 1535.
17. Liu Z, Cheung HH. Stem cell-based therapies for Parkinson disease. *Int J Mol Sci*. 21, 2020, 8060.
18. Tseilikman VE, Lipatov IA, Novak J, Shatilov VA, Yegorov ON, Aristov MR, et al. Unraveling the serotonergic mechanism of stress-related anxiety: focus on co-treatment with resveratrol and selective serotonin reuptake inhibitors. *Biomedicines*. 12, 2024, 2455.
19. Samanci B, Tan S, Michielse S, Kuijf ML, Temel Y. The habenula in Parkinson's disease: anatomy, function, and implications for mood disorders - a narrative review. *J Chem Neuroanat*. 136, 2024, 102392.
20. Niebergall EB, Weekley D, Mazur A, Olszewski NA, Deschepper KM, Radant N, et al. Abnormal morphology and synaptogenic signaling in astrocytes following prenatal opioid exposure. *Cells*. 13, 2024, 837.
21. Ettcheto M, García ML, Busquets O, Folch J, Beas-Zarate C, Olloquequi J, et al. Benzodiazepines and related drugs as a risk factor in Alzheimer's disease dementia. *Front Aging Neurosci*. 11, 2020.
22. Osler M, Jørgensen MB. Associations of benzodiazepines, Z-drugs, and other anxiolytics with subsequent dementia in patients with affective disorders: a nationwide cohort and nested case-control study. *Am J Psychiatry*. 177, 2020, 497-505.
23. Agatonovic-Kustrin S, Morton DW, Gegechkori V, Kustrin E. Anxiolytic terpenoids and aromatherapy for anxiety and depression. *Adv Exp Med Biol*. 1260, 2020, 283-296.
24. Lumley LA, Marrero-Rosado B, Rossetti F, Wasterlain CG, Schultz CR, Stone MF, et al. Combination of antiseizure medications phenobarbital, ketamine, and midazolam reduces soman-induced epileptogenesis and brain pathology in rats. *Epilepsia Open*. 6, 2021, 757-769.
25. Ríos JL, Schinella GR, Moragrega I. Phenolics as GABAA receptor ligands: an updated review. *Molecules*. 27, 2022, 1770.
26. Sousa Martins Silva A, De Azevedo Marques Périco C, De Mendonça GPRR, Ventriglio A, Paiva HS, Galvão LP, et al. Benzodiazepines and sleep architecture: a systematic review. *CNS Neurol Disord Drug Targets*. 22, 2023, 172-179.
27. Wichniak A, Jarema M, Wierzbicka A. Treatment of insomnia - effect of trazodone and hypnotics on sleep. *Psychiatr Pol*. 55, 2021, 743-755.
28. Chiu HY, Lee HC, Liu JW, Hua SJ, Chen PY, Tsai PS, et al. Comparative efficacy and safety of hypnotics for insomnia in older adults: a systematic review and network meta-analysis. *Sleep*. 44, 2020.
29. Soong C, Burry L, Greco M, Tannenbaum C. Advise non-pharmacological therapy as first line treatment for chronic insomnia. *BMJ*. 372, 2021, n680.
30. Gidal B, Detyniecki K. Rescue therapies for seizure clusters: pharmacology and target of treatments. *Epilepsia*. 63, 2022.
31. Thompson SM. Modulators of GABAA receptor-mediated inhibition in the treatment of neuropsychiatric disorders: past, present, and future. *Neuropsychopharmacology*. 49, 2023, 83-95.
32. Cosci F, Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychother Psychosom*. 89, 2020, 283-306.
33. Zhang MM, Tan X, Zheng YB, Zeng N, Li Z, Horowitz MA, et al. Incidence and risk factors of antidepressant withdrawal symptoms: a meta-analysis and systematic review. *Mol Psychiatry*. 30, 2024, 1758-1769.
34. Phelan EA, Tannenbaum C, Williamson BD, Cook AJ, Turner JP, Balderson BH, et al. Reducing central nervous system-active medications to prevent falls and injuries among older adults. *JAMA Netw Open*. 7, 2024, e2424234.
35. Fu JL, Perloff MD. Pharmacotherapy for spine-related pain in older adults. *Drugs Aging*. 39, 2022, 523-550.
36. Ornoy A, Koren G. The effects of drugs used for the treatment of attention deficit hyperactivity disorder on pregnancy outcome and breast-feeding: a critical review. *Curr Neuropharmacol*. 19, 2021, 1794-1804.
