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Exploring the Landscape of Alertness-Enhancing Drugs: A Contemporary Review

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Abstract: *This review paper explores the multifaceted concept of alertness, encompassing its diverse meanings, connections with wakefulness, general mechanisms of action of alertness-producing drugs. Alertness spans a continuum from heightened vigilance to a state of overall readiness, and its nuanced interpretations are examined across various disciplines, neurobiology. The paper critically analyzes the existing literature on alertness-producing drugs, ranging from traditional stimulants like caffeine to modern pharmaceuticals like modafinil. The mechanisms of action, efficacy, and potential side effects associated with these drugs are scrutinized. Additionally, natural compounds and herbal remedies acknowledged for their impact on alertness are explored. The review delves into the interplay between alertness and wakefulness, shedding light on their connections and distinctions. By synthesizing knowledge from theoretical frameworks to practical applications, this review serves as a comprehensive resource for researcher and individuals interested in the multifaceted nature of alertness and the pharmacological tools available for its modulation*

Keywords: Alertness, Caffiene, Modafinil, Vigilance, Wakefulness

I. INTRODUCTION

The idea of "smart pills"—medication that could improve cognitive function and increase productivity—has gained a lot of attention lately. The idea of utilising medications to increase brainpower is not new, though. People used to rely on caffeine and nicotine to stay awake and attentive in the past when they had a lot of work to complete and short deadlines.[1] Different mental abilities, such as thinking, learning, language, reasoning, attention and focus, and visuospatial ability, are typically referred to as cognitive functioning.In order to carry out daily tasks, one needs to have good cognitive health, which refers to the capacity for clear thinking, learning, and memory. Only a small portion of overall brain health is cognitive.Human cognition can be conscious or unconscious, concrete or abstract, intuitive (such as linguistic understanding) or conceptual (such as a model of a language). It includes a wide range of cognitive processes and abilities, including comprehension and language production as well as attention, knowledge development, memory and working memory, judgement, and assessment. Although traditionally regarded of as a non-cognitive process, there is now a great deal of study being done on the cognitive psychology of emotion. This review also focuses on metacognition, or the understanding of one's own tactics and ways of cognition and various wakefulness promoting drugs, how they act and their doses.

Cognitive processes both produce new knowledge and employ current knowledge.Cognitive functions refer to the mental processes we use to understand and interact with the world. They are interconnected and sometimes overlap. The main cognitive functions include:

1. Attention: Selecting relevant stimuli from the environment and internal thoughts or emotions to perform tasks effectively.

- Focused Attention: Being alert and responsive to a stimulus.
- Sustained Attention: Maintaining focus for at least 3 minutes (concentration). Selective Attention: Concentrating on a task while ignoring distractions.
- Alternating Attention: Shifting focus between tasks.
- Divided Attention: Handling multiple tasks simultaneously.[2]

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2. Reticular Activating System (RAS) or Arousal System: Optimizes processing of sensory stimuli in the cerebral cortex, involving various brain structures like the reticular activation system, thalamus. limbic system, basal ganglia, and frontal cortex.

3. Posterior Attention System: Guides orientation and localization of stimuli, especially visual ones. Involved in perception, visual-spatial attention, and processing new information. Key structures: posterior parietal cortex, lateral pulvinar, hippocampus, and anterior cingulate

4. Anterior Attentional System: Enables directing attention to specific actions and supports complex cognitive tasks. Components: anterior cingulate, dorsolateral prefrontal cortex, orbital- frontal cortex, neostriatum, supplemental motor area, and ventral tegmental area.

These cognitive functions rely on various brain circuits and structures working together to support mental processes and interactions with the world. [3]

Several significant cognitive processes of the brain, including but not limited to perception, attention, memory, motor abilities, and language, are briefly outlined in Table 1.

