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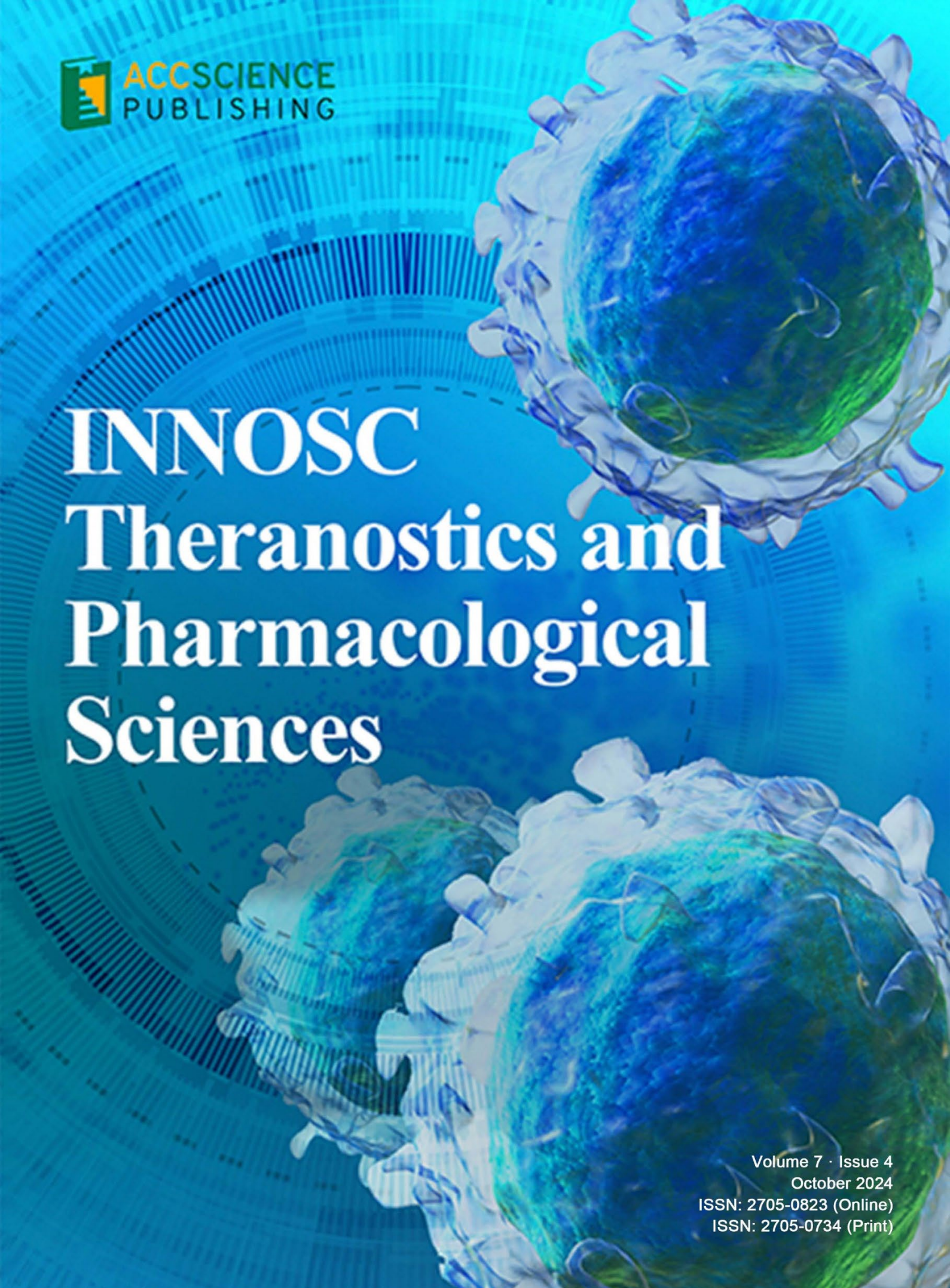

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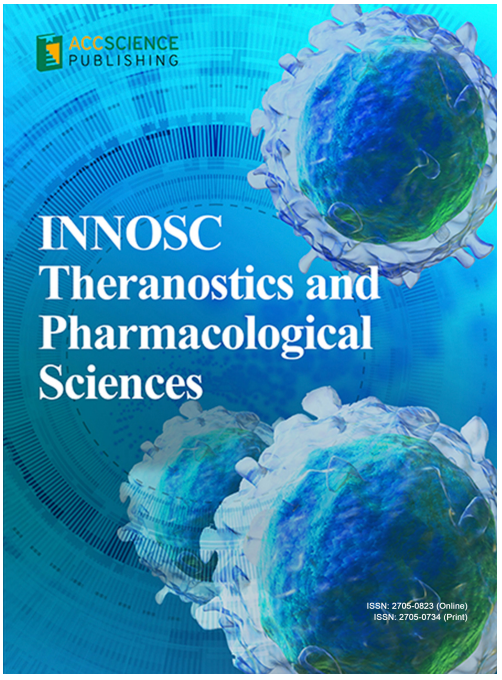

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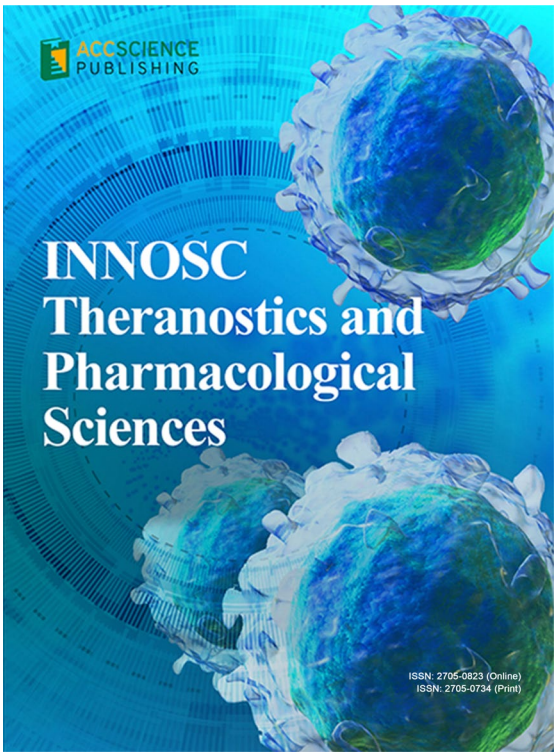

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REVIEW ARTICLE

A narrative review on gender disparities in the pathogenesis and pathophysiology of Takotsubo syndrome: Implications for novel approaches to treatment?

Carola Y. Förster[1]* and Martin J. Herrmann[2]

[1]Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Würzburg University, Würzburg, Germany

[2]Center of Mental Health, Department of Psychiatry and Psychotherapy, University Hospital Würzburg, Würzburg, Germany

Abstract

Takotsubo syndrome is a type of cardiomyopathy characterized by transient and reversible left ventricular wall motion abnormalities within the ventricle. Depending on the severity of the injury, recovery can occur within a few hours or weeks. According to studies, older people are more likely to be affected by it, and the prevalence is particularly high among postmenopausal women. Stress factors, both physical and emotional, are widely discussed and generally recognized as triggers. The hypothalamic-pituitary-adrenal axis and its glucocorticoid-dependent negative feedback also play important roles in the resulting gender-specific immune response. Transcutaneous vagus nerve stimulation is proposed as a potential novel personalized therapeutic strategy in light of the gender disparities in autonomous nervous system activity and inflammatory response. Considering the modifiable risks involved in this pathology, such as stress which affects the heart and psychology, a strong emphasis should be placed on preventive medicine. In this paper, we propose the use of non-invasive (transcutaneous) vagus nerve stimulation, as a means of dampening sympathetic overdrive with negligible side effects.

Keywords: Takotsubo syndrome; Heart-brain; Inflammation; Gender; Central autonomic network; Stress

***Corresponding author:**
Carola Y. Förster
(foerster_c@ukw.de)

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1. Introduction: the heart–brain axis

Cardiovascular system regulation is a part of the modulation of the cortical structure throughout the entire body. Although little is known about the mechanism of the "heart-brain axis," various cardiac and neurological diseases have been implicated as being influenced by one another. Insular cortex (IC), anterior cingulate gyrus, and amygdala comprise the cortical modulation network. The central autonomic nervous system (CAN) is regulated by this network, for example, in response to physical stimuli or emotional stressors like excitement, sadness, or anxiety. Functionally, the IC can be separated into the left insula, which is characterized by the parasympathetic tone and causes the heart rate to drop and the depressor responses to rise, and the right insula,

which is linked to sympathetic dominance and causes the heart rate to rise and pressor responses to rise.[1,2] Along with its reciprocal connections to other brain regions such as the limbic system, the IC is also linked to autonomic, sensory, and motor functions. In a series of studies investigating the functional neuroanatomy of sustained fear, defined as a situation of unpredictable threat over a period of time, the IC was co-activated together with the bed nucleus of the stria terminalis, anterior and posterior cingulate cortex, and the periaqueductal gray in healthy controls[3] as well as anxiety disorder patients.[4,5] According to our current understanding about the cortical modulation network, sympathovagal balance is essential for homeostasis and involves major portions of the IC. An imbalance resulting from a damaged IC affects the cardiovascular system, promoting the development of Takotsubo syndrome (TTS). A middle cerebral artery hemorrhage stroke, sexual hormones such as estrogen or emotional processing are some of the various factors that can cause an interruption of the IC.

Different brain nuclei are known to be activated in response to both physical and psychological stressors. Actually, the neuroendocrine and autonomic nervous systems (CAN) are primarily activated, which results in alterations in behavior.[6] Research utilizing brain functional magnetic resonance imaging to track brain functional connectivity during resting states revealed hypoconnectivity of limbic and central brain regions' parasympathetic and sympathetic associated subnetworks in TTS patients when compared to group controls.[7]

Stress becomes a deleterious factor, in the case of compromised of self-regulation, subjecting the body more susceptible to immune system disease, psychiatric disorder, and cardiovascular disease.[8,9] The paraventricular nucleus of the hypothalamus (PVH), amygdala nuclei, septal-hippocampal complex, parabrachial and raphe nuclei, prefrontal and cingulate cortexes, and locus coeruleus (LC) all play significant roles in the stress response. The hypothalamic-pituitary-adrenal (HPA) axis is stimulated by the signals that follow. The anterior pituitary gland releases adrenocorticotropin hormone (ACTH) in response to the release of the corticotropin-releasing factor (CRF), which is triggered by the PVH in the signaling chain. The adrenal glands then begin secreting glucocorticoid (GC) as a result of ACTH.[10,11] For the coordination of certain physiological systems, CRF is essential because it can be produced both in the peripheral and central nervous systems (CNS). In fact, during stressful situations, CRF plays a crucial role in regulating the sympathetic response brought on by stress and in the peripheral and central release of norepinephrine (NE). It is crucial to note the connection of the alterations in behavior and physiology with the levels of stress experienced. Of note, increased NE synthesis is believed to occur in chronic stress situations when there is a sustained increase in the excitability of the adrenal-medullary axis and the HPA.[12] The issue of whether decreased GC self-regulation in the pituitary and PVH is a major factor in poor stress management emerges. The disruption of negative GC feedback and the resulting prolonged activation and maintenance of elevated systemic GC levels account for the loss of GC self-regulation. The increased availability of these hormones causes alterations in behavior and normal physiology, as well as enhanced activation of the HPA axis in brain structures such as the LC and amygdala.[13-15] Prolonged elevation of systemic GC levels can lead to immunosuppression, as well as facilitate the onset of autoimmune diseases and mood disorders.[16]

In consideration of the above, it is appropriate to discuss the condition of chronic unpredictable mild stress (CUMS). This well-established model explains mood disorders and stress-induced brain plasticity, which are psychological and physical stressors brought on by a brain's inability to adapt to a variety of stressful stimuli that are comparable to stressors encountered in daily life.[17,18] In this context, the connection between loss of HPA self-regulation and NE release is discussed.[19] Using blood samples from TTS patients, a recent study1 was able to demonstrate that patients in various stages of the disease showed several validated biological and psychological indicators of chronic stress, as defined by the trier social stress test.[20] The authors consistently demonstrated the presence of elevated levels of interleukin 6, tumor necrosis factor-α, nuclear factor "kappa-light-chain-enhancer" of activated B-cells, blood cortisol, dehydroepiandrosterone, aldosterone, adrenaline, NE, and dopamine. As a result, chronic psychosocial stress as an underlying factor driving the development of TTS must be recognized.[21]

2. Pathophysiology involving physical and emotional triggers

TTS is believed to be primarily caused by physical and emotional triggers, but psychological and psychosocial stress factors may have a greater influence than previously thought. TTS is associated with several major risk factors.

2.1. TTS triggers

Almost universally, TTS is associated with stress as a major feature of its development. In most cases, an emotional or physical trigger precedes such an event. There is some evidence to suggest that emotional triggers are more prevalent than physical stressors, with the prevalence distribution of these triggers showing gender-specific characteristics. In general, men seem to be more likely to respond to physical events, whereas women are more likely

to be affected by emotional events.[22] By breaking down the total number of TTS cases by gender, it is possible to determine that the notable variation in TTS prevalence between men and women is also a result of the social standing and roles that women play in various nations and cultures. These triggers can happen alone or in combination; for example, a panic attack or an emotional event that follows surgery or an accident can trigger anxiety.

2.1.1. Stressors on an emotional level

Anxiety, fear, anger, earthquakes, floods, interpersonal conflicts, and traumatic experiences are just a few examples of the wide range of emotions and situations that can be described as "stressors".[23-26] An important aspect of this process is the identification of psychological and psychosocial stressors. There is very little information about the living conditions of patients with TTS at the moment. The study by Wallstrom *et al.*[21] examined the psychological and psychosocial stress experienced by postmenopausal women. Many of the patients reported that they felt burdened by responsibility, injustice, and uncertainty long before the onset of TTS. The respondents' defenses were so weakened by this prolonged stress that even minor stressors could cause them to lose their equilibrium. The findings suggest that the respondents' circumstances may also be influenced by the gender-based social structure. The large proportion of female respondents could be a reflection of these factors.

Furthermore, it should be noted that even situations associated with pleasant emotions[27] such as weddings, surprise parties, and employment offers can serve as stressors.[28] These various emotional stressors could all be regarded as TTS triggers. When it comes to stressors, the severity of a single incident or the confluence of multiple relatively insignificant emotions likely matters more than the specific type of emotion.

2.1.2. Stressors on a physical level

The development of TTS is significantly influenced not only by emotional but also by physical stress factors. These physical stressors therefore include incredibly strenuous activities and illnesses, such as surgery,[29] traumatic injuries, radiotherapy,[30] sepsis,[31] or even pregnancy,[32] drug addiction, and disorders of the neurological system. However, the occurrence of TTS has so far been primarily associated with conditions like intracerebral hemorrhage,[33] seizures,[34] stroke,[29] and head trauma.[35]

Moreover, the following two conditions could be linked to TTS:

(i) An adrenal gland's enterochromaffin cells give rise to pheochromocytoma, a neuroendocrine tumor. It has been proposed that catecholamines are released as a result of this illness. The elevated catecholamine level is thought to be the cause of the left ventricular dysfunction, electrocardiogram abnormalities, band necrosis, and hypercontraction of sarcomas that are indistinguishable from TTS.[36]

(ii) Coronary artery disease (CAD), which has a prevalence of 10 – 29%, is frequently linked to TTS. According to some theories, CAD and TTS coexist or CAD even act as a trigger for the development of TTS.[37-39]

3. Gender disparities in TTS

When comparing the gender distribution of TTS cases in the USA, Europe, and Japan, it is important to note that while the percentage of male cases varies from study to study, TTS affects women more often than men.[40] Of note, TTS affects particularly postmenopausal women.[40]

This is in opposition to how the illness manifests itself: accumulating evidence points out that men are frequently more severely affected by TTS than women. Taking into account the gender disparities in the USA, Europe, and Japan, recent reports suggest that women tend to respond more to emotional stressors, while men respond primarily to physical stressors (Figure 1).

Since TTS is a relatively uncommon disease, the only sources of data available at this time are the Tokyo Cardiovascular Care Unit,[40] the International Takotsubo Registry,[22] the US National Inpatient Sample Registry,[41] and the Cardiovascular Research Consortium-8 Universities.[42] Actually, according to the Tokyo Cardiovascular Care Unit, male patients (50%) are more likely than female patients (31.3%) to have experienced prior physical stress. On the other hand, female patients experience emotional stress at a higher rate than male patients (19.0% vs. 31.0%).[40] In detail, according to reports from the International Takotsubo Registry, 29.2% of females and about 14.5%

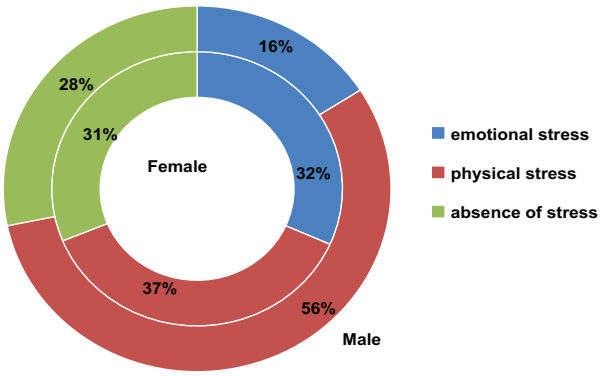

Figure 1. Prevalence of emotion and physical stressors leading to Takotsubo syndrome among female (inner circle) and male individuals (outer circle)

of males developed the disease due to emotional stress, whereas 34.3% of females and 50.8% of males developed TTS through physical stress. This is very similar to the Japanese reports.[42] These reports suggest that women tend to respond more to emotional stressors, while men respond primarily to physical stressors.

As previously mentioned, TTS is mainly explained by stress responses, even though the pathophysiology of TTS is poorly understood. The sexes' varying reactions to stress could be the cause of this. Remarkably, postmenopausal women make up the majority of patients. The effects of estrogen concentration may be more significant than previously believed in relation to their susceptibility to emotional stress as a trigger for TTS, which calls for more research. Women are thought to have stronger immune responses to both self-antigens and foreign invaders. In addition, autoimmune diseases are more common in women than in men. The distinct role that men and women attribute to sex hormones plays an important part in immune cell activity.[43,44] Through the use of experimental rat models, the Cidlowski group demonstrated that there is a gender difference in the prevalence of numerous major diseases that have an inflammatory component. Interestingly, the sex-specific variations in prevalence may be related to a relationship between inflammatory diseases and the sexually dimorphic effects of GC. These findings suggest that while a lack of GC receptors (GR) may contribute to certain diseases in women, GR's anti-inflammatory effects seem to be more potent in men. This has been observed *in vivo* in the liver in a systemic inflammatory sepsis model.[45] This suggests that in homeostatic female mice, a primary mechanism guarantees a quicker reaction to inflammatory stimuli, which in turn leads to a stronger expression of the most prevalent proinflammatory genes.

Apart from emotional stress, postmenopausal women may also be significantly triggered by behavioral stress reactions, psychological stress, and changes in estrogen concentration. Research has demonstrated that premenopausal and postmenopausal women react to psychological stress in quite different ways. Crucially, it seems that estrogen reduces the impact of reactions instigated by stress. This indicates that an imbalance in the levels of androgen and estrogen in TTS could exacerbate the stress response.[46] Furthermore, the dexamethasone/corticotropin-releasing hormone (Dex-CRH) test shows that older women have altered HPA axis negative feedback, as demonstrated by studies on hormonal and psychological reactions to psychosocial stress and Dex-CRH in young, healthy controls and postmenopausal women in good health.[46] Furthermore, the available evidence indicates that supplementing with estradiol seems to alter human HPA feedback sensitivity.[47]

Finally, the impact of catecholamine excess on the different ballooning patterns that are characteristic of TTS has not been fully explained, although there is now substantial evidence that sympathetic activation plays a central role in TTS. Thus far, several rational recommendations have been put forth. For instance, it has been proposed that myocardial damage could result from a catecholamine surge. Various mechanisms that lead to increased cardiac work can be mentioned in this context, including microvascular coronary vasoconstriction and damage mediated by adrenoreceptors.[48]

4. Discussion

4.1. Role of sex steroids in modulation of behavioral and psychological aspects

Stress is recognized to have an impact on the endocrine, behavioral, and molecular responses of stress systems. The implications of rats' sex differences for stress response have been reported, indicating that stress had a distinct sexual dimorphic effect on the behavioral, endocrine, and molecular response of the stress systems in the rats' hypothalamus. Remarkably, this effect is also observed in human data on stress and depression.[49] Interesting findings presented by Dumas *et al.*'s research demonstrate how age and estrogen status affect older women's stress,[50] indicating that estradiol plays a significant role in regulating the emotional response to stressful situations.

Another fascinating study from the field of psychology revealed that older women have altered negative feedback of the HPA axis using the Dex-CRH test.[47] After comparing the behavioral stress responses of premenopausal and postmenopausal women with the effects of estrogen, they were able to draw the following conclusion: premenopausal and postmenopausal women differ significantly in how they respond to psychological stress.[46] The higher risk of cardiovascular disease in women who have gone through menopause may be partially explained by this lack of adaptation. It seems that estrogen reduces the reaction brought on by stress. The TTS framework discussed in the present review may heighten this circumstance, which shows a clear androgen/estrogen imbalance and a strong inflammatory background.

4.2. Possible female sex steroid-mediated modulation of functional cerebral asymmetry

Studies on the gender-specific differences in sympathovagal regulation and functional cerebral asymmetry imply that the female pattern of dominance is characterized by the left hemisphere, which is believed to have parasympathetic predominance, whereas the male pattern indicates dominance of the right hemisphere, which is believed to have sympathetic

predominance. This theory is in line with the concept of decreased magnitude of inter-hemispheric cortical lateralization in premenopausal women compared to men and postmenopausal women. Decrease of endogenous female sex steroid levels in postmenopausal women leads to reduced influence of estrogens on the left hemisphere, which is believed to have parasympathetic predominance. This results in sympathovagal imbalance, increasing sympathetic system activity in postmenopausal women, rendering postmenopausal women more susceptible to sympathetically mediated syndromes such as TTS.

4.3. Role of GCs in modulation of stress response

GCs are hormones produced in response to stress to control inflammatory and immunosuppressive responses as well as the growth and function of CNS, intermediate metabolism, vascular tone, and – most importantly – the process of programmed cell death.[45] The GR acts as a mediator for their action. Hence, GR expression is proposed as a stress-related surrogate marker for a diverse range of stress situations, including post-traumatic stress disorder and chronic stress.[51]

Of note, stress can have negative effects and cause diseases in people who exhibit poor self-regulation, such as increased inflammation:[52] it was convincingly presented that male rats exposed to CUMS showed elevated expression of GR in response to CUMS. Malta *et al.*'s study[19] emphasizes that GR is involved in regulating CUMS responses, which are dependent on GC and NE signaling in male rats. The authors provide specific evidence that the 14-day treatment of CUMS to male rats resulted in a persistent hyperactivity of the HPA axis, as demonstrated by an increase in plasmatic corticosterone and hypertrophy of the adrenal glands. These effects were dependent on the increased release of GCs and NE that were generated during each stress session. GR protein levels were shown to be elevated in key brain regions linked to HPA regulation and behavior after exposure to CUMS.[53] In a recent study, these findings were expanded by measuring blood hormone and hormone receptor levels of TTS female patients.[1] While more research is required to investigate additional CUMS-related brain GR expression patterns in TTS patients or animal models, these findings clearly indicated that TTS-prone postmenopausal females have a higher corticosteroid response as compared to healthy individuals, providing a molecular perspective on the gender disparity in stress response.

4.4. Role of GCs and gender aspects in modulation of inflammation

In addition to physical and emotional triggers, female gender, and age-related deficiency of female sex hormones, inflammation emerges as a pathophysiologic factor. Stronger immune responses to foreign and self-antigens are observed in women than in men, providing an explanation regarding the higher prevalence of most autoimmune diseases among women.[54] There have been some investigations suggesting that CUMS leads to the development of GC receptor resistance, which results in its upregulation and failure to inhibit the inflammatory response.

Notably, it has been demonstrated that the sexually dimorphic effects of GC are linked to inflammatory diseases that differ in frequency between genders. With the use of experimental rat models and gene editing techniques, the Cidlowski group demonstrated that the underlying inflammatory components seem to play a crucial role in the recognized gender difference of the prevalence of many major diseases. They emphasized that inflammation is a reflection of the balance between pro- and anti-inflammatory signals and looked into the responses that are specific to gender. They discovered sex-specific GC-regulated genes in a number of canonical pathways linked to the development and susceptibility to pertinent diseases with prevalence differences between genders. Specifically, they opine that either the anti-inflammatory properties of GC are more potent in men or their absence may encourage the onset of specific illnesses in women.[45] In a different article,[55] the same group described a priming mechanism in female mice in homeostatic condition that causes them to respond to an inflammatory stimulus more quickly. This mechanism causes the female mice to express more of the proinflammatory genes that are most frequently regulated. This idea is supported by research from other groups, which recently suggested that CUMS might lead to the development of GR upregulation and resistance impairing the suppression of inflammation.[1]

5. Conclusion

Chronic unpredicted mild stress is reportedly to exert a potentially bigger influence on TTS development than previously thought.[53] Specifically, it pertains to the relationship between the aforementioned reduction in GR and beta-adrenergic receptor sensitivity and persistent psychological stress. GC resistance may cause the HPA axis to be dysregulated and GR to be overexpressed. Increased GC levels and long-term immunosuppression with elevated levels of peripheral proinflammatory markers may be caused by dysregulated negative feedback.[54] As a result, the parasympathetic nervous system becomes less active and the sympathetic nervous system becomes more active.

The HPA axis's GC negative feedback appears disrupted in TTS, causing the GCs to maintain at elevated levels in the system and sustaining their activation in a gender-

disparate manner. Long-term stress might lead to the development of GR resistance, which raises GR levels and impairs the suppression of inflammation. Consequently, a persistent rise in the systemic concentrations of GCs can lead to immunosuppression, metabolic diseases, autoimmune diseases, and mood disorders due to their pleiotropic action, which appears to be more prevalent in women.

In every area of medicine, there should be a strong emphasis on preventive medicine. This is especially true when there are modifiable risk factors involved, such as stress, which affects the heart and psychology. The non-invasive (transcutaneous) vagus nerve stimulation (VNS) therapy, which is beneficial for parasympathetic activity and plays a significant part in lowering chronic inflammation, has high therapeutic value for TTS, according to research by Frank *et al.*[54] It should be highlighted that gender differences must be taken into account with regard to VNS.[56]

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Carola Y. Förster
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

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REVIEW ARTICLE

Neurobiological understanding of gaming disorder: A narrative review

Mi Jung Rho*

College of Health Science, Dankook University, Cheonan-si, Chungcheongnam-do, Republic of Korea

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Abstract

Gaming disorder (GD) is a mental disorder characterized by impaired control over gaming behaviors and the continuation of gaming despite negative consequences, resulting in functional impairments in important areas of life. Based on a growing body of scientific evidence demonstrating its neurobiological similarities to substance use disorders, GD is listed in the latest 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* and the 11th revision of the *International Classification of Diseases* as a behavioral addiction. Therefore, this review aims to understand the neurobiological underpinnings of GD by reviewing current literature on structural and functional changes in the brain. It is suggested that prolonged and excessive gaming may lead to alterations in the structure or function of the brain reward circuit and fronto-striatal circuit, affecting both reward processing and cognitive control. Changes in brain areas involved in executive function have been observed, indicating that GD is associated with reduced response inhibition and impaired decision-making. Furthermore, brain regions associated with craving exhibit heightened activity in response to gaming stimuli. This review highlights the significance of conducting further research to uncover the underlying mechanisms of GD and to develop effective interventions for its prevention and treatment.