37. Miskowiak KW, Obel ZK, Guglielmo R, Bonnin CDM, Bowie CR, Balanzá-Martínez V, et al. Efficacy and safety of established and off-label ADHD drug therapies for cognitive impairment or attention-deficit hyperactivity disorder symptoms in bipolar disorder: a systematic review by the ISBD targeting cognition task force. *Bipolar Disord*. 26, 2024, 216-239.

38. Ronnebaum S, Patel D, Lucas E, Kratochvil D, Bujanover S, Bron M, et al. Indirect treatment comparison of solriamfetol, modafinil, and armodafinil for excessive daytime sleepiness in obstructive sleep apnea. *J Clin Sleep Med*. 17, 2021, 2543-2555.
39. Dominic P, Patterson JC, Kevil CG, Gopinathannair R, Goeders NE, Olshansky B, et al. Stimulant drugs of abuse and cardiac arrhythmias. *Circ Arrhythm Electrophysiol*. 15, 2021.
40. Ferreira M, Carvalho F, Costa VM, Meisel A, Carneiro P, Capela JP. Amphetamine and methylphenidate potential on the recovery from stroke and traumatic brain injury: a review. *Rev Neurosci*. 35, 2024, 709-746.
41. Hoxhaj D, Bonanni E, Pascazio A, Siciliano G, Ricci G, Fabbrini M, et al. Excessive daytime sleepiness in myotonic dystrophy: a narrative review. *Front Neurol*. 15, 2024.
42. Sakurai T, Yanagisawa M, Saito YC. Interaction between orexin neurons and monoaminergic systems. *Front Neurol Neurosci*. 45, 2021, 11-21.
43. Plumber N, Majeed M, Gorantla VR, Ziff S, Bolla SR, Thomas SE. Stimulant usage by medical students for cognitive enhancement: a systematic review. *Cureus*. 13, 2021.
44. 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*. 13, 2021, 75-91.
45. Schifano F, Napoletano F, Sharif S, Catalani V, Corkery JM, Fergus S, et al. Benefits and harms of smart drugs in healthy individuals. *Drugs*. 82, 2022, 633-647.
46. Chiappini S, Gramuglia PD, Mosca A, Cavallotto C, Miuli A, Corkery JM, et al. Methylphenidate abuse and misuse in patients affected with a psychiatric disorder and a substance use disorder: a systematic review. *Front Psychiatry*. 15, 2024.
47. Belfiore CI, Lopis A, Galofaro V, Denaro V, Tringali I, Cotroneo D, et al. A multi-level analysis of biological, social, and psychological determinants of substance use disorder and co-occurring mental health outcomes. *Psychoactives*. 3, 2024, 194-214.
48. Poyatos L, Muga R, Torres A, Hladun O, Fuster D, Pérez-Mañá C, et al. Abuse potential of cathinones in humans: a systematic review. *J Clin Med*. 11, 2022, 1004.
49. Wang J, Huang P, Yu Q, Lu J, Liu P, Yang Y, et al. Epilepsy and long-term risk of arrhythmias. *Eur Heart J*. 44, 2023, 3374-3382.
50. Moran M, Smith DE, Badgaiyan S, Badgaiyan RD, Blum K, Fynman P, et al. High genetic addiction risk score in chronically prescribed severe chronic opioid probands attending multi-pain clinics: an open clinical pilot trial. *Mol Neurobiol*. 58, 2021, 3335-3346.
51. Zhou M, Chang H, Zhang D, Fang Y, Guo Y, Wu J. Adenosine signaling mediate pain transmission in the central nervous system. *Purinergic Signal*. 19, 2022, 245-254.
52. Abdel Shaheed C, Hayes C, Maher CG, Ballantyne JC, Underwood M, McLachlan AJ, et al. Opioid analgesics for nociceptive cancer pain: a comprehensive review. *CA Cancer J Clin*. 74, 2023, 286-313.
53. Spence JD, Fitzgerald GA, Grosser T. Acetaminophen, nonsteroidal anti-inflammatory drugs, and hypertension. *Hypertension*. 79, 2022, 1922-1926.
54. Robinson C, Dalal S, Mahmood S, Hasoon J, Kaye AD, Orhurhu V, et al. A look at commonly utilized serotonin noradrenaline reuptake inhibitors in chronic pain. *Health Psychol Res*. 10, 2022, 1.
55. Wang M, Thyagarajan B. Pain pathways and potential new targets for pain relief. *Biotechnol Appl Biochem*. 69, 2020, 110-123.
56. Nguyen E, Smith KM, Cramer N, Holland RA, Bleimeister IH, Flores-Felix K, et al. Medullary kappa-opioid receptor neurons inhibit pain and itch through a descending circuit. *Brain*. 145, 2022, 2586-2601.