Table 1: Cognitive Development

Cognitive Ability	Detailed Description
Perception	Smell, touch, hearing, and other sensory stimuli are recognised and interpreted.
Attention	Ability to balance competing demands in our surroundings and the ability to maintain concentrate on a certain item, task, or thinking.
Memory	Working memory and long-term memory both have a finite amount of storage.
Motor Skills	Ability to move our bodies and muscles, as well as our ability to control objects
Language	Abilities that enable us to convert sounds into words and produce verbal output.
Visual and Spatial Processing	The capacity to interpret visual input, comprehend the spatial relationships between objects, and visualise scenarios and imagery.
Executive Functions	Abilities, such as the capacity to organise and carry out a goal, that support goal-oriented behaviour. These consist of: • Flexibility: The ability to swiftly shift to the proper mental mode. • Theory of mind: understanding of the thoughts, aspirations, and preferences of others. • Anticipation: a pattern-based prediction method. • Determining the problem accurately will help you produce potential solutions and select the best one. • Decision-making skills: the capacity to choose based on problem-solving, partial information, and emotions (both our own and those of others). • Emotional self-regulation: the capacity to recognise and control one's own feelings in order to perform well. • Sequencing: The capacity to divide complicated acts into digestible chunks and order them appropriately. • Inhibition: the capacity to endure external and internal distractions

II. DETAILED DESCRIPTION TO ALERTNESS

Alertness, vigillence, arousal, attention, and wakefulness are the common terms used to define the Cognitive function. Recent research examines attention-related symptoms in traumatic brain injury and cross-cultural variations. The complex relationship between attention and consciousness is a recurring topic in philosophy, relevant to mental health, consciousness disorders, and artificial intelligence. Alertness refers to the condition of being awake, aware, attentive, and prepared to take action or respond. Research on attention has defined alertness as achieving and maintaining a state of vigilance to adequately respond to specific stimuli. Additionally, alertness may also encompass a subjective feeling of being attentive. In the context of IIL response literature, "alertness" is typically operationally defined by observable task performance, such as faster reaction times in various cognitive tasks, or by subjectively assessing an individual's current state of wakefulness. [4, 5, 6]

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In addition to overtly rewarding or motivating qualities, several cognitive features of the stimuli also have an impact on vigilance. For instance, signal modality, strength, length, background, event rate, signal likelihood, and regularity are psychophysical aspects of external stimuli that influence alertness. Additional psychological factors crucial to the vigilance decline include executive attention as assessed by working memory load or cognitive control. Vigilance executes may also affect criteria for decision-making responses. [7]

Alertness and arousal are different in nature: alertness relates to cognitive aspects, while arousal encompasses a wider range, including peripheral physiological states and forebrain activation. However, they are connected as heightened physiological arousal often accompanies cognitive alertness.[8]Alertness, arousal, and vigilance are distinct cognitive states. Vigilance involves focused readiness to detect and respond to specific stimuli, often heightened by warnings. This increased preparedness is akin to an elevation in vigilance. On the other hand, alertness is at more generalized state of readiness, not limited to any particular event. [8]

Disrupted work schedules often lead to sleep disturbances and excessive sleepiness.Human factors are playing a bigger role in road accidents, which is happening more frequently. The most frequent causes of accidents, out of all the contributing factors, are exhaustion and sleepiness behind the wheel. Drivers' performance suffers and accident risk rises as a result of both circumstances' reductions in attention. Drivers frequently struggle to notice their level of alertness declining. [9]