Keywords: Internet gaming disorders; Neurobiology; Neuroimaging; Event-related potentials; Electroencephalography

***Corresponding author:**
Mi Jung Rho
(romy1018@naver.com, rhomijung@dankook.ac.kr)

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1. Introduction

Gaming is a popular leisure activity in modern society. Although most individuals engage in gaming in a healthy manner, a subset of individuals exhibit problematic behaviors. Gaming disorder (GD) is defined as a behavioral addiction, with a worldwide prevalence estimated at approximately 3%.[1,2] The *Diagnostic and Statistical Manual of Mental Disorders* 5th edition proposed diagnostic criteria for Internet gaming disorder,[3] and the World Health Organization has formally listed GD in the *International Classification of Diseases* 11th revision (ICD-11).[4] GD has been classified as "disorders due to addictive behaviors" alongside gambling disorder, which is a subcategory of "disorders due to substance use or addictive behaviors in the "mental, behavioral, or neurodevelopmental disorders" category.[4] The changes in the latest versions of the international diagnostic manual and the revisions in the classification

of diseases were guided by epidemiologic, clinical, and neurobiological studies, which reflect growing scientific evidence about the similarities of GD with substance-related and other addictive disorders.[5,6] Initially, GD was considered a subtype of Internet addiction, but a review of the scientific literature on gaming revealed that excessive gaming tends to be distinct and more likely to lead to serious consequences independently.[7-9] Furthermore, since the Internet is merely a medium for accessing potentially problematic activities, GD applies not only to excessive gaming through the Internet but also through non-Internet media.

According to the ICD-11,[4] GD is a pattern of persistent or recurrent gaming behavior ("digital gaming" or "video-gaming") characterized by impaired control over gaming, increasing priority given to gaming over other activities, to the extent that gaming takes precedence over other interests and daily activities, and continuation or escalation of gaming despite the occurrence of negative consequences. Gaming behavior can be either continuous or episodic, and it can result in marked distress or significant impairment in personal, family, educational, occupational, social, or other important areas of functioning. This pattern of behavior has been evident for at least 12 months.

The symptoms of GD, which are similar to those of substance-related and addictive disorders, include tolerance, withdrawal, cravings, repeated unsuccessful attempts to control or discontinue the behavior, and impairment in daily function.[10,11] Individuals with GD may express their tolerance to gaming by increasing gaming hours or feeling a perceived need for upgraded computer equipment and additional software. Withdrawal symptoms can manifest as anger, tension, or depression if access to gaming is denied.[12] Research has demonstrated that individuals with GD experience more intense cravings to play games.[13,14] These suggest the possibility that GD shares similar neurobiological underpinnings with substance use disorders (SUD). However, the neural mechanism underlying GD remains unclear.

Therefore, the objective of this paper is to understand the neurobiological underpinnings of GD by reviewing current literature on the structural and functional changes of the brain related to key features of addiction. To identify relevant publications, we conducted a search in PubMed for English-language sources using the following keywords and MeSH terms: "gaming disorder," "video game addiction," "Internet addiction disorder," and "neurobiology." Because the study focuses on research involving individuals with problematic Internet gaming or video gaming, this review included studies on GD, limited to papers within the realm of Internet addiction studies where the primary purpose of Internet use has been explicitly identified as gaming. In such cases, the term "GD," instead of the term "Internet addiction," is used to describe research results on Internet addiction. In addition, this review excludes studies focusing on GD with comorbid conditions. Table 1 provides brief explanations for the technical terms related to brain imaging techniques.

2. Changes of brain reward circuit

The primary reward circuit is a dopaminergic pathway that originates from the ventral tegmental area (VTA) in the midbrain and extends to the nucleus accumbens (NA), which is part of the ventral striatum (Figure 1A). Classically, addiction is a disorder of this reward circuit.[15] Communication between the VTA and NA is essential for acute drug reward.[16] Addictive substances, such as alcohol, induce and increase dopamine release in the VTA–NA circuit, resulting in positive reinforcement effects, such as pleasure.[15] Subsequently, repeated and intermittent stimulation of the reward circuit leads to neuroadaptation in the dopamine system, causing changes such as a decrease in the availability of dopamine D2 receptors (D2R) and a reduction in the expression of dopamine transporters. These adaptations are associated with rendering the reward pathway hypersensitive to addictive substances and cues associated with them, thereby manifesting characteristics

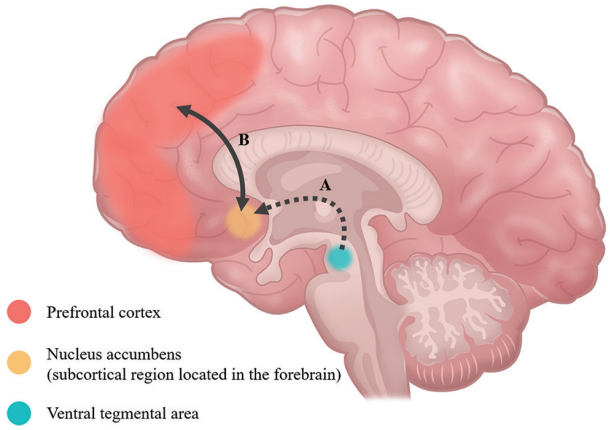

Figure 1. A schematic diagram of the primary reward circuit (A) and fronto-striatal pathway (B). (A) It is well established that primary reward circuitry, such as dopamine outputs from the ventral tegmental area (VTA) to the nucleus accumbens (NA), plays a role in the development of addiction. The addictive properties of drugs and behaviors result from their effects on the dopamine reward pathway, which leads to feelings of reward and reinforcement. The VTA is a group of neurons located close to the midline on the floor of the midbrain. The NA is a region in the basal forebrain rostral to the preoptic area of the hypothalamus. The NA and the olfactory tubercle collectively form the ventral striatum. (B) Fronto-striatal pathways are neural pathways that connect the prefrontal cortex with the striatum and play a crucial role in executive functions and reward processing. This image was created by the author.

Table 1. Brief explanations for the technical terms related to brain imaging techniques

Structural brain imaging	
Voxel-based morphometry (VBM)	Measuring gray matter volume
Diffusion-tensor imaging (DTI)	Observing the anatomical connectivity, primarily by measuring the distribution of nerve fibers in white matter *Fractional anisotropy (FA): An index of integrity and organization of white-matter tracts in DTI, with higher FA suggesting greater structural integrity of white matter
Functional brain imaging	
Functional magnetic resonance imaging (fMRI)	Identifying functionally active regions of the brain involved in various tasks and cognitive processes *Resting-state functional connectivity (rsFC): Functional connectivity between different brain regions during a state of rest in fMRI, reflecting intrinsic functional networks of the brain
Event-related potentials (ERP)	Measuring brain electrical changes recorded through electroencephalography during stimulus presentation to study cognitive process *Late positive potential (LPP): A positive electrical brain response occurring later in time in ERP, often associated with the processing of emotionally significant stimuli *P100: A positive peak in ERP occurring approximately 100 ms after the onset of a visual stimulus, often associated with early visual processing and perceptual mechanisms

of addiction such as tolerance, withdrawal, cravings, and compulsive substance use.[17]

Changes in the reward circuit accompanied by positive reinforcement were also observed in individuals with GD. Koepp *et al.*[18] conducted studies comparing dopamine release in the striatum during gaming and non-gaming periods in healthy adult males without GD. The results showed increased dopamine release in the striatum during gaming compared to non-gaming periods, with higher levels of gaming associated with greater dopamine release, particularly in the ventral striatum. Regarding D2R availability, studies on men with GD found decreased D2R availability in the striatum compared to individuals without GD. Furthermore, the D2R availability negatively correlated with the severity of addiction assessed by the Young's Internet Addiction Test (YIAT).[19,20]

Structural brain imaging studies have shown differences in NA volume between individuals with GD and controls. A study using voxel-based morphometry (VBM) demonstrated a decrease in the volume of the NA in subjects with GD compared to recreational game users (RGU) and its association with lifetime gaming usage.[21] In contrast, in a study by Yuan *et al.*,[22] increased gray matter (GM) volume of the NA was observed in subjects with GD compared to healthy controls, and the NA volume was positively correlated with YIAT scores.

A study using diffusion-tensor imaging (DTI), which may characterize microstructural white-matter organization, showed that online game playing is associated with increased fractional anisotropy (FA), regarded as an index of coherence of white-matter fiber tracts, in the reward circuity and sensory and motor control systems relative to RGU. These findings suggest that individuals with GD may have higher reward sensitivity and improved coordination between sensory and motor processing.[23] In contrast, other studies on GD have used DTI-based structural connectivity and resting-state functional connectivity (rsFC), which have shown a decrease rsFC and structural connectivity of VTA–NA in GD when compared to healthy controls.[24,25] Furthermore, rsFC of these regions was significantly negatively associated with the craving rating for Internet gaming.[24] These findings suggest a decrease in sensitivity to reward, making the individuals prone to seeking more intense rewards in GD.

3. Frontostriatal circuit dysfunction

Changes in the dopamine system also trigger neuroplasticity in the frontostriatal circuits (Figure 1B). These circuits can be divided into two pathways in addiction: the ventral valuation pathway, which is responsible for reward processing, and the dorsal control pathway, which is involved in cognitive inhibitory control.[26] As addiction progresses, the locus of control within the striatum shifts from the ventral to the dorsal region, and the influence of the prefrontal cortex (PFC) weakens.[27]

Previous studies have shown evidence of dysfunction in fronto-striatal circuits in GD, including structural and functional impairments. In a longitudinal study[28] that evaluated structural brain imaging and functional connectivity in individuals with GD, follow-up assessments were conducted after an average of 21.2 months. The results did not show any difference in changes in GM volume of both the dorsal and ventral striatum. However, subjects with GD exhibited a decrease in functional connectivity between the left dorsal putamen and the left medial PFC (mPFC), as well as an increase in functional connectivity

between the right dorsal putamen and the right middle occipital gyrus (MOG) over time, when compared to healthy controls. The mPFC is a region associated with self-regulation and is responsible for maintaining goal-directed behaviors over a long period of time for a larger reward. The MOG is a region responsible for visuospatial processing and is associated with the sensorimotor network. These findings suggest that GD is associated with a weakening of the PFC, whereas the sensorimotor circuit, which is connected to habit formation, strengthens.

In addition, previous cross-sectional studies have also reported differences in the rsFC of fronto-striatal circuits between individuals with GD and controls. Yuan *et al.*[22] demonstrated abnormal rsFC within the ventral and dorsal striatum networks. Specifically, they found a decrease in the strength of rsFC between the dorsolateral PFC (DLPFC) and caudate, as well as between the orbitofrontal cortex (OFC) and NA. Jin *et al.*[29] observed more extensive abnormal prefrontal-striatal circuits in individuals with GD, including the anterior cingulate cortex (ACC)–striatal, OFC–striatal, and DLPFC–striatal circuits. Specifically, the study found negative correlations between the rsFC of the right ACC–left putamen, left OFC–left caudate, and left DLPFC–left pallidum and YIAT scores in the GD group. A previous review on addiction proposed that unbalanced prefrontal-striatal circuits may reflect observable behaviors that characterize the addiction, such as impaired self-control and compulsive drug consumption.[30]

After evaluating the rsFC during a stimulus-response association learning task in GD, Kim and Kang[31] found that, for monetary reward, the rsFC of the ventromedial PFC (vmPFC) with the left caudate and various prefrontal regions, such as the ventrolateral PFC and dorsal ACC with the ventral striatum, was weaker in the GD group relative to controls. In addition, the vmPFC rsFC with the right NA was elevated. Dong *et al.*[32] investigated the directional functional connectivity between the ACC and the lentiform nucleus (putamen and globus pallidus as part of the basal ganglia) during a cue-craving task in individuals with GD. The study found enhanced brain responses in the lentiform nucleus, which may suggest reward sensitivity or cravings in response to specific cues. In addition, the lentiform nucleus typically exhibits greater activity in GD subjects relative to non-GD subjects when exposed to gaming-related cues. The results demonstrated that individuals with GD showed reduced ACC-to-lentiform and lentiform-to-ACC connectivity relative to RGU. Furthermore, when presented with gaming cues, GD subjects showed a trend toward decreased left-hemispheric modulatory effects in ACC-to-lentiform connectivity compared to RGU. The study also found that self-reported cue-related cravings before scanning showed a negative correlation with GD severity measured by DSM-5 scores and the left-hemispheric modulatory effect from the ACC to the lentiform.

A study was conducted to examine glucose metabolism and metabolic connectivity using positron emission tomography (PET) in individuals with GD.[33] The results showed hypometabolism in the ACC in the GD group compared to both healthy controls and those with alcohol use disorder (AUD). In addition, a negative correlation was found between glucose metabolism in the ACC and the duration of gaming use in the GD group. Significant reductions in metabolic connectivity were observed between prefrontal and limbic regions, including the striatum, in both the GD and AUD groups compared to the healthy controls. Another PET study[20] was conducted to assess D2R availability of the striatum and glucose metabolism in individuals with GD under the game task state. The study showed that the GD group had reduced D2R availability in the striatum. In addition, the level of D2R in the striatum was significantly associated with decreased glucose metabolism in the OFC, indicating dysregulation of the prefrontal-striatal circuit.

4. Impairments in executive control

Impairments in executive function, such as reduced response inhibition, increased impulsivity, and impaired decision-making, are closely associated with the pursuit of compulsive addictive behaviors. These impairments play a crucial role in the mechanism of addiction, contributing to its maintenance and relapse.[15]

Several studies have reported structural and functional changes in brain areas, including the DLPFC, OFC, ACC, and insula, suggesting a decline in executive function in the context of GD. Individuals with GD exhibited a significant decrease in GM volume or cortical thickness in the DLPFC,[21,29] ventrolateral PFC,[34] OFC,[29,35,36] ACC,[29,34] insula,[35] and the supplementary motor area[29,34,35] compared to healthy controls or RGU. The left DLPFC's GM density and the ventrolateral PFC's GM volume were associated with lifetime usage of Internet gaming,[21,34] whereas the GM volume in the OFC and insula was negatively correlated with the YIAT scores in the GD group.[35] Another study, which compared GM density among three groups – non-gamer, RGU, and GD group – indicated a marked decrease in the DLPFC in the GD group compared to the other two groups, and this density was associated with lifetime usage of Internet gaming.[21]

Regarding white matter integrity, reduced FA has been identified in the bilateral frontal lobe, corpus callosum, and external capsule in individuals with GD compared

to controls.[35] These findings suggest that Internet game overuse may damage the microstructure of both GM and white matter fibers connecting executive control.

In studies using fMRI, individuals with GD exhibited less activation in the DLPFC and ACC.[37] In addition, they showed decreased brain activation in the ACC when viewing game-related pictures during a forced break[38] compared to non-GD subjects.

A previous study investigated the differences in electroencephalography (EEG) activity between the GD group and healthy controls. The study revealed that subjects with GD exhibited lower activity in the left frontal theta, alpha, and beta bands compared to controls while gaming. Furthermore, a negative correlation was found between left frontal theta power and YIAT scores.[39] Another study compared the resting-state quantitative EEG, which reflects fundamental brain function during rest, among patients with GD or AUD and healthy controls.[40] The results showed that individuals with GD had lower absolute beta power compared to patients with AUD and normal controls.

These findings indicate that individuals with GD may have weaker executive control compared to those without GD.

4.1. Reduced efficiency in response inhibition

Response inhibition is the ability to inhibit inappropriate responses[41] and is evaluated using tasks such as the Go/No-go task, stop-signal task, and color-word Stroop test. Impulsivity is a crucial factor in response inhibition, referring to a tendency to react hastily without considering negative consequences. It is closely related to the loss of control, which is a central symptom of GD.[42]

In individuals with GD, characteristic features include a decline in response inhibition and high impulsivity. They exhibited more errors in the No-go condition of the Go/No-go task and the incongruent condition of the Stroop test when compared to the control group.[22,43-46] Furthermore, they demonstrated higher impulsivity scores, as measured by the Barratt Impulsiveness Scale-11 (BIS-11) or Eysenck Impulsivity Questionnaire.[35,46,47]

Numerous studies have reported structural and functional changes in brain regions that suggest a decline in response inhibition in individuals with GD. The main regions affected are the DLPFC, OFC, and ACC. A previous study using VBM found a negative correlation between GM volume in the ACC and impulsivity, as measured by the BIS-11.[34] Yuan *et al.*[22] found that reduced rsFC between the DLPFC and caudate was associated with more incongruent errors in the Stroop task in individuals with GD. Similarly, Ko *et al.*[48] found that individuals with GD exhibited reduced rsFC between frontal regions, including the DLPFC and OFC, and the amygdala, compared to the control group, and the disrupted rsFC was negatively correlated with impulsivity.

The OFC has been linked to impulse control and is activated during response inhibition.[49] A longitudinal study was conducted to investigate the impact of Internet gaming on brain structure. The study recruited not only excessive Internet gamers but also gaming-naïve subjects. The gaming-naïve subjects were randomly divided into two groups. One group was assigned to 6 weeks of daily gaming, whereas the other group was assigned to a non-gaming condition. Initially, the GM volume in the OFC was lower in excessive gamers than in the gaming-naïve group, and the volume further decreased during the 6-week follow-up interval. Furthermore, the longitudinal analysis revealed that the control group's mean GM volume of the OFC did not significantly change over time, whereas the GM volume in this region reduced in the 6-week daily gaming group.[50] In accordance with the longitudinal study, a cross-sectional study found that individuals with GD exhibited reduced cortical thickness in brain regions such as the OFC, insula, and lingual gyrus. The cortical thickness of the OFC was found to have an inverse correlation with the number of errors made during the incongruent condition of the color-word Stroop task in the GD group.[44] In an event-related fMRI study, the group with GD exhibited higher brain activation when processing the Go/No-go task over the left OFC and bilateral caudate compared to the control group.[47] Although the GM volume and cortical thickness decreased in the OFC of individuals with GD, the activity in the OFC and caudate increased during the Go/No-go task, indicating the need for greater cognitive effort due to reduced efficiency of cognitive control.

The decrease in cognitive control efficiency was also observed in the ACC, a brain region linked to conflict monitoring and error detection in response inhibition. Although individuals with GD demonstrated lower GM density[51] and volume,[28,29,34] as well as lower white matter density[51] compared to the control group, increased activity was observed in the ACC while performing the Stroop test in the incongruent condition[52] or No-go trials,[53] indicating a need for greater cognitive effort in response inhibition.

Error processing is a crucial aspect of response inhibition, and the ACC and insula are the primary areas involved in this process.[54] Error processing refers to the ability to detect errors and evaluate performance,[55] and impairment of this function has been previously reported in patients with SUD.[56] Similarly, an event-related potential (ERP) study found that individuals with GD exhibited significantly diminished error-related

negativity (ERN) following errors. The GD group showed lower ERN amplitudes observed in response to incorrect trials compared to correct trials during a Go/No-go task.[46] The ERN is a negative peak that occurs after incorrect behavioral responses, reflecting rapid and automatic initial error detection. It is assumed to originate in the ACC.[46] In another ERP study during a Go/No-go task, the NoGo-N2 latency at the central electrode site was delayed in the GD group compared to the healthy control. It was also positively correlated with impulsivity and YIAT scores.[57] The N2 ERP component in a Go/No-go task reflects an early stage of response inhibition and conflict monitoring. The latency of the N2 reflects the effort required to inhibit a response.[57] This suggests a reduced ability to handle performance errors in individuals with GD, similar to what is observed in patients with SUD.

4.2. Impairment of decision-making ability

Decision-making is the cognitive process of selecting the best choice among several options, taking into consideration goals, certainty, and risk. The process of decision-making involves both risk evaluation and outcome processing. Cognitive tests, such as the Iowa Gambling Task, the Cups Task, and the Probability Discounting Task, are used to evaluate the decision-making ability of individuals by assessing their choices between high-gain but risky options and low-gain but safe options.[58]

Individuals with SUD have been found to make more disadvantageous choices under both risk and ambiguity[59,60] and to exhibit greater sensitivity to reward.[61] Previous behavioral studies have shown that individuals with GD tend to select risky options more frequently and make decisions more quickly than healthy participants or RGU.[62,63] In addition, GD subjects tend to make more disadvantageous risky choices in the loss domain compared to healthy controls, but not in the gain domain, due to insensitivity to losses and levels of uncertainty.[64]

Several brain regions are associated with decision-making processes. The vmPFC, OFC, and ventral striatum are brain regions engaged in reward anticipation and outcome processing during decision-making.[65,66] The DLPFC is associated with self-control during risky decision-making,[67] and the inferior parietal lobule plays a role in decision-making under uncertainty.[68]

Functional changes were also observed in those brain regions during the Cups Task in subjects with GD.[67] The Cups Task evaluates risk decision-making in both gain and loss domains through elements of uncertainty and reward/punishment outcomes associated with different choices. In comparison to the healthy controls, the GD group exhibited less activation in the DLPFC (weaker modulation) and inferior parietal lobule (insensitivity regarding uncertainty) during risk perception for potential losses. This reduced activation was correlated with the severity of GD, as indicated by higher YIAT scores. During the process of outcomes, the GD group showed enhanced responses to experienced reward in the ventral striatum, OFC, and vmPFC for potential gains, indicating hypersensitivity to reward outcomes. In the GD group, there was a positive association between the severity of GD and increased reward-related activity in the OFC.[65] These findings support a previous study that showed individuals with GD exhibit increased activation in the OFC during gain trials and decreased activation in the ACC during loss trials in a reality-simulated guessing task compared to normal controls.[69] These results suggest decision-making deficits in individuals with GD and indicate an imbalance between the bottom-up system associated with hypersensitivity to reward and the top-down system associated with self-regulation.

5. Increased incentive salience and cravings from gaming stimuli

Cravings in patients with SUD can intensify upon exposure to stimuli associated with the substance, even without its administration.[70] This increased sensitivity to conditioned stimuli associated with substance use is linked to the expectation of obtaining the substance, memories of its positive reinforcing effects from the past, and anticipation of its rewarding effect.[70] Cravings involve not only the fronto-striatal pathway but also the hippocampus and amygdala, which are associated with memory and learning, as well as the OFC and insula, which are associated with incentive salience. Incentive salience refers to the motivational and desirable aspects of a stimulus, such as a drug or addictive behavior, that make it attractive and desirable to an individual. It enhances the perceived value or "wanting" of the addictive stimulus, contributing to the triggering of intense cravings. The DLPFC is also involved in anticipating the reward response.[71] This attractiveness is initially rooted in the "liking" condition. As addiction progresses, the transition from "liking" to "wanting" occurs, accompanied by obsessive-compulsive aspects regarding the addictive substance or behavior. This transition is characterized by cravings that dominate thoughts and behaviors, manifesting as intrusive, persistent thoughts that compel individuals to seek out the addictive substance or engage in the addictive behavior.[72,73]

In individuals with GD, exposure to game-related stimuli resulted in greater cravings compared to healthy controls or even the RGU.[32,74,75] Furthermore, individuals with GD exhibited increased activity in several brain

regions, including the striatum (including NA),[8,65] superior/medial frontal cortex,[8] OFC,[8] ACC,[8,76] DLPFC,[8,76] parahippocampal gyrus,[76] precuneus,[76] and posterior cingulate cortex,[76] when exposed to game stimuli. These activations were positively correlated with subjective gaming urges.[76] These brain regions are similar to those associated with craving in SUD.

In a study comparing cue-reactivity among individuals with GD, subjects with remitted GD for longer than 6 months, and normal controls,[76] the GD group scored higher on craving than the remission group. Furthermore, the GD group exhibited greater activation in the right DLPFC, left parahippocampus, and left middle temporal gyrus when exposed to gaming cues, in contrast to the remission group. This study suggests that these activated areas could serve as potential markers for gaming addiction. A longitudinal study was conducted on RGU who subsequently developed GD.[77] The study showed that the GD group exhibited relatively increased bilateral lentiform nucleus activation following a forced break from gaming compared with the remaining RGU group. Significant correlations were observed between the activation of the right lentiform nucleus and self-reported craving for gaming cues during periods of deprivation in the GD group. The evidence indicates that activation of the lentiform nucleus in response to cues related to deprivation may be a predictor of the transition from RGU to GD.

Incentive salience amplifies the significance of substance-related stimuli compared to other stimuli, leading to an attentional bias toward these cues. In a study comparing cue-related attentional bias between GD, obsessive-compulsive disorder (OCD), and controls,[78] individuals with GD exhibited increased late positive potential (LPP) amplitude in response to game-related pictures, indicating the enhanced salience of game-related cues. The GD group did not exhibit LPP changes in response to OCD-related cues. The LPP is a component of the ERP that arises following specific stimuli and represents motivated attention to salient stimuli. Another study[79] used ERP to observe changes in the brain during face recognition in a group of subjects with GD. Participants were presented with images of both human faces and cartoon faces resembling characters from a game. The study found that individuals with GD showed a significant increase in P100 peak amplitude when presented with cartoon faces compared to the control group. In addition, within the GD group, cartoon faces elicited a larger P100 peak amplitude than human faces. The P100 component is associated with the early automatic perception of stimuli. These results suggest that individuals with GD have an attentional bias toward stimuli related to gaming.

6. Conclusion

GD is characterized by persistent gaming behavior that leads to impairment in various life domains. Neurobiological investigations have revealed alterations in the brain reward circuit, fronto-striatal circuit, and executive control among individuals with GD. These changes parallel those observed in SUD and are associated with heightened sensitivity to gaming-related cues, increased cravings, and impaired decision-making abilities. These neurobiological findings provide insights into the treatment of GD. Pharmacological interventions that modulate the dopaminergic system, such as naltrexone or bupropion, may reduce cravings by targeting neurobiological pathways such as the reward circuit. Approaches to treatment for diminished response inhibition and impaired decision-making may include cognitive-behavioral therapy (CBT). CBT can help individuals recognize maladaptive cognitions and manage cravings. Moreover, CBT can facilitate a transition from short-term decision-making to longer-term goals or more adaptive decision-making. Research on GD is still in its early stages, and further in-depth studies across various fields are required in the future. In particular, longitudinal neurobiological studies are important, as well as studies to understand the interactions with comorbid conditions. The results of these studies will provide the fundamental knowledge needed to enhance understanding of GD and to develop effective prevention and treatment strategies.

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REVIEW ARTICLE

Pediatric drug regulations: A global perspective and the imperative for implementation in India

Mangesh Tatar†, Swati Jadhav*, Lisha Wadhava†, Aman Upaganlawar*, and Chandrashekhar Upasani

Department of Pharmacology, Faculty of Pharmacy, SNJB's Shriman Suresh Dada Jain College of Pharmacy, Nashik, Maharashtra, India

Abstract

The pediatric population differs from adults in various ways, including physiological factors, pharmacokinetics, pharmacodynamics, and dosage administration. However, many medications prescribed for children are formulated for adults, necessitating dose adjustments throughout childhood. This underscores the need for pediatric drug formulations and regulations worldwide. This review delves into the intricate landscape of international pediatric drug regulations to elucidate key initiatives, challenges, and advancements shaping this field. Commencing with a historical backdrop, the review outlines the evolution of regulatory frameworks across major regions, including the United States (US), Europe, Japan, and China, while underscoring the imperative for the implementation of pediatric drug regulations in India. These regulations mandate age-appropriate dosing, rigorous clinical trials, and thorough labeling to prevent misuse. They require pediatric-specific studies to understand drug effects and dosages and enforce guidelines for off-label use. Agencies such as the US Food and Drug Administration oversee these regulations, ensuring pediatric drugs meet safety standards before approval. In addition, regulations often include provisions for informed consent and parental involvement in treatment decisions, aiming to protect children from adverse effects while providing effective therapeutic options tailored to their developmental needs. In summary, this review emphasizes the importance of global cooperation and harmonized regulations in advancing pediatric drug research. It highlights recent progress while acknowledging ongoing challenges and opportunities in this critical area.

Keywords: Pediatric drug regulations; Drug development guideline; Clinical trials; Best Pharmaceuticals for Children Act; Pediatric Research Equity Act; Pediatric use marketing authorization; Food and Drug Administration; European Medicines Agency

†*These authors contributed equally to this work.*

***Corresponding authors:**
Swati Jadhav
(jadhav.sscop@snjb.org)
Aman Upaganlawar
(upaganlawar.abcop@snjb.org)

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1. Introduction

Pediatrics focuses on the physical, social, and mental well-being of individuals from birth through adolescence.[1] The pediatric population is divided into preterm newborn infants (from childbirth to 27 days after the predicted date) and post-term newborns (0 – 27 days old), infants and toddlers (28 days – 23 months old), children (2 – 11 years old), and adolescents (12 – 16 or 18 years old, depending on the region) according to the International Council for Harmonization (ICH) topic E11 (CPMP/ICH/2711/99)

and the ICH E11.[2] Figure 1 illustrates the pediatric age classification along with physiological and biological changes.

It is crucial to establish and specify the necessary instruments for acquiring trustworthy information to ensure the quality, safety, and effectiveness of medications intended for children.[3] Due to a lack of readily accessible and age-appropriate formulations, providing pharmaceuticals to the pediatric population can be challenging.[4-7] Many medications prescribed for children are formulated for adults, necessitating dose adjustments throughout childhood.[8] This may involve physically altering a dosage form to achieve a smaller dose, such as splitting a tablet or diluting an injection.[9] While these practices are common among health-care professionals, there is limited information on the potential risks associated with these manipulations, including time-consuming procedures and uncertain effects on drug stability and effectiveness.[10] Consequently, there is a risk of administering either toxic or ineffective doses to children.[11,12]

Error risk may also increase due to drug manipulation. In pediatric and neonatal treatment, dosage calculation errors are the most common pharmaceutical errors.[13] Economic factors have led to the encouragement of tablet manipulation among adults in several nations. There may be a small distinction in tablet characteristics[14,15] (Tables 1 and 2). Thus, splitting tablets might be more economical than purchasing them in the correct dosages. An efficient survey conducted in this region[6] recognized only one product (including suppositories) that did not have a correlation with tablet splitting.[16]

2. Need for clinical trials on the pediatric population

Clinical trials conducted on pediatric populations are essential for several reasons. Firstly, children have different physiological and metabolic characteristics compared to adults.[17] These differences can greatly impact the safety and effectiveness of medications, making it crucial to study them specifically in pediatric populations.[18] Secondly, certain diseases and conditions may manifest differently or exclusively in children, necessitating the need for targeted research and clinical trials in this population. Thirdly, ethical considerations play a significant role in conducting clinical trials on pediatric populations. Children cannot provide informed consent like adults, so it is essential to have specialized regulations and guidelines in place to protect their rights and ensure their safety during clinical trials. In addition, performing clinical trials in pediatric populations allows health-care providers to gather valuable information on the safety and effectiveness of medications in pediatrics of different age groups.[19] Furthermore, the lack of available child-appropriate dosages and application forms for medications also highlights the need for pediatric clinical trials in India.[20] Figure 2 represents the considerations during the pediatric clinical trial.[62]

By conducting advancements in the regulations of clinical trials, specifically in pediatric populations, we can bridge the knowledge gap and provide evidence-based treatment options for children, ensuring their optimal welfare and health care.[21]

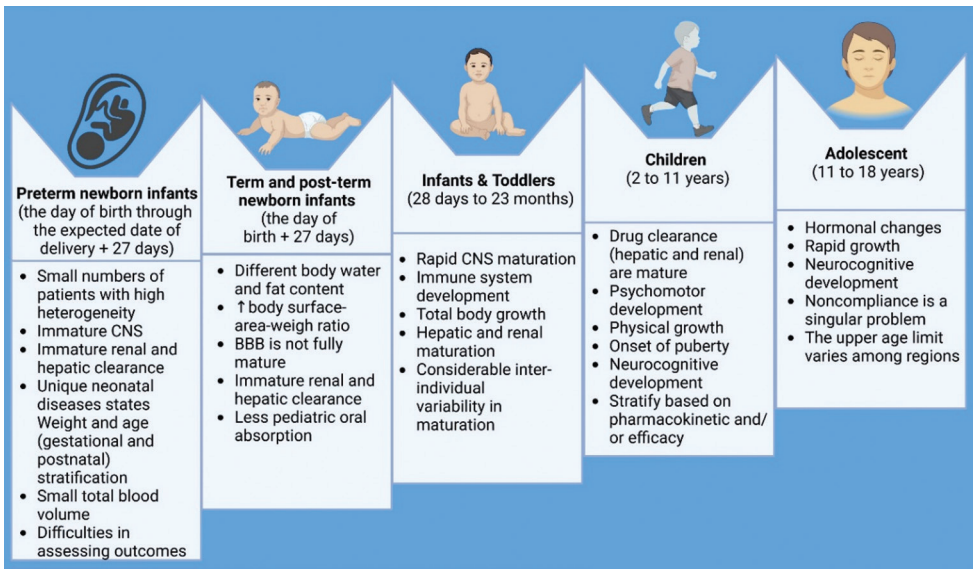

Figure 1. Pediatrics age classification with physiological and biological changes
Abbreviations: BBB: Blood–brain barrier; CNS: Central nervous system.

Table 1. Physiological parameters of pediatrics comparable to the age of adults[14,29,65,66]

Physicochemical specifications	Age at which comparable to adults*
Enteric pH	2 – 3 years
Gastric emptying	8 months
Intestinal colony formation	1 – 4 years
Passive and active transportation in the gastrointestinal tract	4 months
Hepatic circulation	1 year
CYP3A expression in the duodenum	6 – 18 months
Plasma protein levels	1 year
Liver Phase I metabolism	0.5 – 3 years Few attain maturity levels at 10 – 12 years Some changes occur during childhood
Hepatic Phase II metabolism	3 years (Few reach maturity by 10 years)
Glomerular filtration rate	1 – 2 years

Note: *These ages are approximate and may vary according to the literature.

3. The imperative for implementing pediatric drug regulations in India

3.1. Current challenges in pediatric drug development

Guidelines and the acceptance of pediatric drugs are critical aspects of ensuring the safety and effectiveness of medications for pediatrics. Different countries have established their own regulatory frameworks and processes to facilitate the advancement and accessibility of age-appropriate medications for pediatric use.

3.2. Global regulatory frameworks and their impact

One of the main reasons for the absence of age-appropriate versions of original medications and their generic equivalents is due to lower anticipated profits, logistical challenges, and extra developmental work.[22] This can make it challenging for pharmaceutical industries to invest in the development and testing of pediatric drugs.

3.2.1. The pediatric research equity act (PREA) in the United States (US)

For instance, in the US, the PREA was enacted in 2003, requiring pharmaceutical companies to perform pediatric clinical research on new pharmaceutical medicine and biological products before they can be marketed.[18]

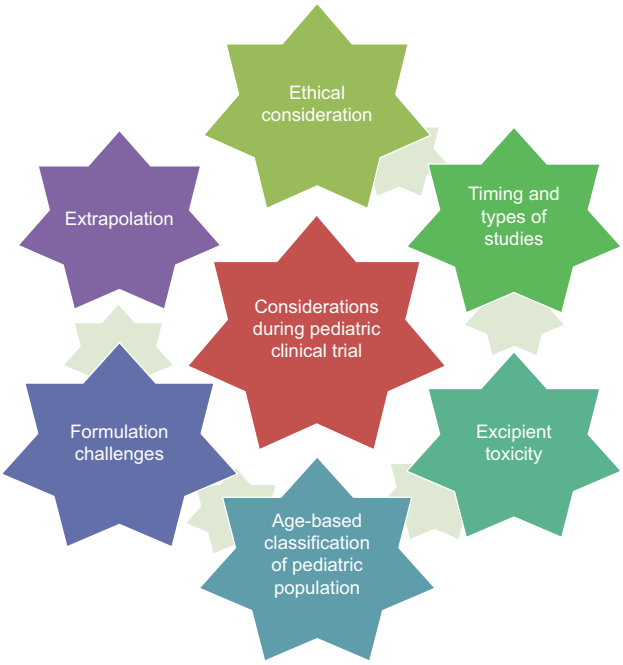

Figure 2. Considerations during pediatric clinical trials[62]

3.2.2. European Union (EU) guidelines on pediatric use

Similarly, in 2007, the EU published the EU guidelines on medicinal formulations for pediatric use, which mandate that pharmaceutical industries submit pediatric investigation plans (PIPs) to the European Medicines Agency (EMA).

These regulations aim to ensure that children can take safe and effective medication that has been specifically tested and approved for their age group. In contrast, the current scenario in India lacks specific drug development regulations for pediatrics. Similar to the EMA's Pediatrics Committee or the US Food and Drug Administration (FDA)'s Office of Pediatric Therapeutics.

3.3. Efforts and recommendations for improvement in India

India currently lacks a distinct department or regulatory structure devoted to pediatric medication development. This lack of specific guidelines for pediatric drug development poses challenges in ensuring the safety and effectiveness of medications for pediatrics. Furthermore, the lack of pediatric-specific guidelines in India has led to irrational drug use and the unavailability of proper dosing information for children.[23] However, it is important to note that there have been recent efforts in India to improve the regulation of pediatric drugs. One such effort is the incorporation of pediatric clinical trials into the regulations for new drug approvals, ensuring that new

Table 2. Problems and remedies in pediatrics clinical trial execution[67-69]

Parameters	Problems	Solutions
Small patient populations	Lack of enrolment increases the chance of unsuccessful study	• Modified research designs • Bayesian architecture • Expert protocol that enables data gathering for various prescription drugs, brands, signs and symptoms, uses, and/or biomarkers • Modeling and simulation techniques to reduce sample size • Careful site selection and use of pediatric research networks • Decentralize, patient-centric approaches to enable wider access
Dosage selecting	Selecting the right dose is essential to increase the probability that the dose under study will have a positive safety and effectiveness profile.	• Pharmacokinetic, pharmacodynamic modeling, and simulation techniques can be utilized to enhance selecting the dosage
Blood volume	Because newborns and babies have small blood volumes, it can be difficult to characterize the pharmacokinetic and pharmacodynamic characteristics of a medication in them.	• When testing blood, think about utilizing ultra-low volume bioanalytical tests and sparse sampling.
Selection of end-points and outcomes	Children should not use adult end-points and outcome measures, which increases the probability of research failure. Caregivers reporting on behalf of children when they are unable to do so on their own	• Make sure the FDA and the key opinion leaders are included early in the study design process to determine • Make sure to utilize validated patient-reported outcomes clinical outcome assessments specifically designed for children • Access reputable online repositories containing approved child-report assessments such as pediatric patient-reported outcomes, common terminology criteria for adverse events, and patient-reported outcomes measurement information system • Make sure target age groups are taken into consideration while designing and testing patient diaries
Adverse event reporting	It can be difficult to get unpleasant incident inf. from pediatrics whose prescription drugs, brands, signs and symptoms, uses, and/or biomarkers are short and their non-verbal interactions with caretakers may be large prevalent	• Apply Ped-PRO-CTCAE to evaluate adverse consequences in kids and teens from 7 to 17 years old, or use it to report caregivers of younger kids
Visits schedule and logistics	Scheduling issues related to schools and families may prevent participation	• Decrease the amount of clinic visits using telemedicine • Take home health and direct patient's medication delivery into consideration • Plan to visit the clinic on the weekends or after work or school
Informed consent	The intricate nature of consent, the impact of cultural aspects and personal experiences, and the lack of regional guidelines	• Using phased informed consent • Using interactive computer technology to explain difficult concepts and changing how to get children's assent depending on multifactorial competence assessments • Individualized instruction for those conducting pediatrics clinical training

drugs are analyzed for safety and effectiveness in pediatrics before they can be marketed. In addition, there have been discussions on the establishment of a separate regulatory body or division within the existing drug regulatory authorities in India to focus specifically on pediatric drugs and their regulation.[24]

These efforts in India aim to address gaps in pediatric drug regulation and ensure that children have access to safe and effective medications. The differences in pediatric drug regulations among India, the US, Europe, and Japan highlight the need for comprehensive and specific guidelines to protect children's health and well-being.

In conclusion, while the US and Europe have made significant progress in pediatric drug regulation by implementing specific laws and regulations, India still lacks comprehensive and specific legislation for pediatric drug development. This regulatory gap poses challenges in ensuring the availability of safe and effective medications for pediatrics in India. However, efforts are being made in India to improve the regulation of pediatric medications, including the inclusion of pediatric clinical research in new drug approval processes.[25] Figure 3 represents the categorization of juvenile age groups.[21]

4. Background: Pediatric drug regulations

Throughout history, there has been a lack of attention given to the development of medications specifically designed for children.[26] In 1968, Shirkey[27] referred to this group as "therapeutic orphans," highlighting their exclusion

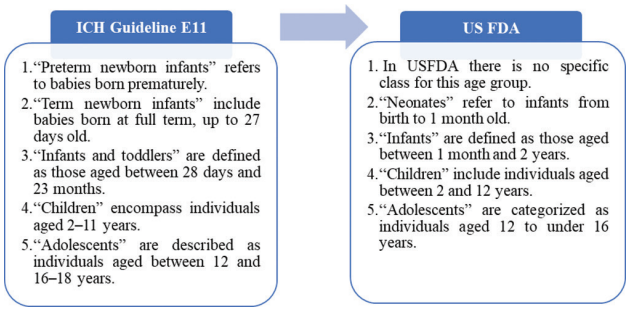

Figure 3. Categorization of juvenile age groups[21]
Abbreviations: ICH: International Council for Harmonization; US FDA: United States Food and Drug Administration.

from research, legislation, and the availability of suitable formulations compared to adults.

The lack of a mandate for studying the efficacy and safety of medicines in pediatrics, considering their particular and distinct qualities, has led to numerous unfortunate incidents over time, some of which have even resulted in fatal consequences.

One of the earliest instances of concern occurred in 1938 when children were administered the antibiotic elixir sulfanilamide. Although adults had previously utilized this antibiotic in the form of pills and capsules, a liquid form was created for pediatric use due to their difficulty swallowing solid dosage forms. To make the antibiotic more palatable, diethylene glycol – a sweet solvent whose safety had not been investigated before – was added to elixir sulfanilamide.[28] Tragically, it later became evident that this substance caused over 100 pediatric deaths. This incident highlights the toxicology implications of excipient safety, which is an essential consideration in pediatric drug development.

In addition, during the 1950s, the thalidomide tragedy – widely recognized for causing irreversible birth defects in over 1000 babies whose mothers used it for its anti-nausea properties during pregnancy – demonstrated the critical importance of pediatric research and the need to ensure drug safety concerning teratogenic effects.[29]

This discussion highlights the serious outcomes of insufficient research on medications for children, particularly among the youngest age groups. Several notable adverse reactions have been linked to commonly prescribed drugs for pediatric use, emphasizing the importance of targeted research in this vulnerable population.

4.1. Sulfisoxazole (Kernictures)

The most significant incident of drug-related harm in children occurred in 1956 when it was discovered that newborns administered sulfisoxazole were experiencing increased cases of kernicterus. This disorder is caused by bilirubin entering the brain, leading to seizures, yellowing of brain tissue, and eventually death. This susceptibility is due to reduced glucuronosyl transferase activity in infants, which reduces their ability to process bilirubin. In addition, the immature blood–brain barrier allows more free bilirubin to reach the brain and cause injury. Since bilirubin is expelled from plasma proteins, a higher proportion remains free in plasma, making it easier for bilirubin to enter the brain.[30]

4.2. Chloramphenicol (Gray baby syndrome)

Gray baby syndrome is an uncommon yet severe adverse reaction observed in infants, particularly premature ones, after receiving chloramphenicol – a bacteriostatic antibiotic – through intravenous administration. This syndrome was initially documented in neonates in 1959. It is believed that the underdeveloped glucuronyl transferase activity and the lack of renal excretion of chloramphenicol and its by-products contribute to the development of the gray baby syndrome.[30]

4.3. Benzyl alcohol

In 1982, benzyl alcohol, a commonly used additive, was linked to neonatal gasping syndrome and preterm infant fatalities. It is utilized as a preservation agent in intravenous line flushes but has been found to cause severe symptoms such as acidosis, respiratory distress, circulatory failure, bleeding in the brain, seizures, and eventually fatalities. This situation serves as a reminder that additives can have significant effects on the body. The issue with the differential metabolism of benzyl alcohol in infants further complicates matters; it is believed that neonates process benzyl alcohol into benzoic acid, which then stores and leads to toxic effects.[19]

Other adverse drug reactions seen in children include liver damage from sodium valproate use,[31] increased risk of Reye's syndrome when using salicylates during viral infections,[32] growth suppression or adrenal function effects from long-term corticosteroid use,[33] gastrointestinal bleeding caused by non-steroidal anti-inflammatory drugs,[34] and arthropathy[35] risk associated with ciprofloxacin use in children resulting in serious consequences.

Adverse reactions such as bronchospasm from antiasthmatic drugs,[19] due to benzalkonium chloride, headaches, and seizures,[36] induced by aspartame, cross-sensitivity reactions in pediatrics with allergies to sulphonamides caused by saccharin-induced compounds, and hyperosmolality and lactic acidosis induced by propylene glycol are among the effects resulting from improper use of excipients in pediatric formulations.[37]

It is reasonable to assume that due to the short availability of pediatric information, children often end up taking medications meant for adult use. This off-label usage is not officially approved according to the product's summary of characteristics.

The global off-label use of pediatric medications exceeded 50% until the late 1990s, especially common in neonatology and intensive care. This trend reduced as children grew older. As a result, it has become crucial to establish regulations and define processes for obtaining accurate information to guarantee the safety, quality, and effectiveness of pediatric medications.

In 2010, the Pediatric Medicines Regulator's Network was established by the WHO in collaboration with Japanese regulators, the FDA, and the EMA to enhance cooperation among regulators through promoting dialog and exchange of information related to regulating pediatric medicines at WHO headquarters in Geneva, Switzerland, on dated February 15 – 17, 2010.

The list of participants in the Pediatric Medicines Regulator's Network is Australia, Azerbaijan, Brazil, Canada, China, Chile, Croatia, Egypt, Europe, Ghana, Indonesia, Malaysia, the Maldives, Moldova, Nigeria, Saudi Arabia, Singapore, Switzerland, Thailand, Ukraine, the United Republic of Tanzania, and the US. In that list of participants, it does not include the name of India because it is not a participant in PMRN.[38]

In contrast to the Pediatrics Regulation and the Best Pharmaceutical for Children Act, there is no benefit to complying with this regulation, leading to the exclusion of orphan drugs. These drugs are intended for rare conditions and are exempt from any obligation, which differs from the earlier pediatrics regulations. Therefore, pediatric research for medications targeting rare diseases (orphans), which are not covered by the PREA, will need to adhere to the Best Pharmaceuticals for Children Act (BPCA) process if they were not originally included in the marketing authorization application (Figure 4).

5. Summary of laws concerning the pediatric population

5.1. EU

In 2007, the pediatric regulation came into effect to make it easier to develop and access medicinal products for children. Its goal is to guarantee that children receive therapies that are duly authorized. Its goal is to guarantee that children receive therapies that are duly authorized and to expand the data on the use of these medications across various pediatric demographics. In the EU, juvenile research has been required for all new products since 2007. This also applies to novel uses, dosage forms, or pharmaceutical versions of products that are already patented or covered by a supplementary protection certification (SPC). Usually, a PIP is necessary unless the EMA grants an exemption based on product-specific reasons or class waiver approval. Compliance with this regulation makes the product eligible for incentives under this legislation's provisions.

5.2. US

In the US, there have been laws and regulations put in place since 1997 to support the development of medical products for children. The existing legislation includes the BPCA, which offers incentives voluntarily, and the PREA, which mandates pediatric development under specific conditions without providing incentives. According to Chapter 5 of the FDA's Safety and Innovation Act, these two regulations were strengthened and enacted in 2012.

5.3. BPCA

Industries financially benefit from the BPCA's enhanced marketing exclusivity, which extends an existing patent or exclusivity for 6 months for the entire product, provided that the sponsor completes the studies outlined in the written request (WR) from the FDA that grants this exclusivity. However, the extensive exclusive period applies only to the specific item being studied. It is important to note that conducting these specified studies is voluntary for sponsors. By submitting a pediatric trial request, they can ask for a WR. Any modifications to a WR can only be made before the sponsor submits the requested studies.

The range of conditions to be evaluated in children is wider than those authorized for use in adults or currently undergoing approval processes. It encompasses all potential benefits of the active ingredient for pediatric patients, regardless of its prior approval status for adults. Therefore, BPCA regulations in the US permit studies for conditions not included in adult indications, which is specifically crucial for uncommon and specific pediatric classifications. The BPCA also offers incentives for orphan categories.

To be eligible for these incentives, sponsors must meet the criteria outlined in the "Guidelines for Industries Qualification for Pediatrics Exclusion Within Section 505A of the Federal Food, Drug, and Cosmetic Act." These guidelines, established in 1999, are presently under revision. For more information about the WR procedure under the BPCA, there are resources available that answer common questions related to pediatric exclusivity. It is noteworthy that the FDA will neither award pediatric exclusion nor issue a WR for studies submitted to them before the issuance of a WR.[39]

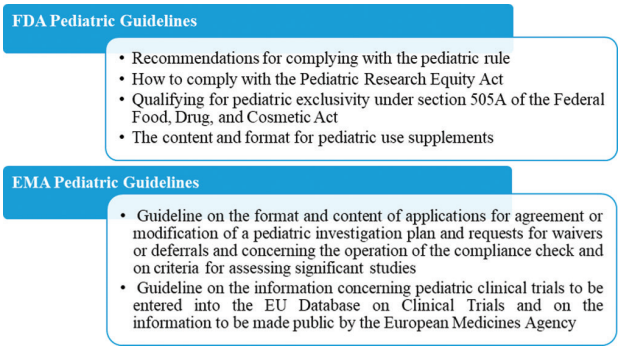

Figure 4. Progress of pediatric drug regulations[64]
Abbreviations: AAP: American Academy of Pediatrics; BPCA: Best Pharmaceuticals for Children Acts; FDA: Food and Drug Administration; FDAMA: Food and Drug Administration Modernization Act; FDASIA: Food and Drug Administration Safety and Innovation Act; FD&C: The Federal Food, Drug, and Cosmetics Act; PAC: Premature Atrial Contraction; PREA: Pediatric Research Equity Act.

5.4. PREA

The PREA mandates that sponsors assess the safeguards and effectiveness of novel items, including pharmaceuticals and biological agents, in youngsters under particular circumstances. However, a waiver from the FDA can be granted. The PREA applies to any product registration for a novel dosage type, novel effective component, novel dosing schedule, novel mode of administration, or novel indications. These studies are compulsory but are confined to the approved indications in adults. The submission of an initial Pediatric Study Plan (iPSP) is mandatory for all product development programs subject to PREA. Product development programs for biosimilars, unless exempted by orphan classification, must comply with PREA regulations.[40]

At the start of the medication development process, the PSP aims to determine critical juvenile research needs and start preparations for these studies. Any marketing proposal covered by PREA should incorporate an agreed-upon preliminary PSP. It is critical to discuss with the FDA if a pediatric developmental project is deemed inappropriate.

The FDA urges sponsors to include all possible juvenile advancement plans in the PSP, even those that fall within BPCA, even though a PSP is only necessary for pharmaceutical advancement projects under PREA. Proposed pediatric study requests (PPSR) may use these strategies as the foundation to get a WR. As a result, a single product might include a WR and a PSP also, enabling both required and optional studies as well as the possibility of BPCA incentives if the product complies with the trials in the WR. It is noteworthy that although exclusivity is granted under the BPCA utilizing an approved WR, as opposed to a PREA, the PSP is ineligible to function as a PPSR. Furthermore, when seeking pediatric exclusivity under PREA requirements, it is essential to obtain an FDA-approved WR before submitting pediatric studies. The FDA will not grant exclusivity until after receiving an approved WR submission, which can occur without requiring sponsor proposals.

Research projects covered by the BPCA or PREA need to have a pediatric-specific security review done by the Pediatric Advisory Committee within 18 months of the FDA approving a label update.[41] Table 3 represents the conventional "standards" for pediatric medication registry.[70]

6. Regulatory mandates and conditions

6.1. Plan for pediatric development

6.1.1. EU

The requirement to consent to a pediatric investigational plan or waiver is relevant in the following situations:

(i) For all new products, regardless of whether they are safeguarded through patent or supplemental protective certificates
(ii) When a petition is filed for a new diagnosis, dosages, or mode of administration for approved drugs protected by a relevant patent or SPC (designed for usage by adult or juvenile classification).

These regulations also cover items that have been granted orphan status inside the EU. The exceptions include biological products that are hybrid, biosimilar, or generic; they also include homeopathic and ayurvedic remedies, as well as those that are approved under the ethical principle of "well-established use."[42]

It is important to remember that fulfilling a responsibility in the EU entails incentives. The particular benefits are attainable in the context of accepting a PIP (and carrying out research). Stated differently, as the EU has a unified legislative framework for both incentives and requirements, adhering to it qualifies one for a biannual patent extension or a 2 years extension of exclusivity on the market (for items designated as orphans). In addition, a brand-new category of marketing permission called pediatric use marketing authorization (PUMA) was created to promote the advancement of approved products for pediatric markets that are currently not covered by intellectual property rights.

Ten years of data exclusivity are awarded to a PUMA for goods created specifically for usage within the juvenile patient following a PIP.[43]

6.2. Exemptions/waivers

6.2.1. EU

The EMA has the power to give an exemption (waiver) that applies to some pediatric subsets, such as age groups, or to

all pediatric subsets, such as full waivers, where a product is subject to the following responsibilities. There are three established legal justifications:

(i) If a certain medication or class of medications is anticipated to be harmful or ineffectual for pediatric patients
(ii) If the ailment for which the medication(s) is prescribed solely affects adults (or only specific pediatric subgroups); and
(iii) If the medication(s) does not provide pediatric patients with appreciable therapeutic advantages over current therapies.

When conducting informative studies is impractical (for instance, in cases of incredibly rare illnesses in children such as arrhythmia) or in situations when clinical trials employing the specific drug are unlikely to significantly improve pediatric patient outcomes, the third legal basis may be utilized to approve exemptions. Certain items or entire classes of medications may be exempt. Any exception can subsequently be changed or revoked if needed in light of breakthroughs in science and medicine. A waiver that is changed or revoked will only become enforceable 3 years following the termination date.

6.2.2. US

The PREA gives the FDA the authority to disregard or omit the need for submitting a juvenile program under certain conditions for specific age ranges. The FDA can grant either whole or half waivers of this requirement upon its initiatives or at an applicant's proposal. If an applicant seeks a waiver, they must furnish written justification and supporting evidence for their request.

The legal basis for such waivers is as follows:

(i) If conducting necessary studies is not feasible or highly impractical (for example, because there are very few participants)
(ii) Should there be strong proof that the medication or biological substance will be harmful or useless for any or all juvenile class

When a medication or biological substance:

(a) does not significantly improve pediatrics' current therapy; and
(b) is not expected to be utilized by a significant number of individuals;

(iii) Furthermore, a waiver may be considered when it is impossible to develop a suitable pediatric formulation for certain age groups. If this situation arises, the waiver will only apply to those specific pediatric age groups requiring that particular formulation, with a detailed explanation outlining why developing such a formulation is unfeasible.

The legal basis shares many similarities but is not entirely identical between both regions. For instance, the EU regulation does not explicitly permit waiving "highly impracticable" studies, as seen in rare or very rare diseases; thus, lacking feasibility criteria within its legislation per se compared to the US standards. Furthermore, unlike the EU system, which does not grant waivers solely based on lack of meaningful therapeutic benefit unless there also is not substantial usage among pediatric patients – contrary to what is applicable in the US regulatory framework.[44]

6.3. Deferrals

The deferral regulations are alike in both areas.

6.3.1. EU

A PIP that has been agreed upon may permit deferrals for part or all of the pediatric investigations and measures. This means that after requesting a marketing license for adults for the same ailment, these studies may begin and/or end.

Deferrals need to have one of the following justifications:

(i) Research involving children will take more time to complete than research involving adults
(ii) Technological and scientific justification
(iii) When adult studies should be conducted before beginning research on the pediatric group; and
(iv) Causes related to general health.

A precise completion deadline for the research must be chosen and agreed upon when a delay is granted. If the anticipated date of the adult marketing approval application is postponed past the designated date of the pediatric study's completion, the juvenile research might be due.

6.3.2. US

While acknowledging the necessity of a pediatric evaluation, a deferral permits the candidate to provide the research findings following the submission of a new drug application (NDA), BLA, or supplemental NDA or BLA. The FDA may decide to postpone any or all of the pediatric trials until a given time after the drug's adult authorization or the biologic's licensing is issued.