This, in turn, raises the risk of accidents. Anecdotal evidence suggests that persons who naturally choose the boost provided by stimulants may take cognitive enhancers more frequently since their working hours are long and their professional environment is supportive of substance use. [1] Alertness producing agents are also given in diseased condition like alzimer, schizophrenia chronic fatigue condition, disorder of consciousness, depression etc. To counter fatigue at work, strategies such as improved work scheduling, napping, manipulating the circadian phase through light exposure, or using alertness-enhancing drugs are employed. This drugs are often prescribed depending on the specific condition required. They might include smart pills, nootropic drugs, cognitive enhancers, or brain tonics. Caffeine may boost cognition. Yet, due to mounting pressures, people are turning to prescription drugs like modafinil and methylphenidate, amphetamines, especially for narcolepsy and ADHD, replacing or complementing readily available stimulants, but inappropriate use of stimulants for cognitive improvement in the medical industry can result in addiction and an exaggerated view of one's own talents, which puts patients at risk.The key question is whether these drugs make the brain work better or just bring it back to normal when it's tired from lack of sleep. Substances that boost dopamine, noradrenaline, and glutamate can increase activity in the memory and learning parts of the brain, potentially making healthy people smarter than their usual selves. The most common drugs for this are modafinil and methylphenidate, both of which boost these brain chemicals.[1] The use of herbal cognitive enhancer are also taken account for their long term effect. Natural cognitive enhancer can be consumed as entire foods, plants, tablets, capsules, powders, or even in these forms. Natural nootropics have less of a physiological danger of adverse effects because they are sources of nutrition that have changed over time and have been consumed by people for thousands of years. In general, natural nootropics tend to complement your body's functions.The main advantage of utilising natural nootropics, such as foods and plants, is that they are loaded with a wealth of nutrients. In addition to the substances that improve cognition, foods and herbs also include vitamins, minerals, and phytonutrients that are beneficial for overall health. [11]

The use of "Medhya Rasayanas," a group of medicinal herbs that enhance memory and intelligence, is mentioned in an ancient Ayurvedic medical text from around 6,000 BCE.[12] Some plants belonging to this category are Ashwagandha (Withania somnifera), Brahmi (Bacopa monnieri), and Jyotimatr[13]

III. GENERAL MECHANISM OF ACTION

Cognitive enhancer don't directly influence neurotransmitters or receptors but enhance brain oxygen and glucose supply, protect against neurotoxicity, and boost protein and nucleic acid production in neurons. Some also help eliminate harmful molecules, improve blood properties, and enhance brain blood flow. While they're metabolically active, most don't show immediate effects after a single dose; instead, they require extended use for results. Crossing the blood-brain barrier and long-term use are often necessary for stable changes. [14]

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General plan of action

- Support neurotransmitters: Provide the body with what it needs to make neurotransmitters, like acetylcholine, dopamine, norepinephrine, and serotonin. This aids concentration, memory, and focus.
- Regular cardiovascular exercise improves brain oxygen supply, complementing nutritional support for cognitive function. Exercise and nutrition work together for better cognitive health

1. Restoring and enhancing neuro-transimmiters:

Thinking uses up brain chemicals, which, when depleted, reduce mental performance—resulting in difficulty concentrating, slow thinking, and memory problems. Stress makes this depletion worse. To keep your brain sharp, it's vital to replenish these chemicals through diet, potentially boosting mental abilities even as you age.

2. Recreational substance with cognitive enhancement potential:

At incredibly low doses (1 mcg), LSD, a highly restricted substance (Schedule I / Class A), can exhibit effects similar to those of hydergine. However, at doses as low as 20–30 µg (micrograms), it can provide deep experiences and hallucinations, especially at larger concentrations that could cause upsetting "bad trips." Additionally, it could result in flashbacks, strange sensory impressions, and mental changes. A person's personality and perspective on life may undergo long-lasting changes. Conditions like post-LSD psychoses and Hallucinogen Persisting Perception Disorder are linked to LSD and are occasionally linked to 4-methylaminorex.

3. Strategies for alleviating depression, fostering adaptability, and stabilizing mood:

Depression and low mood negatively impact cognitive performance, causing sadness, guilt, helplessness, anxiety, and fear that hinder productive thinking. Apathy, induced by depression, leads to a lack of motivation and the absence of driving moods like curiosity and determination. Symptoms also include disrupted sleep patterns, mental fatigue, energy loss, difficulty concentrating, and a general slowing of cognition. Mitigating these effects enhances intelligence and mental performance, making countering and preventing depression effective cognitive strategies. The strong link between depression and decreased neurotransmitters (dopamine, acetylcholine, and serotonin) in the brain explains why replenishing neurotransmitters alleviates depressive symptoms. Stress exacerbates neurotransmitter depletion, forming a detrimental cycle, emphasizing the value of stress management and anti-stress substances for cognitive enhancement.

"Nootropics like ashwagandha [14] and isothiol [15] have demonstrated efficacy in improving depression and stress tolerance by replenishing specific neurotransmitters. Ashwagandha, an adaptogen, serves as a stress-reducing tonic, while isothiol, a B-vitamin-like chemical, exhibits anti-anxiety properties by enhancing GABAA receptor binding. Inositol, another nootropic, acts as an alternate energy source for the brain and muscles and is beneficial for providing a sugar high without the subsequent low.

Theanine and theophylline, present in tea, enhance alert relaxation through alpha waves, reducing tension. The amino acid theanine in tea increases dopamine and serotonin levels in the brain, promoting alertness relaxation based on alpha waves.[15]

4. Cognitive flexibility, Focus, Endurance, and Concentration:

Caffeine boosts focus and creativity but hinders memory encoding and may induce nervousness. It's a widely used psychoactive substance found in coffee beans, which also provide antioxidants. Nicotine aids concentration but has a side effect known as the stimulus barrier rebound effect.

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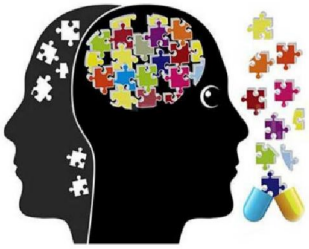

Fig. 1 Effect of Alertness Producing Drugs on Brain Health

IV. UNVEILING THE POWER OF HERBAL AND SYNTHETIC DRUGS

Herbal remedies exert diverse effects on the physiological system, whereas pharmaceutical treatments are more focused on specific diseases. Some plant medicines mimic the properties of pharmaceuticals, displaying "drug-like" characteristics.

Herbal remedies, though generally gentler with a focus on healing, can lead to mishaps due to misidentification of plants and improper handling or administration. These issues often arise when naturopathic practitioners lack adequate training.Despite the fact that synthetic pharmaceuticals are relatively new in Western medicine, we trust them more than traditional medicines that have been used for thousands of years. This is because our knowledge of them and how they affect the body has grown significantly.

Compared to natural medications, synthetic drugs are more standardised. Strict standard operating procedures are followed in their preparation, ensuring that every batch is of the same quality as the last.

As a result, batches of herbal medication may differ in quality because producers are not required to adhere to the same set criteria, even though some are in place throughout Asia. The manufacturing process of a herbal medication involves numerous factors, such as:

The identification of plants and the methods used in their parts' extraction growth circumstances influenced by climate.

Herbal medications, with their multifunctional effects, are underexplored for safety and effectiveness. Public perception, supported by statistics, suggests that natural products are safer than synthetic pharmaceuticals. In the US, adverse effects of synthetic drugs lead to 8% of hospital admissions

V. WHAT IS ENHANCED?

Cognitive neuromodulators, such as dopamine and serotonin, are not exclusively linked to specific cognitive functions. While dopamine is associated with working memory and attention, other neurotransmitters like noradrenaline and acetylcholine also impact working memory. Affective processing, typically linked to serotonin, is also influenced by dopamine. Establishing a direct correlation between a single neurotransmitter and a broadly defined cognitive function, like working memory, becomes implausible.

Evidence suggests that neurotransmitters may function differently when delivered in a prolonged (tonic) versus a brief (phasic) manner. For instance, in the noradrenergic cells of the locus coeruleus, different levels of alertness lead to varied baseline firing patterns. Phasic firing in these cells is linked to optimal reactions to significant environmental events, occurring only at moderate tonic activity levels. Therefore, adjusting overall neurotransmitter concentrations may impact the ability to respond to external stimuli through phasic firing.