The criteria for granting a deferral include:

(i) If the medication or biological item is ready for adult authorization before juvenile research is finished
(ii) If childhood studies must be delayed until more security or efficacy data are gathered; and
(iii) If there is a different acceptable reason for deferring (such as incomplete advancement of juvenile manufacturing).

In both areas, though, economic reasons cannot be used as a reason for postponement.[45]

Table 3. Conventional "standards" for pediatric medication registry[70]

Important subject	Potential response
Standardization of terminologies	• Encourage cooperation across authorities to promote discourse on the Pediatric Development Plan (PDP)
PDP	• Provide recommendations for safety, effectiveness, and efficiency • Provide general guidance on dose formats • Give technical guidance on age ranges, particular illnesses, pediatric medication dosages, and parts of research in underdeveloped nations • Provide guidelines for the PDP's assessment and material • Offer education and development of capacity
Proposal for permission to perform clinical research	• Gather frequently asked questions on conducting clinical studies, with a focus on developing nations; respond to them and offer references to previously published material (such as that from the FDA or EMA) • Create a reference document • Create a useful guide with FAQs and answers
Pharmacovigilance	• Recognition of interested parties and available resources (networks, databases, etc.) • Creation of suitable documentation
Authentication for The commercialization	• Provide guidelines for the assessment of the application dossier's contents • Specify the supporting documentation that should be sent with the marketing authorization application in cases where a different NMRA has previously evaluated the pediatric plan or dataset • Create retraining and capacity-building initiatives for NMRAs
Transparency of the Network's activities	• Utilize the World Health Organization (WHO)'s website to share knowledge, such as national regulatory documents. • Send out the Network Newsletter biannually • Hold network meetings yearly
Advocacy for research on and development	• Track global network activity (e.g., WHO to secure a time slot for the 2010 ICDRA summit) • Reporting network operations (e.g., Ministries of Health) • Determining the National Center of Excellence for pediatric issues

Abbreviations: EMA: European Medicine Agency; FAQ: Frequently Asked Questions; FDA: Food and Drug Administration; ICDRA: International Conference of Drug Regulatory Authorities; NMRA: National Medical Regulatory Authority; WHO: World Health Organization.

6.4. Incentives and rewards

Financial incentives are linked to the right to intellectual property in both the US and the EU. This is implemented in the EU as a 6-month SPC prolongation, which prolongs the patent. In the meantime, the complete product line with an active moiety will have its market protection extended for an additional 6 months in the US.

Regardless of whether new pediatric indications are granted or studies fail to demonstrate efficacy ("negative" studies), companies can obtain these financial incentives in both regions. What matters is that results from these studies are incorporated into product information (labeling). Instead of focusing only on successful studies, the emphasis is on rewarding pediatric development activities. Both areas value "negative" information, which tells us when it is inappropriate to provide medication to a child and requires it to be listed on product labels.[46]

6.4.1. EU

An SPC is required to be eligible for the primary EU benefit; the patent alone is insufficient. As to the ruling of the European Court of Justice, sponsors can still pursue an SPC to receive the pediatric benefit, even in situations when the calculated length of the SPC is either negative or zero.

As opposed to the typical 10-year period provided as part of the orphan reward, designated orphan products in the EU receive a separate payment (whether or not they are covered by a patent), which includes two additional years of market exclusivity, regardless of patent status.

Finally, off-patent items that receive a PUMA in the EU following the completion of a PIP qualify for an additional benefit: extended data protection lasting for several years.

6.4.2. US

The initial term of exclusivity is covered by market security and can be extended for 6 months for the products containing the active component. A second exclusivity period would apply only to the particular product under investigation. In the US, an internal FDA review process is followed. If the submission was issued before September 27, 2007, and contains research defined in the WR, it will be evaluated within 90 days. For applications submitted beyond this date, a decision must be made within 180 days of receipt.

(i) In the US, pediatric exclusivity is obtained through a different legislative framework than the obligation, as PREA and BPCA are two distinct laws with separate legal foundations and procedures. This distinction may lead to different requirements for pediatric research. However, in the EU, since the specifications and rewards are covered by the same laws and regulations, no further research is required to ensure exclusivity

(ii) The EU and the US have different legislative frameworks. While "condition" is broadly construed in EU legislation according to their policy on determining condition(s) for a pediatric research plan/waiver (pediatric research plan/waiver scope), the US statute limits the requirement to adult indications. The BPCA exclusivity procedure must be used for some pediatric disorders that do not arise in adults

(iii) The primary benefit is associated with the SPC/patent in the EU, while it pertains to security for patents and exclusivity as outlined in the US Orange Book for every medication item that includes the investigated active component

(iv) In the EU, products approved centrally can be promoted across every country of markets, but SPC/patents are granted by every member country, potentially resulting in variations or absence of SPCs across different member countries. Meanwhile, in the US, a medication authorized by the FDA can be marketed nationwide

(v) The incentive in the US applies solely to the optional BPCA-written application regulatory procedure. When research is required due to PREA obligations (e.g., under a PSP), there is no cash reward. However, if a medication falls under both a PSP and WR and consequently has both required and discretionary studies included, there is potential eligibility for incentives if required conditions are met

(vi) Incentives in the US are limited to the optional BPCA-written application regulatory procedure. There is no financial incentive when research is required as part of PREA responsibilities (such as under a PSP). However, if a product is covered by both a PSP and WR As a result, both necessary and elective studies are incorporated; if prerequisites are satisfied, there may be an opportunity for incentives

(vii) For any medications containing the active moiety, a further 6 months of pediatric exclusion is permissible in the US but impermissible in the EU. It is noteworthy that in the US, pediatric exclusivity is only applicable for the first 6 months for all medicines containing the active moiety. Only the product under study is eligible for the second exclusivity period, which is awarded if a pediatric indication is provided

(viii) About orphan products: Orphan products are likewise subject to pediatric exclusion in the US, unlike in Europe, where there are distinct rewards (as previously indicated). In addition, it prolongs the current patent and marketing durations as well as orphan exclusivity and Hatch Waxman Act protection, which are designed to shield novel pharmaceutical goods from competition from generic versions (Figures 5 and 6).

In contrast, sponsors of research involved in a PIP agreement in the EU are granted a 10-year data protection period under the PUMA.[47]

7. Guidelines and procedural advice for PIP, PSP, and WR submission, evaluation, and modification procedures and timelines

7.1. EU

The European Commission Guidelines on the layout and substance of PIP and waiver submissions are the primary regulation accessible in the EU for producers of medical goods concerning pediatric legislation. It was most recently amended in 2014. Additional procedural guidance can be found on the EMA website.

To streamline overall development and integrate the pediatrics program into the adult program, early discussion of it is essential. Obtaining a PIP before requesting clinical trial permission for pediatric research is strongly advised. Within the EU, clinical trials are not EMA, but the appropriate participating country's jurisdiction or states where the trial would take place are in charge of granting authorization. A member state does not need to validate an earlier PIP agreement to obtain authorization. Nevertheless, requesting a retrospective PIP after receiving authorization could not ensure the Pediatric Committee (PDCO)'s consent and might result in further requirements that waste time and resources.[48]

PIP applications are submitted by sponsors to the EMA for assessment by the PDCO. The commission is in charge of evaluating PIPs from a scientific standpoint and reaching a consensus. Under these plans, sponsors may be permitted to implement all or certain PIP measures following their application for marketing permission for adults, with the option for deferrals. The EMA will decide on the approved PIP (or complete waiver) within 10 days of obtaining the PDCO's final opinion. Excluding any clock-stop periods — that is, the time applicants take to reply to PCDO requests – the EMA has a maximum of 7 months to decide on a PIP. In actuality, the full process often takes a year because the average interval is roughly 135 days long.[49]

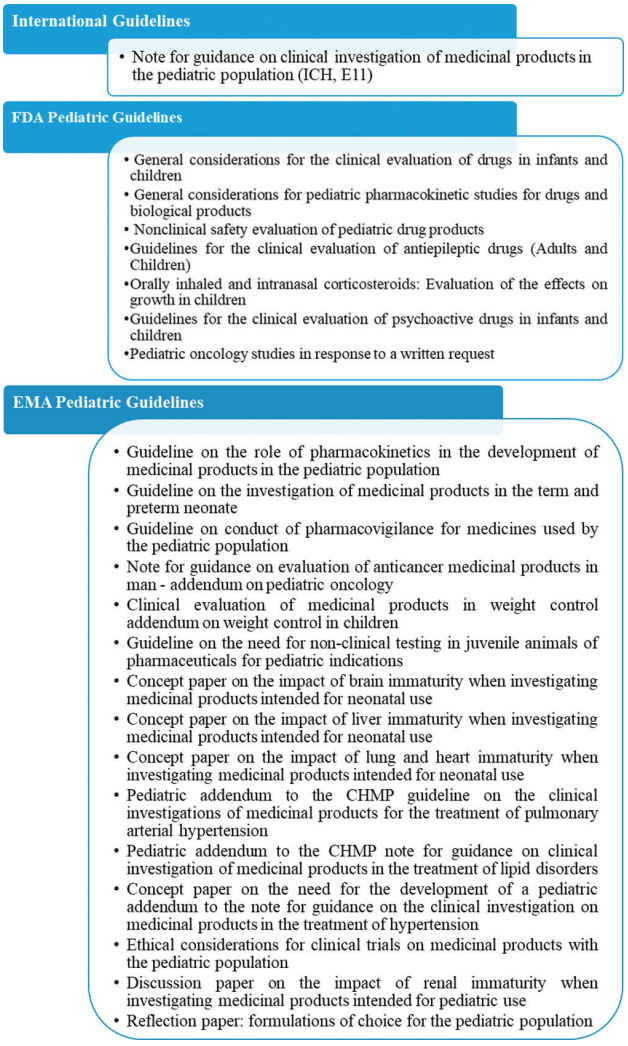

Figure 5. Guidelines for the development and study of pediatric medications[63] Abbreviations: EMA: European Medical Agency; FDA: Food and Drug Administration.

7.2. US

This information on the advancement of medications for pediatrics can be found on the FDA website under "Pediatric Product Development."

7.2.1. Pediatric study plans

Furthermore, by consulting the preliminary guideline paper entitled "Content of and Procedure for Submitting iPSP and Amended iPSP," sponsors can receive assistance in accomplishing the initial PSP applications. A preliminary PSP template that is similar to the PIP application template is also included in this document.

7.2.2. WR

A frequently asked question (FAQ) concerning the pediatric exclusivity process is accessible to offer details on the BPCA-WR procedure, and there is also availability for a 1999 advisory document that is currently undergoing revision.

Based on an individual initiative or a request from a stakeholder, the FDA can issue a WR. To accelerate the FDA's issuing of a WR, sponsors are strongly advised to submit a PPSR to ensure pediatric exclusivity. Sponsors are advised to refer to the "Guidelines for Industries Qualifying for Pediatric Exclusion within Section 505A of the Federal Food, Drug, and Cosmetic Act" for guidance on what should be included in the PPSR. We are at the moment revising this policy document. Sponsors must make sure that their PPSR is submitted with adequate time (about 120 days) for both FDA review and Pediatric Review Committee discussion.[50]

7.2.3. Variations in documentation submission

When comparing PIP and PSP, the section titles in the PSP template closely resemble those of the EU PIP model for intellectual documents (parts B to E), even appearing in the same order.

The FDA generally requires less detailed background information on aspects such as a product's characteristics and its development in adults, as their technical review divisions handle all studies and data related to both mature and juvenile patient development from the opening of an investigational NDA by the sponsor. Conversely, when sponsors reach out to EMA with a PIP application in the EU, they may need to provide more detailed information since it is often their first interaction with them.

Despite this difference, both regions expect concise, stand-alone applications: In the EU, it is suggested that each scientific document for a PIP application should not exceed 40 pages per condition, whereas PSP applications submitted within the US should include between 12 and 60 pages.[51]

7.3. The initial submission of relationships with regulations

7.3.1. EU

EMA has been providing free early pediatric interaction sessions with sponsors since June 2015 to encourage timely conversations about pediatric advancement and the timing and substance of PIP submission. Before submitting a PIP, this new initiative seeks to enable discussion regarding addressing pediatric necessities relating to a particular product. In addition, to guarantee a quick validation procedure at the time of application, a professional initial submission discussion can be set up several months before applying for a PIP or waiver. The PIP/waiver application questions and answers offer guidance.

Figure 6. Scientific guidelines for the development of pediatric medications
Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medical Agency; FDA: Food and Drug Administration.

7.3.2. US

When it comes to juvenile advancement, the FDA is in favor of early participation and conversations. These can start as early as the pre-investigated new drug (IND) phase or at the finish of phase I discussions. This is particularly valid for medications intended to treat life-threatening or fatal diseases. Before the initial PSP filing, these exchanges should occur for advancement programs covered by PREA. Sponsors of advancement programs covered by the BPCA can file a PPSR at any stage of the legislative advancement procedure. WRs can be issued by the FDA at any point during the product developmental process as long as there is enough evidence. There are no costs

associated with filing a PPSR; however, sponsors who wish to complete WR as a component of a marketing proposal or supplementary application must supply the studies and pay any associated fees.

7.4. When should the PIP, PSP, and PPSR be submitted?

7.4.1. EU

A PIP proposal has to be filed early in the medication advancement procedure in the EU, usually after completing pharmacokinetic trials in adult individuals. The EMA accepts the sponsor's ambiguity and specifies that submissions must coincide with the conclusion of pharmacokinetic study and preliminary tolerance research for healthy subjects or patients, or with the beginning of adult Phase II research (proof-of-concept), but not before Phase III studies.

7.4.2. US

Under PREA, the sponsor is required to submit the first PSP within 2 months following the conclusion of the phase II discussion in the US. The sponsor should submit the first PSP as soon as possible, but before starting any phase III investigations or combining phase II and III research, if there is not an end-of-phase (EOP2) conference. The sponsor must submit the first PSP application at least 7 months before submitting a marketing application or supplementary if no phase III or combination phase II and III studies will be completed. It is strongly advised to send an initial PSP before the EOP2 meeting for serious or fatal disorders with limited pediatric treatment options. This will enable product discussions during the initial IND stage or during the EOP2 meeting.[52]

7.5. Method of assessment

7.5.1. EU

In the EU, the method of assessment for PIP involves a thorough evaluation and expert advice from the Pediatric Commission of the EMA. The final decision is made by the EMA. The EMA reviews and validates proposed PIPs within 30 days and then provides a review analysis to the PDCO. After receiving a valid proposal, which is delivered by EMA to sponsors within 10 days of adoption, the PDPC has 60 or 120 days to adopt its opinion. If there is no request for reexamination from sponsors within 30 days, the advice becomes final and results in an EMA conclusion on PIP issuance within a further 10 days.

The maximum review time that an evaluator agency can take includes:

(i) A validation stage of up to 30 days
(ii) A specific timeframe for the EMA to review a PIP:
   (a) Validation: up to 1 month
   (b) Evaluation phase: 1 + 1 month
   (c) Conclusion phase: 40 days (which can be shortened to 10 days upon the application).

This creates a total of 190 days. However, during the time between the first and second (obligatory) evaluation phases, the sponsor has an infinite amount of time to reply to the inquiries from the PDCO for modifications (referred to as the clock-stop period). Although the EMA suggests a response time of 90 days, in practice, it typically lasts about 4.5 months.

7.5.2. US

Under the US PSP evaluation guidelines, the first PSP must be examined within 75 days after receipt, according to Pediatric Epilepsy Research Consortium regulation. Within 90 days of receiving the PSP, the FDA must hold a meeting or provide the sponsor with a written answer. After the meeting with the FDA, the sponsor has 90 calendar days to submit an agreed initial PSP or to receive written comments from the FDA. The FDA provides written confirmation of its agreement within 30 days after the agreed initial PSP submission.

The review period for a PSP in the US would normally last 7 months, and the sponsor could begin the process as soon as 60 days following the EOP2 conference, according to the previously outlined protocol. Initiation should happen before beginning a phase III trial or a combined phase II and III trial (i.e., sooner) if an EOP2 conference is not held. If not, initiation must take place up to 210 days before marketing application submission.

Regarding WRs in the US, the FDA may not respond to the sponsor with a suitable answer for up to 120 days following the submission of the PPSR.

8. Pediatric drug regulations in China

The Drug Administration Law, which became effective on December 01, 2019,[53] clearly outlines the nation's responsibility to promote and prioritize the creation of new forms, dosages, and precise information of pediatric medications that align with children's physiological characteristics. Regulatory agencies are in the process of establishing guidelines, enhancing communication and technical support, as well as securing high-quality resources for clinical trials related to pediatric drugs.[54] The regulatory documents issued in China are represented in Table 4**.** We have received a comprehensive list of all oppositional defiant disorders from 2000 up to December 2012 from EMA. This includes designation dates and numbers, indications, and age categories indicating whether they are intended for use in children or adults (i.e., potential pediatric usage or

not).[55] Figure 7 represents the schedule of modifications to regulations for the advancement of pediatric medications.

9. Pediatric drug regulations in Japan

Since there are no legal requirements for the production of pediatric medication in Japan, the Ministry of Health, Labor and Welfare (MHLW) has implemented a range of initiatives since 2000 to encourage its advancement.[56]

On December 22, 2014, the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (issued by the Ministry of Education, Culture, Sports, Science and Technology and MHLW) were established by merging two existing government guidelines: "Ethical Guidelines for Epidemiologic Research" and "Ethical Guidelines for Clinical Research." These new ethical guidelines marked the first instance of incorporating regulations on "obtaining assent," a procedure particularly relevant to children. This development indicates that Japan is taking initial steps toward addressing issues related to children.

New and distinct pathways for regulation, such as the "high-need medical devices," "system for designating orphan medical devices," the "Sakigake strategy,"[57] "fast-break scheme for innovative medical devices," and "clinical evaluation report system" were introduced to assist the advancement of orphan medical devices in Japan. A significant obstacle in obtaining approval for medical devices targeting rare diseases is meeting clinical evaluation requirements. As alternatives to the traditional submission procedure needing clinical study data, novel approval routes such as the "fast-break scheme" and the "clinical assessment reporting system" have been put into place.[58]

The FDA recently published three guidelines to encourage the initial advancement of medical devices for pediatrics.[58] These include the 2014 Guidance on Pre-market Assessment of Pediatric Medical Devices, the 2014 Guidance on Providing Information about Pediatric Uses of Medical Devices, and the 2016 Guidelines for Using Clinical Data Already Available to Extrapolate to Pediatric Medical Device Usage. Together with these initiatives centered on pediatrics, other programs, such as the Breakthrough Device Program, have been initiated by the FDA to encourage innovation in medical devices. Furthermore, regulatory authorities such as PMDA in Japan have also supported using registry data to enhance evaluation processes for pediatric medical devices while reducing costs and enhancing efficiency.[59]

In addition, three distinctive Japanese projects that are expected to greatly improve the development of pediatric medical devices were found through a search on the PMDA webpage in December 2019: "Conditional Early Approval System for Innovative Medical Device Products," "PMDA Science Board on Evaluation of Medical Devices in Pediatric Use," and "Subsidization Program for Application of Pediatric Medical Device." Each initiative's goals and achievements were examined using data that were made public by the MHLW and the PMDA. The Japan Federation for Development of Medical Devices website was another source of information regarding the Orphan Medical Equipment Registration System that was examined.[60]

Table 4. Regulatory documents issued in China[71]

Guidelines	Regulations	Important considerations
"Guideline 2014"	"Guideline on Pharmacokinetic Studies in Pediatric Population"	(i) Pharmacokinetics in the pediatric population: Study design, methodology, and regulatory considering
"Guideline 2016"	"Guideline on Clinical Trials in the Pediatric Population"	(i) Monitoring and ensuring the safety of data categorizing patients by age (ii) Commencement duration for drug administration (iii) Testing drugs in clinical trials involving children (iv) Planning clinical trials for pediatric patients (v) Choosing suitable dosage forms for children (vi) Conducting clinical trials for rare diseases in the pediatric population (vii) Ethical factors to consider
"Guideline 2017"	"Guideline on Extrapolation from Adults to Pediatric Patients"	(i) Idea of extending beyond known data (ii) Process of predicting based on existing information (iii) Modeling and simulation (iv) Fundamental principles and necessary conditions
"Guideline 2020"	"Guideline on the Use of Real-World Research to Support Development and Regulatory Evaluation for Pediatric Drugs"	(i) Distinctions and suitable integration of experimental in relation to conventional randomized controlled clinical studies (ii) Typical circumstances for the application of practical studies in China's medicine discovery for children

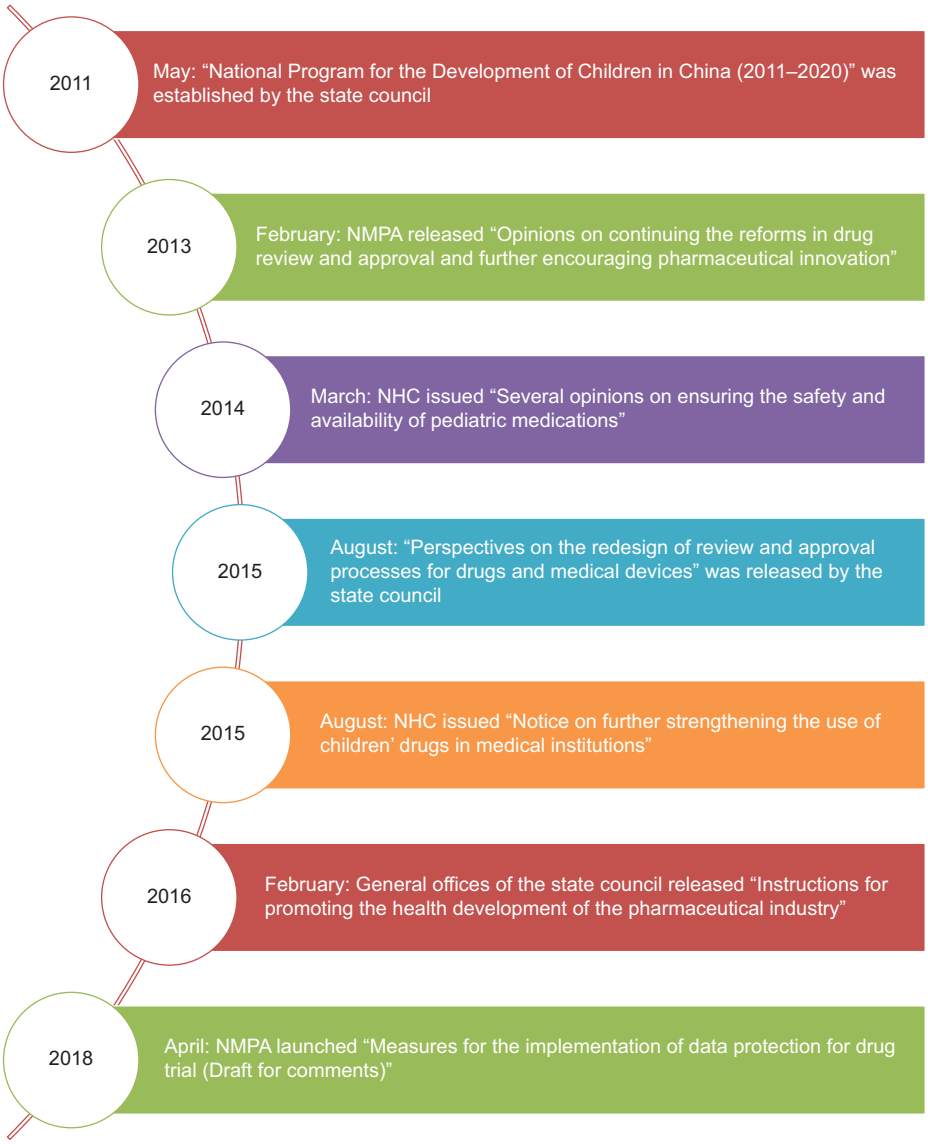

Figure 7. Schedule of modifications to regulations for the advancement of pediatric medications
Abbreviations: NHC: Neonatal Head Circumference; NMPA: National Medical Product Administration.

The Clinical Trials Act, established in 2017 and effective from 2018, along with the Ethical Principles for Medical and Health Studies Including Participants, regulates clinical studies. In addition, the Pharmaceutical Affairs Law and Good Clinical Practice standards govern these clinical studies. Following revisions to the Pharmaceutical Affairs Law in 2002, it became possible for doctors and dentists to act as principal investigators for investigator-initiated trials (IITs). Instead of the sponsor-initiated trials (SITs) that firms normally perform, these IITs arise when industries refuse to sponsor studies for novel uses of pharmaceuticals or medical devices.[61] The duties of SITs and IITs are reported in Table 5.

10. Conclusion

Regulations governing pediatric drug development in India represent a critical step toward ensuring the safety and efficacy of medications for children. The establishment of specific guidelines and requirements by regulatory authorities such as the Central Drugs Standard Control Organization has helped streamline the process of pediatric drug approval and promote the development of age-appropriate formulations. However, despite these advancements, several challenges persist, including the limited availability of pediatric clinical trial data, ethical considerations in conducting research involving children,

Table 5. In performing clinical studies, the duties of sponsor-initiated clinical trials (SITs) and investigator-initiated trials (IITs)

Responsibilities	IITs	SITs
Responsibility holder	Principal investigators conduct their own clinical studies	Pharma Industries
IB, protocol, and SOP before clinical studies	Principal investigators conduct their own clinical studies	Pharma Industries
Production or importation of IP	IP Supplier (Pharma Industries)	Pharma Industries
Clinical study center	Hospital	Hospital
When conducting clinical studies reaction to the regulatory agency throughout as well as after studies (notice of clinical trials submitted, safety reports)	Principal investigators conduct their own clinical studies	Pharma Industries
Monitoring/audit	Principal investigators conduct their own clinical studies (or the individual to whom they allocate)	Pharma Industries
Records (data management, statistical analysis, CSR)	Principal investigators conduct their own clinical studies	Pharma Industries
NDA	Pharma Industries	Pharma Industries

Abbreviations: CSR: Corporate social responsibility; IB: Investigator's brochure; IP: Investigational product; NDA: New drug application; SOP: Standard operating procedure; SIT: Sponsor-initiated clinical trial; IIT: Investigator-initiated trial.

and the need for greater collaboration between regulatory agencies, health-care providers, and pharmaceutical companies. However, we have covered a comparison between countries such as the US, EU, Japan, and China and the need for pediatrics regulations in India.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Swati Jadhav
Writing – original draft: Mangesh Tatar, Swati Jadhav, Lisha Wadhava
Writing – review & editing: Aman Upaganlawar, Chandrashekhar Upasani

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Availability of data

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REVIEW

Role of biomarkers in disease management and drug development in Africa: A narrative review

Komal Zulfiqar[1], Maria Qadri[2], Sulafa Rasheed Ahmed Ali[3], Ummsalamah Adenike Musa[4], and Malik Olatunde Oduoye[5]*

[1]Department of Medicine, Allama Iqbal Medical College, Bihar Sharif, Pakistan

[2]Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

[3]Department of Microbiology, Elfarabi College for Science and Technology, Khartoum, Sudan

[4]Department of Medicine, Medicine and Surgery, Yusuf Maitama Sule University, Kano, Kano State, Nigeria

[5]Department of Research, The Medical Research Circle (MedReC), Goma, Democratic Republic of Congo

Abstract

Biomarkers are quantifiable components in the body or its byproducts that can be used to evaluate human health or pathogen development. This review aimed to explore and evaluate the utilization, challenges, and prospects of biomarkers in enhancing drug development in Africa. We searched for relevant articles in online databases, such as PubMed, Science Direct, and Google Scholar, covering the period from 2013 to 2024. The use of biomarkers can be traced back to the 1800s when they were initially referred to as surrogate markers and later as surrogate endpoints. Biomarkers are specific molecules or cells in the body that serve as indicators of underlying biological processes, aiding in disease diagnosis or measuring pharmacological responses to therapy. Diagnostic biomarkers are biomolecules that indicate the presence of diseases or help identify specific disease subtypes in individuals. Examples of biomarkers for common diseases, such as malaria, include *Plasmodium falciparum* lactate dehydrogenase, histidine-rich protein 2, and hemozoins; for colorectal cancer, biomarkers include Rat Sarcoma, microsatellite instability, human epidermal growth factor receptor 2, consensus molecular subtypes, and Circulating tumor DNA/Circulating tumor cells. These biomarkers guide targeted therapy and adjuvant chemotherapy approaches by allowing for patient stratification and determining which patients would benefit from adjuvant treatment. Overcoming challenges such as cost-effectiveness and regulatory approval is crucial. Despite initial financial and logistical constraints, these efforts will ultimately result in significant improvements in efficiency.