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How do performance enhancers work? Do they influence diverse cognitive processes or target specific mechanisms like arousal or sustained attention? Investigating in clinical populations is complex, as standard cognitive test batteries in trials may lack sensitivity for specific cognitive modulation inquiries.

Modafinil is popular for enhancing cognitive function and treating narcolepsy. It improves attention, memory, and executive function, particularly in sleep-deprived individuals. Caffeine also enhances performance, possibly due to increased alertness or arousal. Arousal is diverse, selectively regulated by various pharmacological interventions. Neuroimaging studies can help identify mechanisms behind improved mental performance, including arousal, on cognitive tests. [29]

Table 2: Alertness Producing Drugs

Alertness enhancer	**Cognitive functions improved**
Modfinil	Working memory, Episodic memory, Attention
Caffeine	Vigilance, working memory, incidental learning
Methylphenidate, amphetamine	Response inhibition, working memory, attention, vigilance
Memantine	Episodic memory, attention
Pemoline	Vigilance, working memory, incidental learning, Attention
Selegiline	Alertness, Attention
Pitolisant	Alertness, Attention
Atomoxetine	Response inhibition, working memory, attention
Rivastigmine (AChEI	Episodic memory, attention

Amphetamine

Frequent or persistent use of psychotropic medications, like amphetamine and caffeine, can pose issues despite their history as anti-fatigue or alertness-enhancing agents. One kind of phenylethylamine is amphetamine, which is a stimulant, because amphetamine prevents norepinephrine and dopamine from being reabsorbed, it keeps people awake by stimulating the release of catecholamines that are stored in neural cell vesicles. [16]When the desired effects of amphetamine wear off, though, it has a negative rebounding effect that results in anxiety or depression. [17] Amphetamine is utilised in therapeutic settings to treat hypnolesy, attention deficit hyperactivity disorder (ADHD), chronic fatigue syndrome, and traumatic brain injury [18,19,20]. In addition, it is prescribed illegally as a waking medicine for everyday use or as a mood booster. Since amphetamine is very effective and long-lasting, it is frequently utilised; yet, when abused, it turns into a highly addictive drug with a quick tolerance rate and growing dependence. [21]

Caffeine

There has long been a history of using caffeine, a methyl xanthine derivative, as a psychoactive stimulant. Caffeine half-lives in healthy adults are five hours, and for women who are pregnant or taking birth control, they can even be eleven hours. [22]Study was conducted on combination of caffeine and L-theanine it was found that the combination of L-theanine and caffeine decreased subjective weariness, enhanced cognitive performance in terms of task switching performance, and self-reported alertness. This result is consistent with that of Haskett et al. [23], who reported that taking 250 mg of L-theanine and 150 mg of caffeine together led to improved alertness and decreased fatigue.

Caffeine's impact on performance can vary based on the type of cognitive task and the subject's level of alertness at baseline.Although caffeine is a well-known psychostimulant, additional research is needed to determine how it affects users who use it frequently.It appears that short- to medium-term work and infrequent use are the best uses for caffeine. [24]

Modafinil

Modafinil, a schedule 5 stimulant used in South Africa for narcolepsy-related daytime sleepiness, enhances wakefulness. Its mode of action is unclear, but it impacts various brain pathways, possibly boosting cortical activation. Unlike other CNS stimulants like cocaine or amphetamine, modafinil induces psychoactive effects, altering mood,

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perception, and thinking. [26]According to the scant research on alert normal, a 200 mg dose can maximally promote attentiveness, with a peak impact occurring in the fourth hour. Modafinil significantly increased subjective alertness without producing euphoria in a trial examining the effects of 300 mg modafinil, 300 mg caffeine, and 15 mg D-amphetamine given in a single dose at 9:OO to normal (non-sleep-deprived) participants[24, 27]

Since most nations do not record modafinil, it is premature to consider using it regularly to improve alertness.The initial results need to be verified by other research. Regarding effects on real-life performance, there are also no findings at all.With minimal toxicity and no abuse potential, a 200 mg dose would have a noticeable impact on alertness and performance. In most cases, modafinil is a better option than amphetamine when seeking increased alertness, according to the evidence that is currently available. [17, 24]