Keywords: Biomarkers; African region; Drug development; Disease management

***Corresponding authors:**
Malik Olatunde Oduoye
(malikolatunde36@gmail.com)

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1. Introduction

Biomarkers are measurable elements, structures, or functions in the body, including their metabolites, that can help determine their effects on human health or disease development.[1] Biomarkers, or biological markers, are among the characteristics that

can be objectively measured and evaluated as potential indicators of any normal or abnormal pathophysiological process or pharmacological response to a given treatment.[1] They can include proteins, genes, or other types of biomolecules.[2] Biomarkers are essential for drug discovery, development, and personalized healthcare because they provide information on diagnosis, prognosis, and therapeutic response.[2] They also help identify possible therapeutic targets, assess the efficacy and safety of pharmaceutical products, and facilitate monitoring of disease progression and treatment outcomes.[2]

Biomarkers can be classified into several categories such as safety, pharmacodynamic, therapeutic, prognostic, and diagnostic.[2] The domains of cancer classification and biomarker discovery are increasingly utilizing machine learning (ML) approaches, which facilitate the identification of novel biomarkers for personalized therapy programs.[2] Identifying potential targets and evaluating their efficacy and safety are essential for the search and development of new drugs.[2] It is crucial to eliminate certain barriers and restrictions in traditional drug development approaches, such as the need to identify new risk factors, initial diagnostic indicators, or alternative therapeutic methods. Conventional drug development procedures often encounter difficulties in addressing safety and efficacy challenges, such as significant drug accumulation in organs beyond the target or inadequate accumulation at target sites during the later phases of this process.[3] Using biomarkers in the development of medicinal products offers several advantages. First, biomarkers accelerate the development of new medicines by providing unbiased information on normal biological processes, diseases, and pharmacological responses to treatment.[4] These biomarkers can optimize clinical benefits through specific therapies by supporting the co-development of diagnostics and identifying responsive populations.[5]

Biomarker research has advanced significantly in several areas, including cancer detection, chronic pain, and optical biosensors.[6] *UBE2C*, a gene that is differentially expressed in 28 types of cancer, plays a crucial role in both overall survival (OS) and disease-free survival for patients with many of these cancers. Moreover, assessing *UBE2C*'s diagnostic value and its correlation with various immune-related signatures could establish it as a reliable biomarker for cancer diagnosis. *UBE2C* may also serve as a therapeutic gene that enhances treatment responses and OS for cancer patients, making it a promising target for future cancer drugs.[7] Significant progress has been made in the field of cancer diagnostics, including the development of robust, reliable, and cost-effective cancer diagnostic tools.[6] Improving methods for detecting biomarkers could significantly enhance health outcomes. Incorporating biomarker approaches into drug development processes could lead to faster approvals, lower development costs, and better outcomes for patients. By using biomarkers for individualized treatment, researchers can identify patients who are more likely to respond to specific medicinal products and tailor their treatment to meet individual needs.[8] This approach will lead to increased treatment options and improved patient care. In addition, biomarkers can identify individuals at higher risk for adverse reactions to certain medicinal products, enabling more efficient and effective treatments.[9] A recent study on biomarkers for identifying bacterial versus non-bacterial febrile infections in African children has yielded positive outcomes.

Researchers found angiotensinogen (AGT) to be a promising plasma protein biomarker that accurately identified bacterial infections in febrile children from a low-income area in Kenya. Contrary to C-reactive protein (CRP), AGT demonstrated superior performance in differentiating invasive bacterial infections from febrile malaria episodes and in distinguishing bacterial infections from those caused by viruses.[10] The Royal Marsden Hospital (RMH) score has proven effective in various cancers, such as colorectal cancer (CRC), sarcoma, and non-small-cell lung cancer.[7] It serves as a valuable biomarker for both clinical trial participants and as a prognostic marker in real-world contexts.[7] The baseline RMH score independently predicts OS and progression-free survival (PFS) in patients with extensive-stage small-cell lung cancer, being the sole independent prognostic factor for PFS.[7] A large cohort study involving over 100,000 real-world patients confirmed a shorter OS in those with high RMH scores. These results underscore the RMH score's potential as a prognostic tool for both clinical trial selection and real-world clinical applications.[7] Hearing loss linked to immune checkpoint inhibitor (ICI) treatment is generally reversible in melanoma patients and is often accompanied by other immune-related adverse events.[11] It also correlates with a high response rate to ICIs. As ICIs are increasingly used in earlier treatment stages and adjuvant settings, the number of survivors experiencing ICI-related hearing loss is expected to increase.[11] In this review, we aimed to explore and evaluate the utilization, challenges, and prospects of biomarkers in enhancing drug development in Africa.

2. Methods

2.1. Literature search

A comprehensive literature search of many key databases, including PubMed, Scopus, and Web of Science, was conducted for this narrative review. Search terms included

"Biomarkers," "African disease," "drug development," and "precision medicine."

2.2. Methods

2.2.1. Inclusion criteria

English-language articles published between 2010 and 2024 that focused on biomarkers in African disease and drug development were included. This specifically encompassed original research articles, reviews, case studies, cross-sectional studies, randomized controlled trials, non-randomized controlled trials, and case reports, with a particular emphasis on human populations, primarily those prevalent in Africa or of relevance to African populations.

2.2.2. Exclusion criteria

Non-English-language articles, publications before 2010 or after 2024, studies not focused on biomarkers or African disease/drug development, editorials, letters to the editor, case reports, non-human studies or research not centered on African populations, diseases not relevant to Africa or lacking biomarker focus, and articles without available full text were excluded. Duplicate publications or studies with overlapping data were also excluded.

3. Results

3.1. Biomarkers based on applications

3.1.1. Diagnostic biomarker

A diagnostic biomarker is an indicator that helps diagnose, detect, or confirm the presence of a specific disease or condition or distinguishes between different subtypes of a disease, allowing for precise identification and classification of affected individuals.[12] These biomarkers can not only diagnose diseases but also revolutionize how to classify them. For instance, cancer diagnosis is shifting from a traditionally organ-based approach to a more modern molecular and imaging-based classification system, enabling a more precise and personalized understanding of the disease.[13]

3.1.2. Monitoring biomarkers

A biomarker that can be repeatedly measured to track the progression of a disease or medical condition, detect exposure to a therapeutic or environmental agent, or monitor the effectiveness of a treatment is considered a monitoring biomarker.[12] These biomarkers can be detected in various bodily samples, including blood, urine, and tissue specimens. By measuring the levels of these biomarkers, doctors can achieve a better understanding of disease progression or treatment effectiveness. Some examples of monitoring biomarkers include cancer antigen 125 for ovarian cancer, prostate-specific antigen for prostate cancer, and viral load for human immunodeficiency virus (HIV) infection.[12]

3.1.3. Pharmacodynamics biomarkers

Pharmacodynamic biomarkers play a role in assessing the efficacy and pharmacological impact of a drug, enabling healthcare professionals to determine whether treatment has the desired effect. An example is *PI3K* inhibitors, which are used to treat various cancers. The *PI3K* signaling pathway includes multiple downstream targets, including *AKT*. On activation of the *PI3K* pathway, *AKT* becomes phosphorylated. Therefore, phosphorylated *AKT* (pAKT) can serve as a pharmacodynamic biomarker to confirm that *PI3K* inhibitor treatment is effectively inhibiting the *PI3K* pathway. A decrease in *pAKT* levels indicates that the inhibitor is working.[14]

3.1.4. Predictive biomarkers

A predictive biomarker indicates the probability of an individual or group experiencing a beneficial or harmful effect from a medical intervention or environmental agent, enabling healthcare professionals to predict treatment outcomes and make informed decisions.[15] An excellent example of a predictive biomarker is the human epidermal growth factor receptor 2 (*HER2*) biomarker for breast cancer. Women with breast cancer who test positive for *HER2* have a better chance of responding to treatment with targeted drugs, such as trastuzumab (Herceptin). In this case, the *HER2* biomarker predicts the likelihood of response to a specific treatment. Other examples of predictive biomarkers include the *KRAS* biomarker for colon cancer and the *BRCA* biomarker for breast and ovarian cancers.[15]

3.1.5. Prognostic biomarkers

Prognostic biomarkers are indicators that predict the potential course and outcome of a disease if left untreated, providing valuable insights into the likely progression and severity of the condition. Prognostic biomarkers, such as low-density lipoprotein (LDL) cholesterol, predict the likely outcome of a disease if left untreated. Elevated LDL cholesterol levels indicate a higher risk of developing atherosclerosis and experiencing severe events, such as heart attack, stroke, or death, in individuals already diagnosed with the disease.[13]

3.1.6. Imaging biomarkers

Imaging biomarkers can be used to detect diseases, track disease progression, and evaluate treatment effectiveness. There are two main types of imaging biomarkers. Structural imaging biomarkers indicate changes in the body structure,

such as tumor size or the number of lesions. Examples include magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans. Functional imaging biomarkers indicate changes in function or metabolism, such as blood flow or oxygen use. Examples include functional MRI, single-photon emission CT, and PET.[16]

3.1.7. Molecular biomarkers

Molecular biomarkers can detect molecular changes or specific molecules. There are two main types. Biochemical biomarkers detect changes in specific chemicals in the body. Examples include blood glucose, cholesterol, and creatinine levels. Molecular profile biomarkers detect changes in the DNA, RNA, or proteins of a cell or tissue. Examples include gene expression, microRNA, and proteomic profiles. Molecular biomarkers are useful for diagnosing diseases, predicting prognosis, and monitoring treatment response.[17]

3.2. Current scenario of biomarkers in diagnosis and personalized medicine

Biomarkers play a crucial role in predicting prognosis, choosing suitable treatments, and tracking therapeutic responses.[17,18] They facilitate early disease detection, patient stratification based on disease risk or treatment response, and personalized treatment decision-making.[17,19] Biomarkers are essential for diagnosing and tailoring treatment for various diseases, such as breast cancer and sarcoidosis. They help identify conditions early, predict prognosis, anticipate treatment response, and guide therapy, ultimately enhancing patient outcomes.[9,20] Similarly, novel biomarkers discovered through gene expression profiling and omics sciences offer the potential for improving diagnosis and predicting disease progression in sarcoidosis, underscoring the need for better diagnostic tools in this area.[21] Breast cancer subtypes are classified and targeted therapies (e.g., tamoxifen and trastuzumab) are guided using biomarkers such as the estrogen receptor, progesterone receptor, and *HER2*. Treatment selection with *BRAF* inhibitors in patients with melanoma is guided by biomarkers such as *BRAF* mutations.[22,23] Diagnostic biomarkers also play a crucial role in autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis for confirming diagnoses and tracking disease activity. In addition, biomarkers for disease severity are used to help tailor treatment for inflammatory skin conditions such as atopic dermatitis and psoriasis.[24]

3.3. Application of biomarkers and their advantages and disadvantages

Biomarkers have demonstrated several advantages; early disease detection can be achieved using biomarkers to identify molecular signatures or abnormalities associated with a condition. Matching patients to the most effective treatments based on their characteristics through biomarker-guided therapy can optimize treatment efficacy and minimize adverse effects.[17,25,26] The evaluation of disease risk, along with diagnosis, prognosis, and treatment, can be supported by using biomarkers as early warning systems.[17,27] They can reduce bias and misclassification in epidemiological research by increasing the sensitivity and specificity of measuring exposures or risk variables. They can help identify patients prone to illness and provide more effective population stratification based on illness risk. They can provide insights into the disease course, prognosis, and treatment effectiveness.[27] Despite their advantages, biomarkers have limitations. One notable disadvantage is the risk of overuse or misuse, which can lead to misinterpretation of results due to a lack of comprehension of the disease's pathophysiology and intervention mechanisms.[28] Furthermore, the diagnostic processes for certain diseases, such as cardiovascular diseases (CVDs), may require a multimarker approach that utilizes various biomarkers. This could potentially increase the cost and complexity of the diagnostic procedures.[26] In addition, regulatory restrictions on the approval and validation of biomarker data create added challenges in the drug development process.[26] These constraints underscore the importance of an equitable and informed strategy for utilizing biomarkers in the healthcare industry.[29]

3.4. Common types of biomarkers

Biomarkers are essential in clinical diagnostics and biomedical research, and they are derived from different biological materials. Immunohistochemistry assays are often used to detect protein biomarkers.[30] Biomarkers in RNA, especially chimeric RNA present in exosomes obtained from bodily fluids, are used to diagnose diseases.[31] Exosomes, which are tiny extracellular vesicles found in bodily fluids, contain abundant tumor-specific material such as nucleic acids and proteins, making them highly useful for cancer diagnostics.[32] Biomarkers can be detected in blood, saliva, urine, peritoneal fluid, and other biofluids, providing a non-invasive method for detecting and monitoring diseases.[33]

4. Discussion

4.1. History of biomarkers

The term "biomarker" dates back to the 1800s.[34] Biomarkers were referred to as surrogate markers in the late 1980s and later became known as surrogate endpoints.[34] The concept began with the discovery of certain molecules or cells in the body that could be used to check biological body processes, diagnose certain diseases, or evaluate pharmacological

responses to therapeutic interventions.[35] The discovery of immunoglobulin-free light chains in 75% of patients with myeloma in a groundbreaking 1848 study marked the detection of the first known biomarker. This breakthrough paved the way for the discovery of numerous biomarkers across a wide range of diseases.[35] Dr. Henry Bence-Jones identified the immunoglobulin-free light chain in 1847, and his research published the following year shed light on this crucial biomarker.[35]

The definition of biomarkers has undergone significant revisions over the past 50 years, adapting to new scientific discoveries and clinical breakthroughs that have enhanced our understanding of their role in healthcare.[35] In 1973, Rho *et al*. used the term "biomarkers" for the 1st time and defined it as the presence or absence of a specific biological material in the body.[36] In the 20th century, scientists began using blood tests to detect substances such as cholesterol and creatinine, which were among the earliest biomarkers used to understand and diagnose conditions related to heart and kidney functions.[36] The advent of molecular profiling techniques in the 21st century has enabled the development of more precise and personalized biomarkers, facilitating advances in personalized medicine and targeted therapies.[36] Today, biomarkers are utilized in a wide range of fields, from medicine to environmental monitoring, illustrating their broad applicability and importance in various scientific disciplines.[36]

4.2. Types and characteristics of biomarkers

There are several ways to categorize biomarkers based on their functions.[12]

- Imaging biomarkers:

Imaging biomarkers are used to visualize and measure biological processes in the body. MRI, CT, and PET scans are non-invasive techniques that enable the observation of disease progression and response to therapy.[36]

- Molecular biomarkers:

Molecular biomarkers include genes, proteins, and other molecules that provide insights into the disease state or treatment effects. They can be detected through blood tests, biopsies, or other samples and are crucial for understanding the underlying mechanisms of diseases.[36]

- Diagnostic biomarkers:

Diagnostic biomarkers are used to identify the presence of a disease or condition and can aid in their early detection, allowing for timely intervention and treatment.[36]

- Predictive biomarkers:

Predictive biomarkers provide information on the likely response of patients to a particular treatment. They are essential in personalized medicine, helping tailor treatments to individual patients based on their predicted response.[36]

- Prognostic biomarkers:

Prognostic biomarkers provide insights into the likely course or outcome of a disease. They can aid in understanding disease progression and in guiding decisions regarding the necessary aggressiveness of treatment.[36]

4.3. Applications and importance of biomarkers

Biomarkers play pivotal roles in numerous aspects of medical research and healthcare.[12]

- Drug development:

In drug development, biomarkers are used to assess the efficacy and safety of new drugs. They assist in identifying potential targets for therapeutic intervention and in monitoring treatment effects.[36]

- Disease monitoring:

Biomarkers are used to monitor disease progression and treatment response. They provide valuable information that can guide adjustments in therapy to improve patient outcomes.[36]

- Personalized medicine:

Biomarkers in personalized medicine enable customized treatment plans based on the individual characteristics of the patient. This approach can lead to more effective and targeted therapies, minimizing side effects and improving overall health outcomes.[36]

- Environmental monitoring:

Beyond healthcare, biomarkers are also used in environmental monitoring to assess the impact of pollutants and other environmental factors on human health and ecosystems.[36]

The ongoing research and development in the field of biomarkers continue to expand their applications and improve their accuracy, making them indispensable tools in modern science and medicine.[36]

4.4. Biomarkers in African diseases

Throughout history, biomarkers have become increasingly precise and reliable, allowing for more specific and personalized approaches to medicine.[37] An ideal biomarker must meet certain criteria, including accessibility, specificity, and sensitivity to the investigated pathology and the ability to be translated from research to clinical practice.[37] In sub-Saharan Africa, the leading causes of illness and death include infectious diseases such as malaria, tuberculosis (TB), and HIV infection as well as non-infectious diseases such as diabetes and CVDs, which together account for the majority of the region's disease burden.[38] Early detection of specific biomarkers for *Plasmodium* infection is vital in

malaria management, as it allows for prompt and informed decision-making, enabling healthcare professionals to initiate effective treatment plans and improve patient outcomes.[39] Such biomarker-based detection methods, combined with appropriate treatment approaches, can considerably help reduce human reservoirs of the parasite, which frequently contribute to the persistence of malaria infection transmission in endemic zones of Africa where asymptomatic malaria is widespread.[39] Some examples of malaria biomarkers are *Plasmodium falciparum* lactate dehydrogenase, histidine-rich proteins (HRPs), and hemozoins.[39] Biomarkers may also be used to distinguish latent TB infection and predict the likelihood of relapse, treatment response, and the development of clinical disease. These insights are urgently needed to establish precise endpoints for clinical trials of new drugs and vaccines.[40] In addition, several biomarkers are now the main focus of efforts to enhance techniques for assessing the risk of CVDs.[41] The use of these biomarkers is appealing because they combine signals from several pathophysiological pathways and offer combined predictive utility.[41] Elevated concentrations of fibrinogen, interleukin-6, CRP, and galectin-3 are known risk factors for CVDs and may serve as biomarkers to partially anticipate the onset of the condition.[41]

4.5. Disease-related biomarkers

Bravo *et al*. reported the discovery of 131,012 disease–biomarker correlations involving 2,803 genes and 2,751 disorders through text mining.[42] Biomarkers associated with neoplasms are crucial for identifying, diagnosing, and managing cancer. This group includes a wide range of disorders involving the nervous system, spine, and brain. Biomarker research in neurological diseases aims to identify markers that can assist in the diagnosis and treatment of neurological disorders.[42] CRC biomarkers, such as *RAS*, microsatellite instability, *HER2*, consensus molecular subtypes, and Circulating tumor DNA/Circulating tumor cells, facilitate targeted therapy and adjuvant chemotherapy by allowing for patient stratification and identifying those who can benefit from adjuvant treatment.[43] In atopic dermatitis, biomarkers are particularly important for selecting appropriate treatments for patients. They assist in prognosis, measuring the treatment response, and assessing disease severity.[44] In rheumatoid arthritis, biomarkers, including autoantibodies and disease-modifying antirheumatic drug pharmacogenetics, are used to identify predictors of treatment response and personalized therapy.[45] The availability of real-world genomic data and advancements in technology have facilitated biomarker-driven drug development, shifting the focus from a "one-drug-fits-all" approach to a more tailored strategy. This has led to the creation of targeted therapeutics and creative clinical trial designs.[46]

4.6. Drug-related biomarkers

In neurodegenerative disorders such as Alzheimer's disease, accurate biomarkers are essential for adaptation to therapy and timely diagnosis.[22] The event-related potential biomarker (ERP), particularly the P300 technique, has shown promise as a surrogate for predicting the cognitive potential of medicinal products in neurocognitive diseases, including Alzheimer's disease.[22] The ERP P300 latency has been established as a measurable, objective parameter for monitoring the progression of cerebral decline and response to therapy in individuals with Alzheimer's disease dementia as well as for identifying changes in brain function. P300 tests are an excellent tool for the early development of pre-cognitive drugs, as they enable direct monitoring of the functioning of large neural networks in response to auditory stimulation.[22] Other neurological and psychiatric conditions, such as multiple sclerosis, epilepsy, Huntington's disease, transient ischemic stroke, intellectual disability, attention-deficit hyperactivity disorder, traumatic brain injury, and mental health issues, have also been researched regarding ERP P300 latency.[22] Serum levels of the enzyme diamine oxidase serve as a diagnostic marker for respiratory allergies. In addition, protein deamination and extracellular vesicles have been identified as novel biomarkers for the early pre-motor stages of Parkinson's disease.[23] DNases have been identified for their role in cleaving extracellular DNA and are considered a potential marker for systemic lupus erythematosus.[47] Table 1 shows an overview of disease- and drug-associated biomarkers with implications for personalized medicine.

4.7. Importance of biomarkers drug development and disease management in Africa

The health of individuals in third-world countries is persistently under threat, accounting for approximately 90% of the global health burden, whereas only 10% of worldwide research is focused on developing effective solutions to alleviate this burden.[48] Biomarkers may include measurements taken directly from biological samples, such as amniotic fluid, cerebrospinal fluid, plasma, whole blood, peritoneal fluid, pleural fluid, saliva, serum, seminal fluid, sweat, and urine.[49] In addition, they may include measurements such as brain imaging, which do not require direct sampling of biological materials but assess modifications in the nervous system's composition or function.[49] Cholesterol levels serve as a biomarker and risk indicator for coronary and vascular diseases.[49] A doctor can assess a patient's cholesterol levels to predict the likelihood of a heart attack. If anticholesterol medications are prescribed,

Table 1. Overview of disease- and drug-associated biomarkers with implications for personalized medicine

Biomarker type	Associated conditions	Key biomarkers	Purpose/use in therapy	Implications in personalized medicine	References
Disease-related	Neoplasms	Various genes	Diagnosis and management	Enables targeted therapy and patient stratification	42
Disease-related	Neurological disorders	-----	Aid in diagnosis and treatment	Provide treatment for neurological conditions	42
Disease-related	CRC	RAS, HER2	Targeted therapy and chemotherapy	Stratifying patients for adjuvant treatment	43
Disease-related	AD	AD biomarkers	Treatment selection	Predicting prognosis and assessing severity	44
Disease-related	RA	Autoantibodies, DMARD pharmacogenetics	Personalized therapy	Identifying treatment responders	45
Drug-related	AD	ERP P300	Therapy adaptation and diagnosis	Monitoring brain function and therapy response	47
Drug-related	Neurological/Psychiatric conditions	ERP P300, DAO, EVs, DNases	Diagnostic and monitoring	Early drug development and personalized intervention	47,48

Abbreviations: AD: Alzheimer's disease; CRC: Colorectal cancer; DMARD: Disease-modifying antirheumatic drug; ERP P300: Event-related potential P300; EVs: Extracellular vesicles; HER2: Human epidermal growth factor receptor 2; RA: Rheumatoid arthritis; RAS: Rat sarcoma; DAO: Diamine oxidase.

cholesterol levels can be measured at a subsequent appointment to evaluate the medication's effectiveness – specifically, whether it has lowered cholesterol levels and decreased the likelihood of a heart attack.[49]

Patients with diabetes can measure their glucose levels using a single test called hemoglobin A1C, which estimates glucose levels over the previous 2 weeks.[49] Globally, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin are widely recognized as the most reliable and authoritative biomarkers for diagnosing heart failure (HF), maintaining their status as the gold standard in diagnostic testing.[50] Although researchers have investigated various new biomarkers to complement established HF biomarkers for risk assessment, prognosis, and treatment monitoring, evidence supporting their practical usefulness is scarce.

Furthermore, most of these novel biomarkers are not specific to the heart, which limits their potential for clinical application.[50] According to a study conducted in Africa, BNP, NT-proBNP, galectin-3, and soluble ST2 have demonstrated diagnostic and prognostic utility in HF.[50] Guidelines for HF management consistently advocate for the utilization of natriuretic peptides and cardiac troponins.[50] The co-epidemic of HIV infection and TB in sub-Saharan Africa presents a significant health challenge, exacerbated by the geographical overlap of the two epidemics and the 18-fold increased risk of TB in individuals co-infected with HIV.[51] Therefore, there is an immediate need to determine prognostic markers for TB in HIV-co-infected patients to advance patient management and accelerate the development of new treatments.[51] A study conducted in South Africa found that elevated levels of lipopolysaccharide-binding protein and soluble intercellular adhesion molecule serve as biomarkers for the risk of TB recurrence in patients co-infected with HIV.[51] Biomarkers are crucial for successful drug development.[33] Unfortunately, in Alzheimer's disease, only a few biomarkers are available due to the involvement of multiple processes. There are a limited number of target engagement biomarkers that can provide early indications of pharmacological proof, and no surrogate markers exist that can predict clinical outcomes. Furthermore, no validated outcome biomarkers have been identified that correlate with clinical outcomes in trials designed for disease modification. These limitations present challenges for drug development in Alzheimer's disease, resulting in higher failure rates, particularly for disease-modifying treatments.[52] Researchers have identified plasma LDH, HRP II, aldolase, and hemozoin formation as key biomarkers with significant potential for drug targeting and malaria detection, paving the way for breakthroughs in diagnosis and treatment.[53] In African children, it is difficult to differentiate severe falciparum malaria from other severe febrile illnesses that also involve *P. falciparum* infection.

However, measuring plasma HRP II levels can help predict the likelihood of severe malaria and distinguish it from other severe illnesses in children with parasitemia. This highlights the potential value of developing plasma HRP II concentration as a diagnostic tool for severe falciparum malaria in African children.[53] This justifies the use of plasma

HRP II concentration as a biomarker for assessing severe falciparum malaria in this population.[53] Several deaths from communicable and non-communicable diseases occur in low- and middle-income countries due to a lack of early diagnosis and treatment.[48] Biomarkers can help by serving as indicators of disease conditions or treatment responses. However, results from developed countries may not be directly applicable to developing countries owing to differences in disease patterns.[48] Biomarker candidates identified through advanced technology hold potential; however, their application is hindered by challenges such as disease heterogeneity and pre-analytical variability.[48] Economic constraints, a lack of education and awareness, and various social and ethical issues also hinder biomarker discovery in developing countries.[48] Africa lacks the essential resources and infrastructure for young researchers to engage in cutting-edge clinical trials.[48] A recent survey in Nigeria showed that traditional health professional training is widely accepted for interdisciplinary research; however, the necessary scientific skills are lacking.[48] Respondents identified gaps in post-doctoral training, clinical trial competency, and bioinformatics. Although efforts are being made to include African genetic diversity in global genomic data, a lack of skilled personnel hinders the storage, retrieval, analysis, and interpretation of clinical, epidemiological, and genomic data.[48] Biomarkers are essential for developing targeted therapies and personalized treatment plans, particularly in Africa, where healthcare disparities and disease burdens present unique challenges. By identifying biomarkers specific to the African population or reflecting regional variations in disease pathology, researchers and healthcare professionals can tailor interventions and accelerate the approval process for novel therapeutics. This is particularly important in the African context, where efficient drug development processes are crucial for delivering innovative treatments to those in needs. Figure 1 shows the importance of drug development and disease management.