Methylphenidate

The sole stimulant approved for use in treating ADHD in South Africa is methylphenidate, available in short-, intermediate, and long-acting formulations. [27] It is believed to enhance the release of monoamines into the extra neuronal space and inhibit the reuptake of dopamine and noradrenaline into the presynaptic neuron. The main way that methylphenidate affects cognition is by raising these catecholamine levels in the prefrontal cortex and the cortical and subcortical areas that project to it. It is believed that this process is what helps people with ADHD think and behave better. The sympathetic nervous system is activated, resulting in elevated blood pressure and heart rate, among other physical symptoms.

Pleasure and the possibility of reliance are produced by the activation of the brain's reward system, which includes the ventral striatum and the nucleus accumbens. Although methylphenidate has been shown to improve learning, working memory, and cognitive control, it is unclear if these benefits result in true increases in cognition. [26, 30]

Pemoline

Oxizolidines include pemoline. It is limited aqueous and lipid solubility causes it to be absorbed slowly in the gastrointestinal tract. Pemoline has also primarily been investigated for the treatment of sleep disorders including narcolepsy, similar to modafinil.Because of its dopamine-like characteristics, pemoline's activity has been investigated in the past to learn more about how dopaminergic systems regulate nocturnal sleep as well as daytime alertness and performance.Nicholson and Pascoe's [31] study is a significant one in this field. They used 2, 4, and 6 mg of pimozide, a popular antidopaminergic neuroleptic, together with 30, 60, and 90 mg of pemoline. Pemoline administration led to longer daytime sleep latencies, higher alertness during nocturnal sleep, and enhanced attentiveness, while pimozide administration decreased daytime performance and increased the propensity to fall asleep [24].

Selegiline

Overdrowsiness during the day, which can happen when engaging in tasks like chatting or driving, is known as excessive daytime sleepiness (EDS). EDS decreased quality of life and increased accident risk in PD patients. [32]The selective, irreversible monoamine oxidase type B (MAO-B) inhibitor selegiline helps people with Parkinson's disease (PD) with their motor symptoms, posture, and gait.By promoting alertness, selegiline reduces narcolepsy symptoms in sleep-deprived patients. [33]

Pitolisant

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved modafinil/armodafinil, sodium oxybate, methylphenidate, solriamfetol, pitolisant, and methylphenidate as wake-promoting drugs for narco-lepsy.In addition to these medications, a novel therapeutic class known as histamine H3 receptor (H3R) inverse agonists/antagonists has been created. In the numerous scientific studies demonstrate the significance of cerebral histaminergic neurons in preserving alertness and regulating various other physiological processes, including learning, memory, and attention [34, 35]it is not possible to abuse pitolisant or have psychostimulant effects. The first-in-class H3R antagonist/inverse agonist pitolisant, a wake-promoting medication that lessens the incidence of EDS and cataplexy attacks in narcoleptic patients, has pharmacological, neurochemical, and behavioural characteristics that set it apart from the psychostimulants that are currently on the market. [36]

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VI. CONCLUSION

Distinguishing alertness from related processes like arousal, attention, and vigilance is beneficial. The term "arousal" historically encompassed various activations, but "alertness" refines this notion, adding a valuable dimension to cognitive processing. Phasic and tonic alertness involve diverse neural systems, cautioning against oversimplification. Differentiating vigilance and alertness is essential in studying these states, requiring experimental control and comprehensive parameter reporting. While fatigue and sleepiness share symptoms but differ in causes, subjective and objective measures aid assessment. Adequate sleep is the most effective remedy, and tailoring treatments based on underlying factors is crucial. However, the systematic use of alertness-boosting medications at work lacks conclusive data, with substances like D-amphetamine posing limitations. Medications such as modafinil and pemoline lack proven efficacy in healthy individuals, and the use of caffeine for work-related alertness requires further clarification on dosage and delivery

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