4.8. Current status, challenges, and future perspectives

To support the next generation of diagnostic platforms, biomarkers are urgently needed.[54] Although there are challenges in using biomarkers as diagnostic or prognostic

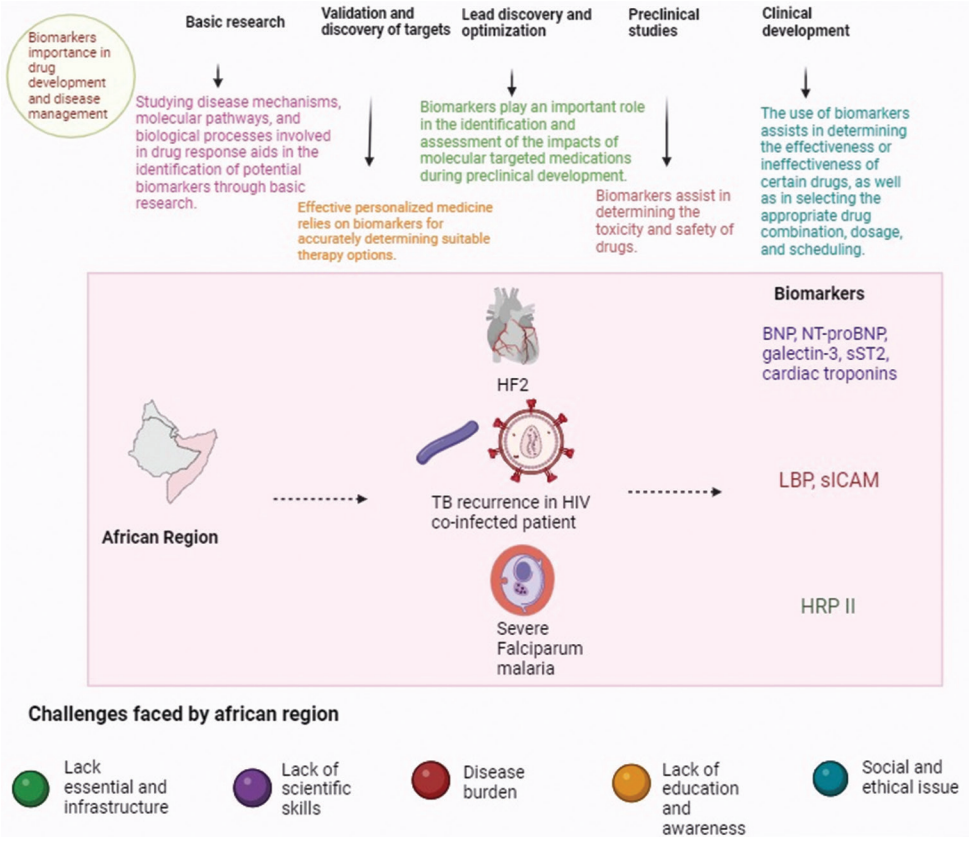

Figure 1. Importance of biomarkers in drug development and disease management
Abbreviations: BNP: B-type natriuretic peptide; HF2: Heart failure 2; HIV: Human immunodeficiency virus; HRP II: Histidine-rich protein II; LBP: Lipopolysaccharide-binding protein; NT-proBNP: N-terminal pro B-type natriuretic peptide; sICAM: Soluble intercellular adhesion molecule; sST2: Soluble ST2; TB: Tuberculosis.

markers, their application may mitigate the drawbacks of existing tests and improve patient outcomes through robust analytical and validation techniques.[54] Advancing research involves integrating favorable biomarkers—both molecular and image-based—and leveraging artificial intelligence to optimize their combinations.[55] Directly comparing these biomarkers in clinical settings would enhance our understanding of their effectiveness.[55] By leveraging the vast data generated through ongoing screening efforts, advanced mathematical and computational models powered by ML can extract valuable insights.[55] However, this requires a systematic collection of patient samples within screening contexts.[55] Moreover, challenges such as demonstrating cost-effectiveness and navigating regulatory approval processes must be addressed.[55] Despite initial logistical and financial hurdles, these efforts will ultimately yield significant efficiency gains.[55] Although such an endeavor may seem daunting initially, the long-term outcomes could prove highly beneficial.[55] This review provides a compelling perspective on the use of biomarkers in drug and disease development in Africa, an area with limited resources. The significance of this topic in such regions cannot be underestimated, particularly given the need to shift focus toward the utilization of biomarkers in drug and disease development. To tackle these challenges, our study has made this issue a central focus. Thus, the potential of biomarkers in drug and disease development in Africa should be investigated through original research studies. In the next 5 years, we anticipate substantial advancements in disease treatment through the creation of groundbreaking medications, facilitated by the utilization of biomarkers.

5. Limitations

This review has some limitations. First, there is a lack of literature on the use of biomarkers in drug and disease development in Africa, resulting in a scarcity of recent references to include. In addition, we have only mentioned specific biomarkers used in Africa due to the absence of original studies on the subject.

While examining the significance of biomarkers in disease and drug development in Africa, it is important to recognize certain limitations. First, the availability of reliable data is restricted due to inadequate representation in global research, potentially resulting in gaps in the analysis. Furthermore, the differing healthcare infrastructures across African nations can impact the relevance and generalizability of findings related to biomarkers. In addition, there is a dependence on studies employing varied methodologies, which could lead to inconsistent conclusions. Finally, the rapid advancement of the field means that this review may not comprehensively capture all recent developments.

6. Conclusion

The African disease landscape and drug development are both critically important, requiring specific biomarkers for effective detection. It would be beneficial to prioritize increased awareness, campaigns, and research opportunities aimed at discovering, utilizing, and implementing more biomarkers to address prevalent diseases in Africa and enhance drug development. Such efforts would not only improve healthcare but also help preserve the African heritage.

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Author contributions

Conceptualization: Komal Zulfiqar, Malik Olatunde Oduoye
Formal analysis: Malik Olatunde Oduoye
Investigation: Komal Zulfiqar
Methodology: Komal Zulfiqar, Malik Olatunde Oduoye
Writing–original draft: All the authors
Writing–review & editing: Malik Olatunde Oduoye

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ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

PERSPECTIVE ARTICLE

The crucial role of drug repositioning in tackling Chagas disease, sleeping sickness, and leishmaniasis

Exequiel O. J. Porta*

Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, University College London, London, United Kingdom

Abstract

Neglected tropical diseases (NTDs), such as Chagas disease, human African trypanosomiasis (sleeping sickness), and leishmaniasis, disproportionately affect low-income populations in tropical and subtropical regions, leading to high morbidity and mortality rates. Consequently, these diseases, historically overlooked in global health agendas, perpetuate cycles of poverty and impede economic development. Drug repositioning, the repurposing of existing drugs for new therapeutic uses presents a promising strategy by reducing drug development time and cost while leveraging known safety profiles. However, despite its success in other therapeutic areas, this approach remains underutilized for NTDs due to challenges such as a limited drug pool, intellectual property barriers, regulatory complexities, and ethical concerns. Essential strategies to overcome these obstacles include expanding approved drug libraries, fostering multi-sector collaborations, streamlining regulatory processes, and adopting innovative funding models. Collaborative efforts among governments, pharmaceutical companies, research institutions, and non-profit health organizations are crucial to fully unlock the potential of drug repositioning. By working together as a united front, these stakeholders can ultimately transform NTD treatment and improve global health outcomes.

Keywords: Chagas disease; Drug repositioning; Drug repurposing; Leishmaniasis; Neglected tropical diseases; Parasitic diseases; Sleeping sickness

***Corresponding author:**
Exequiel O. J. Porta
(e.porta@ucl.ac.uk)

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1. Introduction

Neglected tropical diseases (NTDs) encompass a diverse group of diseases that predominantly afflict low-income populations in tropical and subtropical regions.[1] Historically, these diseases have been overlooked in global health priorities, receiving limited attention and funding. Among these, Chagas disease, sleeping sickness (human African trypanosomiasis [HAT]), and leishmaniasis are particularly notable for their significant morbidity and mortality rates.[2] Along with malaria, these parasitic diseases exert a profound impact on global health.[3] These diseases disproportionately affect millions in economically disadvantaged areas, resulting in substantial health and socioeconomic burdens (Figure 1).

Consequently, these illnesses perpetuate cycles of poverty and impede economic development in affected communities.[4] This critical situation, marked by the significant

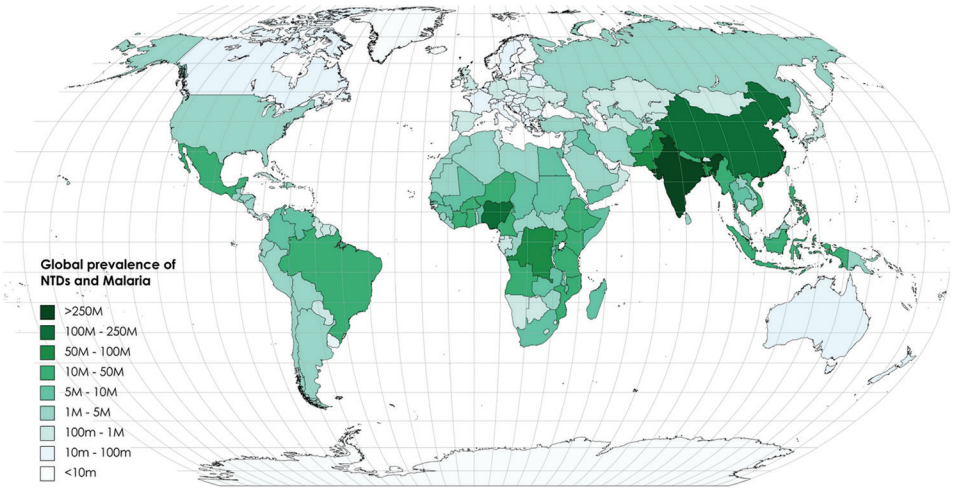

Figure 1. Global prevalence of parasitic neglected tropical diseases, specifically Chagas disease, sleeping sickness, and leishmaniasis, as well as malaria, based on the Global Burden of Disease Data (2019). Collectively, these conditions affect over 1.3 billion people worldwide. Data sourced from: Global Health Data Exchange (https://ghdx.healthdata.org/).

impact of NTDs and a glaring lack of effective and accessible treatments, underscores an urgent need for innovative health-care solutions and therapeutic strategies.[5] However, the development of new drugs for NTDs faces considerable challenges. Primarily, the limited financial incentives for pharmaceutical companies are a major obstacle since these diseases predominantly affect poorer regions with minimal market potential. In addition, the biological complexity of these parasitic diseases makes the development of specific and effective treatments a formidable task.[6]

2. The urgency of utilizing drug repositioning to combat NTDs

Drug repositioning, also known as drug repurposing, involves reevaluating existing drugs for new therapeutic uses.[7] This approach offers a promising alternative to traditional drug discovery by reducing both the cost and time required to bring a treatment to market.[8] Crucially, since the safety profiles of these drugs are already established, the risk of adverse effects is significantly minimized.[9] In the context of NTDs, drug repositioning may be more effective than *de novo* drug design, primarily due to its speed and cost-effectiveness. Repurposing existing drugs circumvents the lengthy and costly process of developing new drugs from scratch,[10] representing a crucial advantage when responding to urgent health needs in resource-limited settings, such as those typical of NTDs. Therefore, these advantages make drug repurposing a practical and efficient approach for addressing these diseases. For comparison, drug repurposing typically shortens the development timeline to 3 – 12 years, as opposed to 12 – 18 years for new drug development (*de novo*). It also reduces costs to US$ 0.4 – 0.8 billion, compared to US$ 1 – 2 billion for developing a new drug.

The potential of drug repositioning is well-documented in various contexts.[11-13] For instance, thalidomide, originally marketed as a sedative, found new purposes in treating multiple myeloma[14] and leprosy.[15] The literature is rich with examples of successful drug repositioning, notably in oncology and cardiovascular diseases.[16-18] Yet, paradoxically, this approach remains considerably underutilized in the realm of NTDs, despite its demonstrated potential in addressing parasitic diseases such as malaria.[19,20] A noteworthy example of the treatment of parasitic NTDs is the repositioning of miltefosine.[21] Initially developed as an anticancer agent, miltefosine made a significant impact in 2002 when it was repurposed as the first oral antileishmanial medication. This milestone in drug repositioning not only exemplifies the versatility of existing drugs but also highlights their potential to address challenging diseases beyond their original intended use. This example of repurposing has set a groundbreaking precedent, paving the way for more innovative and efficient therapeutic approaches in the fight against NTDs.

Although Chagas disease, HAT, and leishmaniasis present unique challenges, including complex life cycles of the causative parasites and diverse clinical manifestations, drug repositioning offers a viable solution to swiftly address these challenges by repurposing existing drugs with known antiparasitic properties.[22] For instance, collectively, the studies by Porta *et al.*,[23] Charlton *et al.*,[24] and Sbaraglini *et al.*[25] present a comprehensive overview of over 100 approved drugs that have been repurposed and are in various stages of development as antiparasitic treatments

for NTDs. Each of these drugs has the potential to evolve into new therapies aimed at eradicating these diseases. These efforts align with the World Health Organization's (WHO) 2021 – 2030 roadmaps for the elimination of NTDs,[26] emphasizing the global commitment to eradicate these illnesses.

Therefore, it is imperative to make a concerted effort to integrate drug repositioning into NTD research and to advance the stages of development and clinical trials of repositioned drugs, specifically targeting these parasitic diseases. Achieving this goal requires increased funding, robust international collaboration, and effective public–private partnerships to facilitate the identification and development of repurposed drugs.[27]

3. Limitations of drug repositioning and mitigation strategies

Despite its significant potential, drug repositioning faces several limitations that hinder its application.[12,23] A significant challenge is the limited pool of drugs available for repurposing. Most existing drugs were developed for diseases prevalent in high-income countries, which may not directly translate to effective treatments for NTDs. This limitation reduces the likelihood of finding suitable candidates for repositioning. In addition, intellectual property and financial considerations pose substantial hurdles. Patents on existing drugs may restrict their use for new indications, creating legal and financial barriers. Moreover, the financial incentives for pharmaceutical companies to invest in NTDs are limited due to the low market potential in affected regions.

Regulatory challenges further complicate the drug repositioning process. Each repurposed drug must undergo rigorous clinical trials to ensure efficacy and safety for the new indication, making the regulatory pathway as complex and lengthy as that for new drug development.[28] This process can be time-consuming and costly. Repositioned drugs often target well-known molecular mechanisms, making the patients susceptible to drug resistance, particularly when the molecular targets are conserved across species (*e.g.*, humans and parasites); this challenge is not exclusive to repositioned therapies. Newly developed drugs face similar risks of resistance. To mitigate these risks, both repositioned and new drugs require careful monitoring and, where appropriate, the use of adaptive treatment strategies, such as combination therapies (*vide infra*). Ethical considerations also play a crucial role, particularly when conducting clinical trials in vulnerable populations. Ensuring informed consent and equitable access to the benefits of such trials can be challenging, necessitating robust ethical frameworks to address these concerns.

To mitigate all these risks, several strategies can be employed.[29] Expanding the drug repositioning pipeline by including compounds from diverse therapeutic areas can enhance the discovery of potential candidates. Encouraging open-access databases and fostering collaborations between academia, industry, and non-profit organizations are essential steps in this direction (*vide infra*). Addressing intellectual property challenges requires the active involvement of governments and international organizations to facilitate agreements that overcome patent barriers. Creating patent pools and offering incentives for companies to share intellectual property can help mitigate legal and financial obstacles. In addition, extending market exclusivity for repositioned drugs can provide financial incentives for pharmaceutical companies.

Streamlining regulatory pathways specifically for drug repositioning can accelerate the approval process. Regulatory agencies can establish dedicated frameworks recognizing the lower risk profile of repurposed drugs due to existing safety data, implementing conditional approvals and adaptive licensing to expedite access to these therapies. Innovative funding models, such as public–private partnerships and advanced market commitments, can attract investment in drug repositioning for NTDs. Leveraging financial instruments such as social impact bonds and global health funds can provide the necessary resources to support clinical trials and development efforts.

Combining repositioned drugs with existing therapies can enhance their efficacy and mitigate the risk of resistance. Research should focus on identifying synergistic drug combinations and exploring novel delivery methods to improve treatment outcomes. Continuous monitoring of resistance patterns and adaptive treatment protocols are essential to ensure long-term effectiveness. Establishing robust ethical frameworks for conducting clinical trials in vulnerable populations is critical. Ensuring transparency, informed consent, and community engagement can build trust and promote equitable access to the benefits of drug repositioning. Collaborating with local health authorities and stakeholders can help align trial designs with the needs and priorities of affected communities.

By proactively addressing these limitations through targeted mitigation strategies, we can fully realize the potential of drug repositioning. This approach offers a pragmatic and efficient pathway to develop new therapies for NTDs, accelerating the availability of effective treatments and aligning with global health goals to improve outcomes for millions affected by these debilitating diseases.

4. Successful implementation of drug repositioning for NTDs

The successful implementation of drug repositioning, along with other strategies, relies heavily on the collaborative and synergistic efforts of all stakeholders involved. The efforts of various consortia and initiatives, including public–public and public–private partnerships, are crucial in advancing the repurposing of compounds through clinical trials.[30] Such collaborative approaches pave the way for more effective therapies against NTDs, offering hope for improved health care in endemic regions.

A notable example of successful collaboration in drug repositioning is demonstrated by the Drugs for Neglected Diseases initiative (DNDi). DNDi's translational research program effectively repurposed fexinidazole, originally developed as a broad-spectrum anti-infective agent in the 1970s, for the treatment of Chagas disease. Fexinidazole, selected from over 700 nitroheterocyclic compounds, was initially repositioned by DNDi for sleeping sickness,[31] before being repurposed for the treatment of Chagas disease. This achievement highlights the critical role of collaborative efforts in advancing drug repositioning initiatives.

Building upon such successful collaborations, countries with robust research capacities, advanced pharmaceutical industries, and significant resources are well-positioned to take a leading role in the implementation of drug repositioning strategies. By forming partnerships with low- and middle-income countries, non-governmental organizations, and global health agencies, these nations can significantly bolster the global fight against NTDs. While international collaborations can face challenges such as resource disparities and regulatory differences, establishing standardized protocols and shared goals can mitigate these issues.

To ensure the success of drug repositioning for NTDs, stakeholders must go beyond scientific collaboration; it necessitates a supportive policy environment, strategic involvement from the pharmaceutical industry, proactive participation from research and academic institutions, and robust engagement from international health organizations and public and non-profit entities (Figure 2). Collectively, acting as a united front, these stakeholders contribute to a cohesive and comprehensive framework that facilitates the advancement of drug repositioning for NTDs, overcoming challenges, accelerating the development of effective therapies, and ultimately improving health outcomes in regions burdened by these diseases.

4.1. Policy recommendations

To facilitate the widespread adoption of drug repositioning for NTDs, specific policy measures are essential. Governments should prioritize funding for NTD research and establish regulatory frameworks that expedite the approval process for repurposed drugs. Streamlined regulatory pathways can significantly reduce the time and cost involved in bringing repositioned drugs to market, enhancing their accessibility to those in need.

In addition to government funding and supportive policies, regulatory bodies such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have developed mechanisms to fast-track drug approvals to meet urgent medical needs.

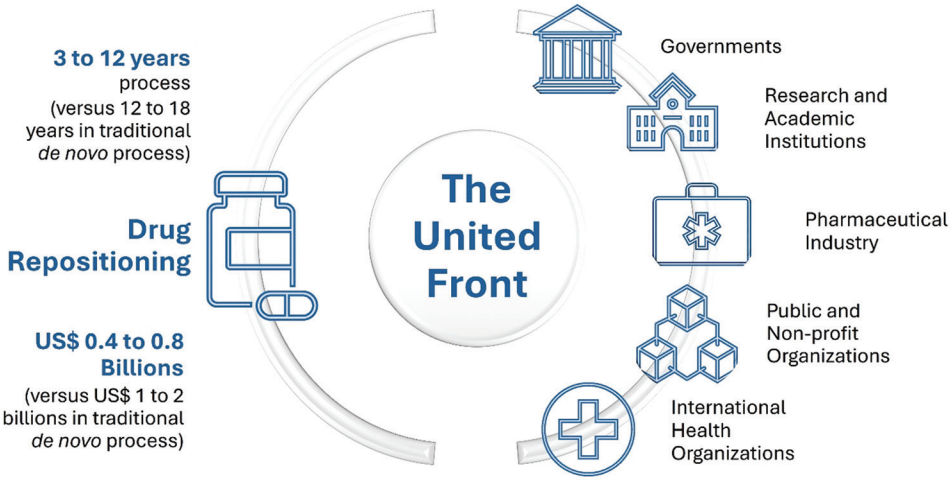

Figure 2. A collaborative partnership between governments, pharmaceutical industry, academic and research institutions, public and non-profit organizations, and health organizations is essential to unlock the full potential of drug repositioning. This cooperation will enhance treatments for neglected tropical diseases and transform global health outcomes.

The FDA offers programs such as Fast Track (to expedite the review of drugs for serious conditions with unmet medical needs), Priority Review (which reduces the FDA review period from ten to six months), and Accelerated Approval (allowing earlier approval based on surrogate endpoints).[32] Similarly, the EMA has introduced the PRIME (Priority Medicines) scheme,[33] offering early and enhanced support to medicines that target unmet medical needs, including those for NTDs. The PRIME program provides early and continuous support to developers of promising drugs, ensuring faster access for patients. These streamlined approval pathways are particularly vital for repurposing drugs, as they accelerate the development and availability of critical treatments, ensuring faster access to affordable therapies for NTDs. Therefore, implementing such regulatory mechanisms globally is essential to accelerate and address the urgent medical needs posed by NTDs through drug repositioning.

4.2. The role of the pharmaceutical industry

The pharmaceutical industry has a pivotal role in embracing social responsibility by investing in research and forming public–private partnerships to unlock the potential of drug repositioning for NTDs. By collaborating with academic institutions and global health organizations, pharmaceutical companies can significantly contribute to developing cost-effective therapies for NTDs, thereby addressing both public health needs and market gaps. These partnerships are particularly crucial in low- and middle-income countries, where the burden of NTDs is highest, and access to affordable treatments is most urgently needed. In these regions, pharmaceutical companies can play a transformative role by ensuring that medical innovations are accessible and affordable. Through these efforts, the pharmaceutical sector can bridge the gap between innovation and access, ensuring that repositioned drugs reach the populations most in need. Furthermore, pharmaceutical companies can leverage their expertise in drug development, manufacturing, and distribution to ensure that repositioned drugs are produced efficiently, meet quality standards, and are delivered promptly to regions in need. By participating in shared intellectual property agreements and open-access research initiatives, the industry can further reduce costs, foster innovation, and accelerate drug development timelines. In addition, pharmaceutical companies play a pivotal role in advocating for regulatory reforms that streamline the approval process for repositioned drugs, thereby making treatments available more rapidly to those in need. By embracing these roles, the pharmaceutical industry can significantly contribute to combating NTDs, ultimately improving global health outcomes and fulfilling their social responsibility.

4.3. Research and academic institutions

Research and academic institutions play a crucial role in driving innovation in drug repositioning. Interdisciplinary collaboration (bringing together experts from multidisciplinary fields such as biology, chemistry, and computer science) and international partnerships are essential for advancing the scientific understanding of NTDs and identifying potential drug candidates. Institutions should focus on innovative research methodologies such as high-throughput screening, which allows rapid testing of thousands of compounds against disease targets, artificial intelligence, and computational modeling, which can predict drug-target interactions and accelerate the identification of promising candidates.[34]

In addition, these institutions play a key role in building scientific capacity in low-income regions by providing training for local researchers and fostering South–South collaborations (partnerships between developing countries). For example, the Global Network for NTDs (a network formed by researchers from Argentina, Brazil, India, Pakistan, the United Kingdom, and Uruguay) has advanced NTD research through shared resources and expertise.[35] This not only strengthens the local infrastructure for NTD research but also enriches the global scientific community by incorporating diverse perspectives and expertise. Moreover, research and academic institutions are pivotal in conducting pre-clinical and clinical trials necessary to evaluate the safety and efficacy of repositioned drugs. By fostering strong partnerships with industry and governmental bodies, they can accelerate the translation of laboratory discoveries into real-world treatments, bridging the gap between research and application and ensuring that scientific discoveries become accessible therapies. By leading innovation and capacity building, research and academic institutions ensure that drug repositioning efforts remain at the forefront of scientific advancement.

4.4. International health organizations

International health organizations, such as the WHO, play a pivotal role in coordinating global efforts to address NTDs through drug repositioning. By advocating for equitable resource distribution and raising the profile of NTDs through initiatives such as the "Uniting to Combat NTDs" campaign,[36] these organizations can help mobilize the necessary resources and support for repositioning efforts. Moreover, they play a critical role in setting global health priorities, establishing guidelines, and fostering cross-border collaborations to share knowledge and resources.

Through initiatives such as the WHO's Roadmap for NTDs (which outlines strategies for the control, elimination, and eradication of 20 prioritized NTDs) these

organizations align the efforts of governments, research institutions, and private industry toward common goals. Furthermore, by supporting local health-care systems, training health-care professionals, and ensuring access to affordable therapies (including repositioned drugs) international health organizations directly improve health outcomes in affected communities.

International health organizations, with their oversight and global reach, are well-positioned to promote regulatory harmonization across countries. By streamlining the approval process for repositioned drugs, they ensure faster delivery to those in need. By leveraging their extensive networks and resources, these organizations play an essential role in uniting stakeholders and advancing the fight against NTDs through effective drug repositioning strategies.

4.5. Public and non-profit organizations

Public and non-profit organizations play a vital role in raising awareness about NTDs and supporting fundraising efforts for research into drug repositioning. Grassroots campaigns and public education initiatives can generate the political and financial support needed to advance these projects. Moreover, these organizations act as crucial intermediaries, bridging the gap between affected communities, policymakers, and researchers. By advocating equitable access to treatments and promoting global partnerships, they ensure that drug repositioning efforts are tailored to the specific needs of low-income regions, directly addressing the challenges faced by these communities.

In addition, they often lead advocacy initiatives that pressure governments and international bodies to prioritize NTD research, allocate funding, and streamline regulatory pathways for repositioned drugs. Organizations such as Médecins Sans Frontières[37] and the Bill and Melinda Gates Foundation[38] have launched campaigns and funded projects that significantly contribute to NTD research and drug repositioning efforts. Their sustained advocacy and influence help maintain momentum in the fight against NTDs, fostering a more inclusive and collaborative global health agenda that prioritizes neglected communities.

5. Conclusion

Drug repositioning has emerged as a pivotal strategy in the battle against NTDs, offering the potential to rapidly deliver effective treatments for these devastating diseases. As we look to the future, harnessing this approach will be crucial in changing the landscape of NTD treatments and bringing hope to millions affected. Achieving success requires collective action from governments, the pharmaceutical industry, research institutions, international health organizations, and public and non-profit organizations: a united front. This collaborative effort should involve governments aligning regulations to support expedited drug approvals; pharmaceutical companies sharing intellectual property and resources; and research institutions advancing innovative drug repositioning techniques. International health organizations must coordinate funding and implementation efforts, whereas public and non-profit organizations raise awareness and advocate equitable access to treatments. By joining forces and leveraging drug repositioning, this united front can significantly transform the treatment landscape for NTDs, bringing effective and accessible therapies to millions in impoverished regions. Given the urgency of this cause, immediate collaborative action is imperative to develop rapid, cost-effective solutions that will ultimately improve global health. Our greatest strength lies in unity; by working together, we can transform the fight against NTDs and bring hope to millions.

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Conflict of interest

The author declares no competing interests.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

ORIGINAL RESEARCH ARTICLE

The role of saroglitazar in the treatment of metabolic dysfunction-associated steatohepatitis in non-diabetic patients: A prospective observational study

Jata Shankar Kumar*, Priyanshu Bhardwaj, Akul Chadha, and Premashis Kar*

Department of Medical Gastroenterology, Max Superspeciality Hospital, Vaishali, Ghaziabad, India

Abstract

Metabolic dysfunction-associated steatohepatitis (MASH) is a metabolic disease characterized by hepatic fat accumulation and significant inflammation. Patients with hepatic steatosis who also have at least one of the five cardiometabolic risk markers are considered to have metabolic dysfunction-associated steatotic liver disease. MASH is diagnosed when a microscopic examination of liver tissue reveals fat accumulation in hepatocytes along with inflammation and destruction of liver cells. This study aims to assess the role of saroglitazar, a dual proliferator peroxisome-activated receptor agonist, in the medical therapy of MASH in non-diabetic patients. A prospective observational study was carried out in a tertiary care facility in north India. A total of 51 non-diabetic MASH patients (males and females, 18 – 75 years of age, body mass index ≥18.5 kg/m^2) were included in this study. Diagnosis of MASH was based on liver FibroScan (controlled attenuation parameter [CAP] score >238, liver stiffness measurement [LSM] value >7kPa) along with raised liver enzymes (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT] > upper value of normal limits). All these 51 patients received 4 mg once-daily dose of saroglitazar for the treatment of MASH for 24 weeks. In this study, a standard treatment protocol was used. The percentage changes in aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, triglyceride, low-density lipoprotein (LDL), and LSM with CAP were evaluated using an analysis of variance test and multiple regression analysis. About 72.5% of these patients were male and 27.5% were female (male: female ratio of 2.6). The mean age of patients was 51 ± 13.13 years. Pre- and post-treatment values of different parameters were compared. Pre-treatment mean values of ALT and AST were 93.83 ± 6.16 U/L and 76.13 ± 4.1 U/L, respectively, while their post-treatment mean values were 32.97 ± 2.15 U/L and 34.57 ± 1.65 U/L, respectively (*P*-value for AST and ALT <0.001). In conclusion, saroglitazar is effective in the medical management of MASH by reducing liver stiffness and suppressing elevated liver enzymes (SGOT/SGPT) as well as serum LDL levels over 6 months.

Keywords: Hepatic steatosis; Hepatocytes; Metabolic dysfunction-associated steatohepatitis; Proliferator peroxisome activated receptor; Saroglitazar

***Corresponding authors:**
Jata Shankar Kumar (jatashankar.dr@gmail.com)
Premashis Kar (premashishkar@gmail.com)

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1. Introduction

Metabolic dysfunction-associated steatohepatitis (MASH) is a metabolic disease marked by hepatic fat buildup and significant inflammation. From metabolic dysfunction-associated fatty liver to MASH, metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a wide range of chronic liver diseases.[1] Significant data has surfaced in the last 20 years demonstrating the worldwide occurrence of MASLD and linking it to a range of liver conditions, including those that can lead to cirrhosis and hepatocellular carcinoma. Most of the cases with MAFLD are asymptomatic and are diagnosed incidentally.[2]

A severe type of MASLD that affects 35 million individuals worldwide, MASH is linked to hepatocellular inflammation as a result of fat buildup in the cells. MASLD significantly adds to the worldwide burden of illness. The prevalence of MASLD is 25.24% worldwide, with South America and the Middle East having the highest rates. In India, the prevalence of adult MASLD has been reported between 6.7% and 55.1%, whereas that of pediatric MASLD has been reported between 7.3% and 22.4%. Obesity, type 2 diabetes, dyslipidemia, hypertension, and metabolic syndrome are the common metabolic comorbidities linked to MASLD. It has been estimated that 33.5% of adults worldwide will be affected by MASLD and another 27% will have MASH by 2030.

MASLD-related hepatocyte steatosis is typified by the accumulation of fat droplets in the hepatocytes. MASH may occur from hepatocellular damage and inflammation, either in conjunction with or apart from hepatic fibrosis. Factors including insulin resistance, oxidative stress, inflammation, altered adipokine and cytokine secretion, altered lipid metabolism, and endoplasmic reticulum stress are associated with these disorders. These characteristics make MASH a clinically aggressive form of MASLD, and individuals with MASH are more likely to develop cirrhosis. As a result, for the past several years, attempts have been made to study and develop drugs specifically for this condition.

The primary diagnostic subtype of MASLD is MASH, which carries a risk of cirrhosis and liver-related consequences. However, it is important to note that all subtypes of MASLD elevate the likelihood of cardiovascular events and mortality. Projections suggest a steep increase in the prevalence of MASLD patients in the coming years, driven by the growing rates of obesity and type 2 diabetes.[3,4] MASLD often emerges in individuals with a medical history of diabetes and obesity. Our understanding of MASLD's etiology and progression has significantly expanded in recent decades. The well-known "multiple hit hypothesis" suggests that insulin resistance is essential for the development of multiple sclerosis lipogenesis (MASLD) by increasing the liver's ability to use free fatty acids, which in turn causes fatty liver and lipotoxicity.[5,6]

The American Association for the Study of Liver Diseases recommendations emphasize that only biopsy-confirmed MASH warrants medical intervention[7,8] While various medications have been explored for MASH treatment, none have received official approval.[7] Among the medications considered are glitazones, with pioglitazone being one example. Studies have shown that pioglitazone can improve NAFLD activity score, lead to MASH resolution, and enhance fibrosis, along with improving histological aspects like steatosis, inflammation, and hepatocellular ballooning.[9,10]

In MASLD, the primary goal of pharmacological intervention is to manage liver inflammation and fibrosis. This is due to the fact that in individuals with MASLD, the degree of liver inflammation and fibrosis is strongly linked to both extrahepatic and hepatic morbidity and mortality. A dual proliferator peroxisome activated receptor (PPAR)-α/γ agonist called saroglitazar magnesium was created to lessen the negative effects of selective PPAR-γ agonism. For saroglitazar, the proposed mechanism of action involves targeting PPAR-α and PPAR-γ, which leads to an enhancement in insulin sensitivity and lipid oxidation. This dual mechanism reduces lipotoxicity by decreasing fat accumulation in the liver and improving fat metabolism there.[11,12] It inhibits the production and release of triglycerides (TG), increases the hepatic oxidation of fatty acids, and through PPAR-α agonism, improves the levels of lipoproteins in circulation. Furthermore, through PPAR-γ agonism, saroglitazar decreases blood glucose and glycosylated hemoglobin (HbA1c) levels, enhances insulin sensitivity, and controls the transcription of genes that respond to insulin. In India, saroglitazar has been licensed for the treatment of hypertriglyceridemia and diabetic dyslipidemia since 2013. In addition, it has been authorized in some other countries, to treat hypertriglyceridemia and dyslipidemia in type 2 diabetic patients whose condition is not managed by statins.

Numerous investigations, including human and animal MASLD models, have demonstrated its effectiveness in reducing hepatic steatosis, hepatocellular inflammation, and fibrogenic activity.[13,14] Saroglitazar has been shown in animal models to decrease alanine aminotransaminase (ALT) levels and to alleviate hepatic steatosis, hepatocellular ballooning, and lobular inflammation in MASH caused by a high-fat, choline-deficient diet or Western diet. Moreover, saroglitazar was shown to significantly lower insulin resistance, TG, total cholesterol, and metabolically

active lipid species, including diglycerides, ceramides, and sphingomyelins, as well as improve liver fibrosis and inflammation biomarkers in mice with Western diet-induced MASH. Saroglitazar has been shown in clinical trials to be useful for people with MASLD; however, there are very few prospective studies dedicated to studying the role of saroglitazar in the management of MASLD/MASH.

2. Materials and methods

The current prospective observational study was conducted at the Max Hospital in Vaishali, Ghaziabad, India, a tertiary care facility in northern India, for a duration of 6 months, from November 2024 to May 2023. The Indian Council of Medical Research's Good Clinical Practice and Declaration of Helsinki guidelines were adhered to in this investigation. A total of 51 non-diabetic MASH patients (males and females, 18–75 years of age) were prospectively followed up in this study. Diagnosis of MASH was done based on liver FibroScan (controlled attenuation parameter [CAP] score >238, liver stiffness measurement [LSM] value >7kPa) along with raised liver enzymes (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT] > upper value of normal limits). All of these 51 patients received 4 mg once-daily dose of saroglitazar for the treatment of MASH from the hepatology and gastroenterology clinic of the hospital. In the current study, standard treatment protocols were used. Analysis of variance (ANOVA) test and multiple regression analysis were used to assess the percentage change in body mass index (BMI), aspartate transaminase (AST), ALT, bilirubin, TG, low-density lipoprotein (LDL), and LSM with CAP.

2.1. Sample size calculation

Fifty patients were proposed for this study. The primary outcome of interest is the change in ALT level from before therapy to after therapy. This parameter gives a standard deviation (SD) of 15.24 (δ = 15.24), which allows the detection of a change of at least δ = 5 unit/L. This indicates that the minimum sample size of 50 is required to ensure the reliable detection of ALT level changes from before therapy to after therapy.

2.2. Inclusion criteria

The participant inclusion criteria for this study are as follows:

(i) Males or females
(ii) 18–75 years of age
(iii) BMI ≥18.5 kg/m^2
(iv) Non-diabetics (fasting blood sugar <100 mg/dL, HbA1C <5.7 and post-prandial blood sugar <140 mg/dL)
(v) Confirmation of hepatic steatosis through imaging or histologic means
(vi) No history of significant alcohol consumption
(vii) No competing etiologies for hepatic steatosis
(viii) No co-existing causes for chronic liver disease
(ix) Having elevated AST/ALT levels along with liver stiffness value ≥7 kPa and/or liver steatosis CAP >238 dB/m, measured through liver FibroScan.

Patients who received saroglitazar treatment for 24 weeks and came for follow-up during and at the end of therapy were analyzed.

2.3. Exclusion criteria

Exclusions from our study included patients with a history of type 2 diabetes or who had taken diabetic medications within the 6 months before recruitment, dyslipidemia history, the presence of chronic hepatitis B or C infection (positive HbsAg or anti-HCV-ab), evidence of chronic liver disease on abdominal ultrasound and portal Doppler, significant alcohol intake (>20 mg/day for males and >10 mg/day for females), and a history of anti-obesity medication intake in the 6 months before recruitment. In addition, cases who were having a history of drug use that resulted in hepatic steatosis/fibrosis including psychotropic drugs, or cases with a history of hepatotoxic drug consumption were also excluded. Individuals with additional comorbid conditions such as hypothyroidism, ischemic illness, or chronic kidney disease were excluded. The study also excluded the patients with any confounding factors that could cause the FibroScan values to be overestimated, such as liver congestion, ascites, liver inflammation from alcohol consumption or recent liver illness, benign or malignant liver tumors, biliary obstructions, *etc.* Those with a history of severe illness or other conditions that would make the patient, in the investigator's opinion, unsuitable for the study, such as those who have a known allergy, sensitivity, or intolerance to saroglitazar or formulation ingredients, women who are pregnant, nursing, or who may become pregnant in the future but are not using appropriate contraceptive measures, were also excluded from the study.

2.4. Data collection method

All patients underwent general physical examination including recording of vitals. The patients were enrolled and selected as per inclusion and exclusion criteria. If the patient was suffering from any other concomitant diseases while receiving treatment for the same, the details were recorded in a case reporting form. The primary efficacy variable was the mean change in NAFLD fibrosis score at the end of the study (week 24) as compared with baseline; the mean change in TG, LDL, high-density lipoprotein, and cholesterol levels; and the mean change in liver function test (LFT) levels and BMI

values. Every participant was interviewed using a series of questionnaires covering demographic characteristics such as age, gender, anthropometric measurement, family history of metabolic disorders or liver disease, current medications, comprehensive medical history including history of alcohol consumption, and any comorbidities such as diabetes, hypertension, and dyslipidemia. The whole physical examination was performed by a skilled technical assistant. A regular stadiometer was used to measure height, and a typical bathroom scale was used to assess weight. The BMI was computed using weight in kilograms and height in meters. Baseline demographics of patients were documented, including age, gender, height, weight, waist circumference, comorbid conditions, and current medicines.

Comprehensive medical history was documented, encompassing the individual's history of alcohol consumption, concurrent medication use, and metabolic comorbidities such as obesity, hypertension, diabetes mellitus, coronary artery disease, and cerebrovascular disease.

2.5. Statistical analysis

ANOVA test was performed to compare the data collected before and after treatment, and multiple regression analysis was used to determine the percent change in ALT, AST, alkaline phosphatase (ALP), bilirubin, BMI, LSM, and CAP. The collected data were entered into Microsoft Excel 2010 for statistical analysis, which was carried out with the aid of Statistical Package for the Social Sciences software. Categorical data are presented as proportions, and continuous data are expressed as mean ± SD (for parametric data) or median and interquartile range (for non-parametric data).

3. Results

A total of 72 individuals were screened for the study. After excluding 21 patients who met one or more of the outlined exclusion criteria, only 51 patients were included in the protocol analysis. Baseline investigations of all 51 patients were conducted. Table 1 displays the basic demographic characteristics of the patients.

All 51 patients who were treated with saroglitazar at 4 mg once-daily dose for 24 weeks were followed up till the end of the study. Out of the sample, 34 patients (72.5%) were male and 17 (27.5%) were female (male-to-female ratio of 2.6). The mean age of patients was 51 ± 13.13 years. The mean value of the fasting blood sugar level was 92.6 ± 9.7 mg/dL. On baseline investigation, the mean value of BMI was 24.1 ± 3.9. LFT and FibroScan procedures (two variables, *i.e.*, LSM and CAP, were noted) were done for the diagnosis of MASH. At the baseline visit, there was an increased level of liver enzymes such as ALT, AST, and gamma-glutamyl transferase (GGT). Comparisons of pre- and post-treatment values of different laboratory parameters including liver enzymes such as ALT, AST, ALP, and GGT, as well as lipid profile and FibroScan parameters such as LSM and CAP, were done. After treatment with saroglitazar at 4 mg once-daily dose for 24 weeks, we detected a significant decrease in values of ALT (32.97 ± 2.15 U/L; $P < 0.001$), AST (34.57 ± 1.65 U/L; $P < 0.001$), GGT (31.86 ± 2.37 U/L). Mean values of pre-treatment ALT and AST were 93.83 ± 6.16 U/L and 76.1 ± 4.1 U/L, respectively, while mean values of post-treatment ALT and AST were 32.97 ± 2.15 U/L and 34.57 ± 1.65 U/L, respectively (both $P < 0.001$). The mean values of pre-treatment FibroScan parameters such as LSM and CAP were 16.2 ± 1.57 kPa (kilopascal) and 297.80 ± 37.38 dB/m (decibel/meter), whereas post-treatment mean values were 7.67 ± 0.23 kPa and 264.80 ± 6.81 dB/m, respectively (LSM and CAP: $P < 0.001$ and $P = 0.049$, respectively). The average values of pre- and post-treatment LDL were 122.1 ± 4.84 and 93.51 ± 4.12, respectively ($P < 0.001$). A significant decrease in values of LSM and CAP ($P < 0.001$ and $P = 0.049$, respectively) indirectly showed that there was a marked improvement in fibrosis score. The comparison of BMI values between the pre- and post-treatment groups showed no significant change (pre- and post-treatment BMI values were 24.1 ± 3.9 and 24.5 ± 3.05, respectively; $P = 0.565$).

It was noticed that saroglitazar, at a once-daily dose of 4 mg, was safe and well-tolerated because there were no serious adverse events associated with the medication that required treatment cessation. All of the 51 patients completed the follow-up for 6 months and were included in the post-treatment data analysis.

4. Discussion

The purpose of this trial was to evaluate saroglitazar's effectiveness and tolerability in non-diabetic patients with hepatic inflammation and fibrosis as detected on liver FibroScan/elastography. This study found that saroglitazar is safe, tolerable, and effective in the management of MASH. Information about saroglitazar's effectiveness in the Indian population is limited. In this study, liver enzyme and FibroScan parameter improvements before and after therapy were compared in non-diabetic individuals with MASH to determine the efficacy of saroglitazar. Based on the widely accepted recommendations that have been backed by available evidence, all patients were given 4 mg of saroglitazar.[15] Since this is the first study of its kind in India to highlight the potential advantages of saroglitazar, particularly in non-diabetic MASH, it adds considerably to the current medical knowledge.[16]

Table 1. Comparison of demographic, biochemical, and FibroScan values

Parameters	Pre-treatment (mean±SD)	Post-treatment (mean±SD)	*P*-value
Age (years)	51±13.13		
Gender (male: Female)	34:17		
Fasting blood sugar (mg/dL)	92.6±9.7		
BMI	24.1±3.9	24.5±3.05	0.565
ALT (U/L)	93.82±6.16	32.97±2.15	<0.001
AST (U/L)	76.13±4.1	34.57±1.65	<0.001
ALP (U/L)	92.87±4.34	89.59±2.48	0.262
Total bilirubin (mg/dL)	0.90±0.06	0.79±0.05	0.032
Serum protein (mg/dL)	7.2±0.08	7.23±0.08	0.932
Serum albumin (g/dL)	4.5±0.05	4.47±0.05	0.776
LDL (mg/dL)	122.1±4.84	93.51±4.12	<0.001
HDL (mg/dL)	44.47±1.14	46.70±1.25	0.211
Non-HDL (mg/dL)	162.15±4.5	162.15±4.5	0.999
Triglyceride (mg/dL)	232.02±42.38	157.48±2.98	0.086
LSM (kPa)	16.2±1.57	5.67±0.23	<0.001
CAP (dB/m)	297.09±37.38	264.80±6.81	0.049
GGT (U/L)	74.77±5.86	31.86±2.37	<0.001

Note: $P<0.05$ is considered statistically significant.
Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CAP: Controlled attenuation parameter; GGT: Gamma-glutamyl transferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LSM: Liver stiffness measurement; SD: Standard deviation.

Many studies emphasize the significance of pinpointing the optimal pharmaceutical target for the management of mixed hepatic liver disease (MASLD) by addressing multiple aspects of the condition, such as enhancing insulin sensitivity, decreasing hepatocellular inflammation, lowering oxidative stress, addressing mitochondrial dysfunction, and addressing liver fibrosis.[17] With little success, only a number of medications have previously been demonstrated to exhibit efficacy in the treatment of MASLD. Peroxisome proliferator-activated receptors (PPARs) are essential for maintaining lipid homeostasis. PPARα is primarily expressed in hepatocytes and inhibits the accumulation of fatty acids within the liver, preventing steatosis and steatohepatitis. On the other hand, PPARγ is primarily found in adipocytes and improves insulin sensitivity while lowering the availability of fatty acids to the liver.[18]

Medications with antifibrotic qualities, such as pioglitazone (a PPARγ agonist), are reportedly known to improve histology outcomes in MASLD patients. However, because of a number of adverse effects, including weight gain, heart failure, headaches, impaired vision, and bladder cancer, they were not authorized for use in the treatment of MASLD.[19] Furthermore, fibrate PPARα agonists did not show encouraging outcomes in MASLD studies.[12] The efficacy of a PPAR-α/δ agonist called elafibrinor is presently being tested in individuals with MASLD.[20] While metformin, ursodeoxycholic acid, and Vitamin E were once utilized to treat MASLD, more recent research has shown that these medications had no therapeutic benefits.[7,8] Although more extensive research is required to evaluate the safety and effectiveness of obeticholic acid, encouraging information has surfaced regarding its involvement in MASLD patients.[21]

Recently, saroglitazar – a dual PPARα/γ agonist – was licensed to treat MASLD. It has demonstrated potential in lowering alterations in dyslipidemia, decreasing glucolipotoxicity to reduce insulin resistance, and having an agonistic impact on PPARγ, particularly in those with diabetes and dyslipidemia.[20] Notably, in the absence of a histological investigation, increased levels of ALT and AST – markers of hepatic inflammation – play a critical role in the diagnosis of MASH.

The degree of liver damage has historically been determined by quantifying the levels of liver enzymes. Due to its non-specificity and lack of correlation with fibrosis, this method has intrinsic limitations. However, due to the low cost involved and wide availability, it is still broadly utilized, offering substantial assistance in real-world situations. In this study, ALT and AST levels

were dramatically lowered after 24 weeks of therapy, suggesting that saroglitazar is useful in reducing liver inflammation, substantiating its efficacy based on a non-alcoholic steatohepatitis population.[12] These findings are consistent with previous research, such as that conducted by Kaul *et al.*[21] which reported a noteworthy decrease in ALT following 12 – 58 weeks of saroglitazar treatment, and another[15] which demonstrated a reduction of 60% in ALT and 43% in AST in animal models with MASLD after 12 weeks of saroglitazar treatment. Similarly, Goyal *et al.* observed significant reductions in ALT and AST after using saroglitazar for 24 weeks, concluding that saroglitazar can improve hepatic inflammation and resolve transaminitis.[20]

The ultimate goal of pharmacological treatment is to reverse liver fibrosis. However, a liver biopsy is usually required for histopathological examination to accurately detect fibrosis, and this procedure is invasive and impractical.[12] Liver stiffness measurement, which leverages FibroScan as a substitute non-invasive approach for evaluating liver fibrosis and cirrhosis, has demonstrated potential in a number of recent investigations.[22,23] According to LSM measurements utilizing FibroScan, the current study found a substantial decrease in fibrosis. Although in our study we did not compare the fibrosis score directly between pre- and post-treatment groups, a significant decrease in LSM (kPa) value indirectly indicates improvements in liver fibrosis and cirrhosis. Goyal *et al.* also noted a substantial decrease in LSM after 24 weeks of saroglitazar treatment,[20] and another study reported a reduction in liver fibrosis, measured by shear wave elastography, following 9 months of saroglitazar treatment.[24]

In addition to fibrosis assessment, evaluating changes in liver fat content is an essential parameter for gauging the response to MASLD therapy. Although abdominal ultrasonography can be used as a screening method to diagnose fatty liver, it is not very effective in identifying changes in the modest amount of liver fat. With high accuracy in detecting changes in liver fat content, the CAP, as evaluated by FibroScan, provides an acceptable option for diagnosing fatty liver.[12] The analysis of the current study showed a considerable decrease in liver fat, as determined by CAP utilizing FibroScan. According to Goyal *et al.*[20] and Kaul *et al.*,[21] there was a noteworthy improvement in liver fat, as evaluated by CAP, following 12 – 58 weeks of saroglitazar therapy in MASLD, which is consistent with our findings. It has also been reported that CAP values significantly decreased after 24 weeks of saroglitazar treatment.[20]

Very few studies have been conducted to validate the role of saroglitazar in MASH management in non-diabetic patients. It should be highlighted that the sample used, the prospective nature of this study, and the use of non-invasive methods for assessing hepatocellular inflammation and fibrosis are the strengths of this study, despite some limitations. The small sample size and the brief follow-up period were the main limitations of this study. It is a larger sample study covering an extended period of follow-up that would be conducted in the future to provide more in-depth insights. The inability of this study to forecast advantage over other compounds now under investigation for MASH is also a limitation. In addition, there was a lack of follow-up information about whether stopping the medication would result in a reversal of the biochemical and stiffness parameter improvements or a continued benefit. However, the study did not address this crucial question owing to the research design employed. The assessment of cardiovascular outcome was not conducted as well. There is a strong association between MASH and cardiovascular incidents, and the majority of causes of death and morbidity in the MASH population are cardiovascular in nature; however, the present study did not evaluate any cardiovascular parameters, neither in the pre- nor post-treatment context. Hence, it is highly anticipated that a long-term follow-up study will be conducted in the future to determine whether there is an increase or decrease in cardiovascular outcomes, a research topic this study was not intended to cover. Although underweight patients were excluded from this study, the relationship of sarcopenia with outcomes in this study was not explored, making it one of the limitations of this study.

It is important to note that although the adverse effects of saroglitazar such as hypoglycemia, nausea, and chest pain have been mentioned in the literature, none of these side effects were reported by the patients taking part in this study. Similar research using animal models did not find any adverse consequences.[25] Moreover, no major negative effects were reported in human studies.[26] The results of this study support the idea that individuals receiving medication for MASLD may tolerate saroglitazar well.

5. Conclusion

Saroglitazar has a beneficial impact on the medical management of MASH by reducing liver inflammation through normalization of liver enzymes and reduction of liver stiffness. It also curtails fat buildup in hepatocytes, which is manifested in terms of the significant decrease in CAP value. Saroglitazar also lowers the elevated levels of liver enzymes (SGOT/SGPT) as well as serum LDL levels within a duration of 6 months. The findings of this study ascertain saroglitazar as a viable treatment option for MASH management. Nonetheless, further research involving a larger sample and longer follow-up period,

with an emphasis on sarcopenia and advanced cirrhosis, is warranted to help validate saroglitazar as a primary drug for this liver disease.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Premashish Kar, Priyanshu Bhardwaj, Jata Shankar Kumar
Formal analysis: Premashish Kar
Investigation: Priyanshu Bhardwaj, Jata Shankar Kumar
Methodology: Priyanshu Bhardwaj, Jata Shankar Kumar, Akul Chadha
Writing–original draft: Priyanshu Bhardwaj, Jata Shankar Kumar
Writing–review & editing: Akul Chadha

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee, Max Super Specialty Hospital in May 2022. Written informed consent was taken from all the patient before their participation.

Consent for publication

All participants in the study gave their informed written consent for their data to be published.

Availability of data

Data are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Alleviation of oxidized lipid-induced oxidative stress and hypertension by estrogen and selected antihyperlipidemic drugs in post-menopausal Wistar rats

Joy T. Folahan[1,2], Adeoye O. Oyewopo[3], Olumuyiwa A. Adejumobi[4], Abayomi M. Ajayi[5], Saheed O. Afolabi[1], Olubunmi Atolani[6], Mary O. Ologe[1], Temidayo O. Omobowale[4], and Olufunke E. Olorundare[1]*

[1]Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, University of Ilorin, Ilorin, Kwara State, Nigeria

[2]School of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, Louisiana, United States of America

[3]Department of Anatomy, Faculty of Basic Medical Sciences, University of Ilorin, Ilorin, Kwara-State, Nigeria

Abstract

Lipid peroxidation is implicated in the development of hypertension and coronary artery disease, and its deleterious impact is exacerbated by estrogen (ETD) depletion in post-menopausal women. We hypothesize that treatment with ETD and antihyperlipidemic drugs, either alone or in combination, can alleviate the development of cardiovascular disease. In this study, female Wistar rats were divided into 10 groups (n = 6): Group 1 (control) underwent a Sham operation and was fed standard rat chow, whereas the other nine groups were ovariectomized (OVX) and received a diet containing either thermoxidized palm oil (TPO) or thermoxidized soya oil (TSO) for 12 weeks. ETD at 0.2 mg/kg/day, atorvastatin (ATV) at 10 mg/kg/day, and a combination of ezetimibe (EZE) and ATV (EZE at 3 mg/kg/day + ATV at 10 mg/kg/day) were administered for 12 weeks in both TSO and TPO diet groups. Blood pressure and electrocardiogram (ECG) parameters were assessed, along with serum lipid profile, atherogenic indices, and markers of oxidative stress. Both TPO and TSO diets significantly altered blood pressure and ECG parameters in OVX rats. Treatment with ATV, EZE+ATV, and ETD significantly reduced blood pressure parameters compared to the OVX+TPO group. Antihyperlipidemic drugs significantly decreased heart rate, QT interval, QRS duration, and QT corrected (QTc), whereas ETD similarly shortened the QRS and QTc duration. ATV and ETD also reduced total cholesterol, triglycerides, and very low-density lipoprotein levels, while boosting high-density lipoprotein concentrations compared to untreated OVX+TSO rats. This study demonstrates that thermoxidized oil has a deleterious effect on OVX rats by altering blood pressure, ECG parameters, and atherogenic indices. Treatment with antihyperlipidemic drugs and ETD normalized blood pressure and ECG parameters, reversed hyperlipidemia, and restored antioxidant system balance.

Keywords: Thermoxidized oil; Lipid peroxidation; Oxidized low-density lipid; Menopause; Cardiovascular diseases; Estrogen; Antihyperlipidemic drugs

***Corresponding author:**
Olufunke E. Olorundare
(olufunke@unilorin.edu.ng)

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[4]Department of Veterinary Medicine, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Oyo- State, Nigeria
[5]Department of Pharmacology and Therapeutics, Faculty of Basic Medical Sciences, University of Ibadan, Ibadan, Oyo- State, Nigeria
[6]Department of Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Kwara- State, Nigeria

1. Introduction

Palm oil and soya oil are commonly used in food processing.[1] Palm oil is rich in saturated fatty acids, whereas soybean oil predominantly contains polyunsaturated fatty acids.[2] Saturated fats (SFs) are generally believed to raise low-density lipoprotein cholesterol (LDL-c) levels and contribute to atherosclerosis. However, a recent review found that plant-derived SFs, such as those in palm oil, increase both LDL-c and high-density lipoprotein cholesterol (HDL-c), potentially balancing pro-atherogenic and anti-atherogenic lipids.[2,3] While dietary advisories recommend reducing the intake of SFs, the health effects of these SFs remain controversial and vary across studies.[3]

Thermal oxidization of dietary oils, commonly practiced in both homes and industries to enhance palatability,[4] occurs when oils are heated during frying at temperatures of 180°C or higher. Oxidation occurs due to exposure to moisture and air, producing lipid oxidation products,[5] such as peroxides, hydroperoxides, and aldehydes, which compromise the biochemical and nutritional safety of the oil.[6] Lipid peroxidation is implicated in several diseases, including hypertension and coronary heart disease.[7]

The loss of estrogen (ETD) after menopause deprives blood vessels of significant protection, further compounding the harmful effects of the highly reactive products of thermoxidized oils on the vasculature. This can result in a loss of vascular integrity and accelerated development of atherosclerosis and cardiovascular disease (CVD).[8,9] CVD is an umbrella term for conditions that entail structural and functional abnormalities of the heart and blood vessels. These conditions include coronary artery disease, cerebrovascular disease, and acute coronary syndromes such as myocardial infarction, stroke, and peripheral artery disease. CVDs account for the highest rates of morbidity and mortality worldwide.[8,9]

Although the incidence of CVD is relatively low in young women, there is a noticeable increase in risk after menopause.[10] CVD is the primary cause of illness and death among women over 50, responsible for around 80% of fatalities in post-menopausal women.[10] Menopause is associated with a dramatic rise in blood pressure.[11] Physiologically, estradiol serves a modulatory role in the peripheral nervous system, particularly in the sympathetic arm, while also regulating the renin-angiotensin-aldosterone system and maintaining body mass. These effects essentially delay the onset of hypertension in premenopausal women.[12] However, in post-menopausal women, ETD depletion is associated with an increased risk of hypertension and other CVDs.[13] Furthermore, diets rich in SFs have been shown to exacerbate the deleterious effect of ETD depletion on blood pressure.[14,15]

In this study, we hypothesize that early control of circulating lipids through the administration of ETD and antihyperlipidemic drugs can prevent the development of oxidized lipid-induced oxidative stress and subsequently reduce the risk of hypertension and coronary artery disease.

2. Materials and methods

2.1. Preparation of thermoxidized oil diet

Palm oil (Ace, Nigeria) and soya oil (Sunola, Nigeria) were thermally oxidized following the method outlined previously.[16] Five liters of each oil were used to fry 2 kg of potatoes on a hot plate at 180°C for 20 min, and this process was repeated 5 times. After each frying session, the potatoes were removed, and the oil was allowed to cool for 5 h. No additional oil was added to maintain the volume, and the 5-h cooling period was consistent across all cycles. The resulting thermoxidized palm oil (TPO)/ thermoxidized soya oil (TSO) was then incorporated into diets (15% w/w) mixed with standard rat chow (Ladokun Feeds, Nigeria) and formed into pellets.

2.2. Experimental animals

For this study, 60 female Wistar rats, weighing between 200 and 250 g, were sourced from McTemmy Farms in Ogbomosho, Nigeria. The rats were individually housed in cages at the University of Ilorin Central Laboratory animal house, maintained at a temperature of 27±2°C, with a 12-h light/dark cycle and adequate ventilation. The rats had unrestricted access to food and water. Ethical approval for the study was granted by the University of Ilorin Ethical Review Committee under approval number UERC/ ASN/2021/2038.

2.3. Ovariectomy and study design

Rats were anesthetized with a ketamine/xylazine mixture (10:1). Incisions were made to access the abdominal cavity. The fat pad containing the ovary was externalized, and the anterior arm of the bifurcated uterus was traced up to the

uterine horn, where the horn was cut to excise the ovary. The uterus and fat pad were then returned to the abdominal cavity, and the muscle and skin incisions were sutured with 4/0 absorbable sutures (Chromic Catgut Suture, Nigeria). The same procedure was used to remove the contralateral ovary. After surgery, the suture sites were cleaned and treated with penicillin to prevent infection. The animals were administered ofloxacin (100 mg/kg orally) for 7 days to prevent infection.[17] Following surgery, the rats were allowed a 1-week recovery period with unrestricted access to food and water. A further week was allowed for the rats to attain a post-menopausal state before the start of treatment and diet administration.

The study consisted of 10 groups, each containing six rats. The first group was the Sham group, which underwent a simulated surgery for surgical stress and was fed normal rat chow. The other nine groups were ovariectomized (OVX) and fed the test diets containing TPO or TSO. Group 2 received the TSO diet, and Group 3 received the TPO diet. The remaining treatment groups were fed either the TSO or TPO diet and concurrently treated with one of the following: atorvastatin (ATV) at 10 mg/kg/day, a combination of ezetimibe (EZE) and ATV (EZE at 3 mg/kg/day + ATV at 10 mg/kg/day), or estradiol valerate (ETD) at 0.2 mg/kg/day. The diets and treatments were administered concurrently for 12 weeks, after which blood pressure parameters were measured.

2.4. Measurement of blood pressure and electrocardiogram (ECG) parameters

Systolic (SBP) and diastolic blood pressure, as well as mean arterial pressure (MAP), were measured using a non-invasive tail-cuff sphygmomanometer (CODA Tail Cuff Blood Pressure Monitor, Kent Scientific, United States of America). ECG parameters, including PR interval, QT interval, heart rate, QRS duration, P duration, R amplitude, and QT corrected (QTc), were measured using an electrocardiograph machine (VE 1010 Veterinary 6/7 Channel PC ECG Machine, EDAN, United States of America).

2.5. Serum lipid profile analyses

Serum total cholesterol, triglycerides, and HDL-c were measured using specialized kits from Randox (Randox Laboratories, United Kingdom). The concentrations of LDL and very LDL (VLDL), as well as the atherogenic index (AI), coronary risk index (CRI), and HDL-c/LDL-c ratio, were calculated using established formulas.[18-20]

2.6. Serum oxidative stress assessment

Lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels using the thiobarbituric acid reactive substances assay.[21] Markers of oxidative stress, including reduced glutathione (GSH),[22] catalase (CAT),[23] and superoxide dismutase (SOD).[24] activities were determined using previously reported methods.

2.7. Statistical analysis

All data were summarized as mean ± standard error of the mean. The normality of the data was confirmed, followed by a one-way analysis of variance (ANOVA). Bonferroni's multiple comparisons test was applied for *post-hoc* analysis. The confidence level was set at 95%.

3. Results

3.1. ETD and antihyperlipidemic drugs improve blood pressure parameters in OVX rats treated with thermoxidized oils

Blood pressure parameters, including SBP, DBP, and MAP, were not significantly affected in OVX rats compared to the Sham group. However, SBP and MAP were markedly elevated in OVX + TSO rats compared to Sham rats (Table 1). Treatment with EZE + ATV reduced SBP ($P < 0.05$) compared to the untreated OVX+TSO group.

In OVX+TPO rats, there were significant increases in SBP, DBP, and MAP compared to Sham rats (Table 2). However, treatment with ATV, EZE+ATV, and ETD normalized the SBP, DBP, and MAP parameters in these rats.

3.2. ETD and antihyperlipidemic drugs improve ECG parameters in OVX rats treated with thermoxidized oils

Heart rate (Figure 1A), QRS duration (Figure 1B), QT interval (Figure 1C), and QTc (Figure 1D) values were

Table 1. Effects of estradiol and antihyperlipidemic drugs on blood pressure parameters in ovariectomized Wistar rats fed thermoxidized soya oil

Treatment	Blood pressure parameters (mmHg)[a]		
	SBP	DBP	MAP
Sham	107.30±3.87	78.25±3.10	87.46±2.09
OVX	109.20±3.02	83.87±2.15	90.06±1.48
OVX+TSO	138.30±1.91#	98.58±2.99	111.50±2.41#
OVX+TSO+ATV	130.00±4.16	95. 88±4.61	106.9±4.25
OVX+TSO+EZE+ATV	111.80±7.10*	83.84±7.82	92.91±7.59
OVX+TSO+ETD	130.00±11.02	92.45±10.02	104.7±9.83

Notes: [a]Values are presented as mean±SEM. Statistical significance: #$P<0.05$ compared to Sham; *$P<0.05$ compared to OVX+TSO. Abbreviations: ATV: Atorvastatin; DBP: Diastolic blood pressure; ETD: Estradiol valerate; EZE: Ezetimibe; MAP: Mean arterial pressure; OVX: Ovariectomized; SBP: Systolic blood pressure; TSO: Thermoxidised soya oil.

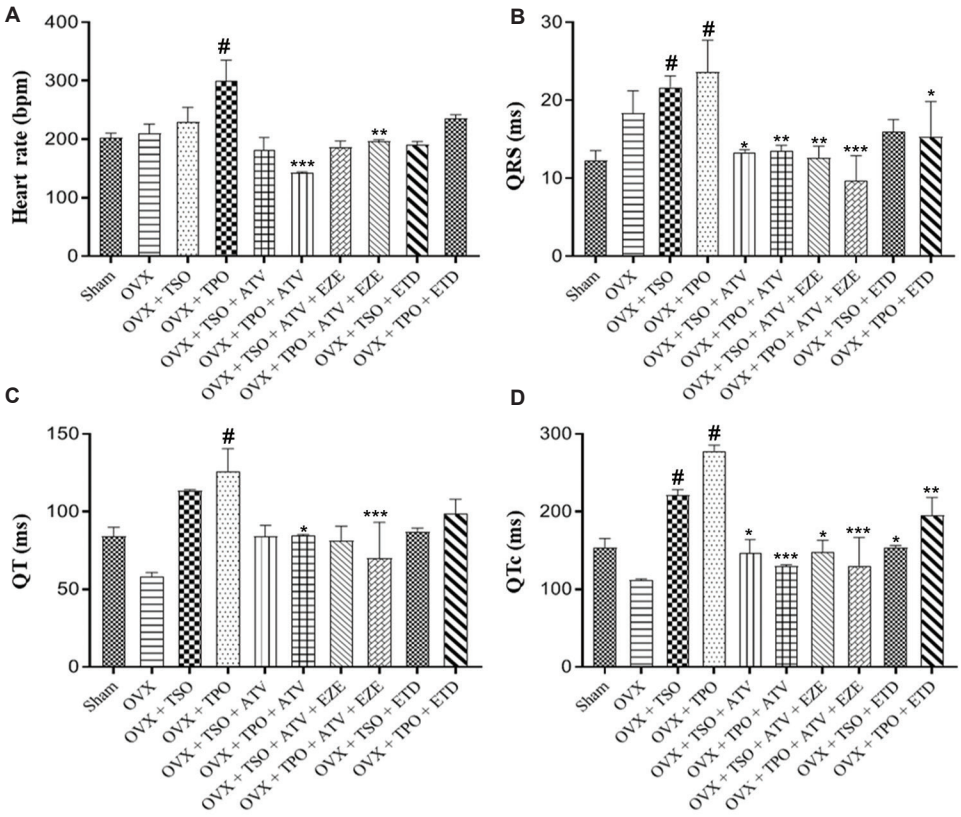

Figure 1. Effects of estradiol and antihyperlipidemic drugs on electrocardiogram parameters in OVX Wistar rats fed thermoxidized soya and palm oil diets. (A) Heart rate; (B) QRS interval; (C) QT interval; (D) QT corrected. Notes: Values are presented as mean±SEM. Statistical significance: #*P*<0.05 compared to Sham; **P*<0.05 compared to OVX+TSO/TPO; ***P*<0.01 compared to OVX+TSO/TPO; ****P*<0.001 compared to OVX+TPO
Abbreviations: ATV: Atorvastatin; ETD: Estradiol valerate; EZE: Ezetimibe; OVX: Ovariectomized; TPO: Thermoxidized palm oil; TSO: Thermoxidized soya oil.

Table 2. Effects of estradiol and antihyperlipidemic drugs on blood pressure parameters in ovariectomized Wistar rats fed thermoxidized palm oil

Treatment	Blood pressure parameters (mmHg)[a]		
	SBP	DBP	MAP
Sham	107.30±3.87	78.25±3.10	87.46±2.09
OVX	109.20±3.02	83.87±2.15	90.06±1.48
OVX+TPO	145.10±4.48#	105.90±3.43#	118.20±3.84#
OVX+TPO+ATV	108.90±8.69**	76.58±4.75*	86.98±6.01*
OVX+TPO+EZE+ATV	110.00±4.52*	76.70±3.59*	87.55±3.31*
OVX+TPO+ETD	110.60±7.60*	77.54±8.01*	88.18±7.74*

Notes: [a]Values are presented as mean±SEM. Statistical significance: #*P*<0.05 compared to Sham; **P*<0.05 compared to OVX+TPO; **P<0.01.
Abbreviations: ATV: Atorvastatin; DBP: Diastolic blood pressure; ETD: Estradiol valerate; EZE: Ezetimibe; MAP: Mean arterial pressure; OVX: Ovariectomized; SBP: Systolic blood pressure; TPO: Thermoxidised palm oil.

largely unchanged in the OVX group relative to the Sham group. Conversely, QRS and QTc ($P < 0.05$) were significantly prolonged in the OVX + TSO and OVX + TPO groups compared to the Sham group. Treatment with ETD, ATV, and EZE + ATV reversed these effects, significantly reducing QRS duration and QTc relative to the diet-only TSO and TPO groups.

3.3. ETD and antihyperlipidemic drugs improve lipid metabolism in OVX rats treated with thermoxidized oils

Lipid metabolism was disrupted in OVX rats, as indicated by significantly elevated total levels of cholesterol, triglycerides, HDL-c, LDL-c, and VLDL compared to Sham rats. OVX + TSO (Table 3) and OVX+TPO (Table 4) rats exhibited similar effects, though more pronounced. CVD indices, such as AI and CRI, were elevated, whereas high-density lipoprotein (HDL)/LDL ratios were significantly decreased ($P < 0.05$) in the OVX and diet-only groups (Tables 5 and 6).

Our results demonstrate that treatment with ETD and antihyperlipidemic drugs restored normal lipid metabolism in the treated rats, although each intervention exhibited a distinct mode of action. ETD increased HDL-c

Table 3. Effects of estrogen and antihyperlipidemic drugs on serum lipid profiles in ovariectomized Wistar rats fed thermoxidized soya oil

Treatment	Serum lipid profile (mg/dL)				
	T-CHOL	TRIG	HDL	LDL	VLDL
Sham	60.79±7.78	73.25±7.49	26.09±3.40	20.05±7.47	14.65±1.49
OVX	79.24±4.13#	150.51±7.57#	19.65±0.83#	23.97±1.06#	31.96±2.23#
OVX+TSO	80.41±3.55#	185.83±39.94#	19.76±1.01#	23.59±1.32#	37.16±7.98#
OVX+TSO+ATV	57.49±6.14***	108.52±31.89***	24.18±2.54***	14.01±1.60***	21.71±6.38***
OVX+TSO+EZE+ATV	69.58±6.08	148.54±45.85	28.03±1.04***	11.84±0.87***	29.71±9.17
OVX+TSO+ETD	74.29±6.24	113.81±23.79***	33.18±1.51***	18.36±0.95***	22.76±4.76***

Notes: Values are expressed as mean±*SEM*. Statistical significance: #*P*<0.05 compared to Sham. **P*<0.05 compared to OVX+TSO; ***P*<0.01 compared to OVX+TSO; ****P*<0.001 compared to OVX+TSO.
Abbreviations: ATV: Atorvastatin; ETD: Estradiol valerate; EZE: Ezetimibe; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; OVX: Ovariectomized; T-Chol: Total cholesterol; TRIG: Triglycerides; TSO: Thermoxidized soya oil; VLDL: Very low-density lipoprotein.

Table 4. Effects of estrogen and antihyperlipidemic drugs on serum lipid profiles in ovariectomized Wistar rats fed thermoxidized palm oil

Treatment	Serum lipid profile parameters (mg/dL)				
	T-CHOL	TRIG	HDL	LDL	VLDL
Sham	60.79±7.78	73.25±7.49	26.09±3.40	20.05±7.47	14.65±1.49
OVX	79.24±4.13#	150.51±7.57#	19.65±0.83#	23.97±1.06#	31.96±2.23#
OVX+TPO	80.27±4.21#	192.40±9.05#	19.69±1.96#	22.10±1.20	38.48±1.81#
OVX+TPO+ATV	77.09±1.91	121.09±15.12***	24.45±2.18***	27.75±1.37	24.22±3.02***
OVX+TPO+EZE+ATV	69.99±8.20	74.24±3.52***	28.24±4.21***	26.90±1.54	14.85±0.70***
OVX+TPO+ETD	61.61±2.26***	103.77±11.39***	24.84±2.01***	16.02±1.02***	20.75±2.28***

Notes: Values are expressed as mean±SEM. Statistical significance: #*P*<0.05 compared to Sham; **P*<0.05 compared to OVX+TPO; ***P*<0.01 compared to OVX+TPO; ****P*<0.001 compared to OVX+TPO.
Abbreviations: ATV: Atorvastatin; ETD: Estradiol valerate; EZE: Ezetimibe; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; OVX: Ovariectomized; T-Chol: Total cholesterol; TPO: Thermoxidized palm oil; TRIG: Triglycerides; VLDL: Very low-density lipoprotein.

Table 5. Effects of estrogen and antihyperlipidemic drugs on serum atherogenic indices in ovariectomized Wistar rats fed thermoxidized soya oil

Treatment	Atherogenic indices		
	AI	CRI	HDL/LDL
Sham	2.03±0.49	2.51±0.46	4.42±2.14
OVX	7.67±0.58#	3.94±0.2#	0.69±0.11#
OVX+TSO	8.87±2.38#	4.19±0.29#	−0.12±1.01#
OVX+TSO+ATV	3.72±1.37***	2.58±0.28***	6.47±5.89***
OVX+TSO+EZE+ATV	4.91±1.91***	3.09±0.76**	0.44±0.71
OVX+TSO+ETD	2.62±0.65***	2.63±0.57***	0.30±2.24

Notes: Values are expressed as mean±SEM. Statistical significance: #*P*<0.05 compared to Sham; **P*<0.05 compared to OVX+TSO; ***P*<0.01 compared to OVX+TSO; ****P*<0.001 compared to OVX+TSO.
Abbreviations: AI: Atherogenic index; ATV: Atorvastatin; CRI: Coronary risk index; ETD: Estradiol valerate; EZE: Ezetimibe; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; OVX: Ovariectomized; TSO: Thermoxidized soya oil.

Table 6. Effects of estrogen and antihyperlipidemic drugs on serum atherogenic indices in ovariectomized Wistar rats fed thermoxidized palm oil

Treatment	Atherogenic indices		
	AI	CRI	HDL/LDL
Sham	2.03±0.49	2.51±0.46	4.42±2.14
OVX	7.67±0.58#	3.94±0.2#	0.69±0.11#
OVX+TPO	9.429±1.39#	4.26±0.43#	1.19±0.34#
OVX+TPO+ATV	4.22±0.89***	3.27±0.27*	0.94±0.16
OVX+TPO+EZE+ATV	1.99±0.57***	2.91±0.76***	3.03±1.67
OVX+TPO+ETD	3.41±0.69***	2.55±0.21***	1.78±0.35

Notes: Values are expressed as mean±*SEM*. Statistical significance: #*P*<0.05 compared to Sham; **P*<0.05 compared to OVX+TPO; ***P*<0.01 compared to OVX+TPO; ****P*<0.001 compared to OVX+TPO.
Abbreviations: ATV: Atorvastatin; AI: Atherogenic index; CRI: Coronary risk index; ETD: Estradiol valerate; EZE: Ezetimibe; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; OVX: Ovariectomized; TPO: Thermoxidized palm oil.

levels, whereas ATV and EZE + ATV reduced triglyceride levels. All treatments significantly decreased AI and CRI indices.

3.4. ETD and antihyperlipidemic drugs alleviate oxidative stress in OVX rats treated with thermoxidized oils

The concentrations of oxidative stress markers – GSH, MDA, and CAT – in OVX rats were comparable to those of Sham rats, except for SOD, which was significantly depleted in OVX rats compared to Sham. Diets containing TSO (Table 7) and TPO (Table 8) markedly ($P < 0.05$) reduced serum GSH, CAT, and SOD levels while significantly increasing MDA levels in comparison to Sham. Treatment with ATV + NCN significantly increased serum GSH levels. In addition, treatment with ATV, EZE + ATV, and ETD reversed the oxidative stress induced by thermoxidized oils, as revealed by the significantly decreased ($P < 0.05$) MDA levels and increased CAT and SOD levels, in contrast to the untreated TSO and TPO groups.

4. Discussion

Post-menopausal women experience a marked increase in CVD risk, including hypertension, hyperlipidemia, and atherosclerosis.[25] Studies have also shown that long-term feeding of TPO or TSO to OVX rats increases the risk of CVD by accelerating the development of hyperlipidemia and atherosclerosis.[26-27] This effect is a result of the generation of oxidized products, such as oxidized LDL, and their interaction with blood vessel components.[25,28,29] Our study explored the potential ameliorative effects of ETD, ATV, and EZE + ATV in this context.

OVX rats not exposed to thermoxidized oil maintained normal levels of SBP, DBP, and MAP. In contrast, OVX rats fed thermoxidized oil diets showed elevated blood pressure compared to the Sham group. These results indicate that prolonged exposure to thermoxidized oil induces hypertension, which aligns with findings from previous studies.[17,30,31] However, treatment with antihyperlipidemic drugs resulted in significant reductions in SBP, DBP, and

Table 7. Effects of estrogen and antihyperlipidemic drugs on serum oxidative stress markers in ovariectomized Wistar rats fed thermoxidized soya oil

Treatment	Serum oxidative stress parameters			
	GSH (µM/mg protein)	MDA (nM/mg protein)	CAT (U/mg protein)	SOD (U/mg protein)
Sham	0.38±0.03	2.20±0.06	6.02±0.34	1.22±0.05
OVX	0.34±0.05	2.61±0.16	5.24±0.31	0.42±0.03$^{\#}$
OVX+TSO	0.20±0.03$^{\#}$	3.09±0.08$^{\#}$	4.26±0.16$^{\#}$	0.38±0.04$^{\#}$
OVX+TSO+ATV	0.41±0.03***	2.39±0.13***	6.26±0.31**	1.48±0.09***
OVX+TSO+EZE+ATV	0.31±0.02	2.28±0.11***	5.12±0.30	0.91±0.06***
OVX+TSO+ETD	0.24±0.04	2.45±0.14**	5.41±0.28	0.66±0.10

Notes: Values are expressed as mean±*SEM*. Statistical significance: $^{\#}P<0.05$ compared to Sham; *$P<0.05$ compared to OVX+TSO; **$P<0.01$ compared to OVX+TSO; ***$P<0.001$ compared to OVX+TSO/OVX+TPO.
Abbreviations: ATV: Atorvastatin; CAT: Catalase; ETD: Estradiol valerate; EZE: Ezetimibe; GSH: Glutathione; MDA: Malondialdehyde; OVX: Ovariectomized; SOD: Superoxide dismutase; TSO: Thermoxidised soya oil.

Table 8. Effects of estrogen and antihyperlipidemic drugs on serum oxidative stress markers in ovariectomized Wistar rats fed thermoxidized palm oil

Treatment	Serum oxidative stress parameters			
	GSH (µM/mg protein)	MDA (nM/mg protein)	CAT (U/mg protein)	SOD (U/mg protein)
Sham	0.38±0.03	2.20±0.06	6.02±0.34	1.22±0.05
OVX	0.34±0.05	2.61±0.16	5.24±0.31	0.42±0.03$^{\#}$
OVX+TPO	0.18±0.02$^{\#}$	3.35±0.14$^{\#}$	4.25±0.20$^{\#}$	0.47±0.06$^{\#}$
OVX+TPO+ATV	0.26±0.04	2.14±0.04***	6.11±0.49**	1.42±0.15***
OVX+TPO+EZE+ATV	0.28±0.05	2.38±0.16***	5.21±0.18	0.47±0.03
OVX+TPO+ETD	0.24±0.03	2.30±0.09***	4.80±0.14	0.69±0.03

Notes: Values are expressed as mean±SEM. Statistical significance: $^{\#}P<0.05$ compared to Sham; *$P<0.05$ compared to OVX+TPO; **$P<0.01$ compared to OVX+TPO; ***$P<0.001$ compared to OVX+TPO.
Abbreviations: ATV: Atorvastatin; CAT: Catalase; ETD: Estradiol valerate; EZE: Ezetimibe; GSH: Glutathione; MDA: Malondialdehyde; OVX: Ovariectomized; SOD: Superoxide dismutase; TPO: Thermoxidized palm oil.

MAP. These reductions are consistent with previous studies demonstrating that lipid control can play a crucial role in managing hypertension and other metabolic syndrome-related diseases.[32,33]

In addition, evaluation of ECG parameters revealed significantly prolonged QTc and QRS intervals in OVX + TSO rats, and prolonged QRS, QT, and QTc in OVX+TPO rats. This finding is consistent with an earlier report where ovariectomy in rats affected all recorded ECG parameters.[34] Prolonged QTc indicates cardiotoxicity and an elevated risk of fatal cardiac arrhythmias.[35,36] A decreasing trend in QRS, QT, and QTc intervals was observed across all treatment groups, suggesting a cardioprotective effect. TPO increases CVD risk, as evidenced by the significant increase in heart rate, QRS, QT, and QTc. Treatment with antihyperlipidemic drugs offers cardioprotection, as demonstrated by the significant decrease in heart rate and reductions in QRS, QT, and QTc upon completion of treatment with ATV and EZE + ATV.

Evaluation of serum lipid profile and atherogenic indices revealed the development of hyperlipidemia, characterized by hypercholesterolemia, hypertriglyceridemia, and overproduction of VLDL, following ovariectomy and thermoxidized oil treatment. The significant increases in total cholesterol, triglycerides, VLDL, and LDL-c in levels in the diet-only groups support this finding. These results also suggest the presence of metabolic syndrome in these groups. Treatments with ATV, EZE + ATV, and ETD effectively reversed hyperlipidemia in OVX + TSO rats. ATV and ETD significantly decreased VLDL levels, whereas EZE + ATV and ETD treatments significantly increased HDL-c levels. HDL-c plays a crucial role in reverse cholesterol transport by scavenging excess cholesterol from tissues and transporting it to the liver for metabolism and excretion. This action of HDL-c can attenuate oxidized LDL-mediated atherogenic progression in the artery walls.[37] Similarly, ETD and antihyperlipidemic drug treatments reversed hyperlipidemia in OVX + TPO rats. This was evident from the significant reductions in triglyceride and VLDL levels across all treatment groups. In addition, EZE + ATV significantly increased HDL-c levels, while ETD treatment significantly decreased triglyceride levels. Overproduction of VLDL is a hallmark of dyslipidemia in metabolic syndrome.[38] Increased VLDL levels negatively impact the composition of HDL, facilitating its degradation through the actions of hepatic lipase and cholesterol ester transfer protein.[38] Thus, reducing VLDL levels helps preserve HDL-c concentration.

Ovariectomy and thermoxidized oil treatment appear to increase the risk of developing atherosclerosis and coronary artery disease in OVX+TSO and OVX+TPO rats. This is evidenced by the significant elevation of AI and CRI, as well as the significant reduction in the HDL/LDL cholesterol ratio. While these indices were mildly elevated in OVX animals, consumption of thermoxidized oil exacerbated them. ATV treatment reversed these effects by significantly increasing the HDL/LDL cholesterol ratio in OVX+TSO rats, and AI and CRI were significantly decreased across all treatment groups. ETD administration effectively attenuated atherogenesis in OVX + TSO rats, with a notable 75% decrease in AI. AI is a predictor of CVD risk, with a higher value indicating a heightened risk of atherosclerosis.[39] Treatments with ETH, ATV, and EZE significantly decreased AI and CRI, though their effects on the HDL-c/LDL-c cholesterol ratio were less pronounced.

These results suggest that early administration of low-dose ETD and antihyperlipidemic drugs in individuals exposed to CVD risk factors, such as menopause and thermoxidized oil consumption, can reduce the risk of CVDs.

Previous studies have proposed that hypertension is an inflammatory disease and have explored the possible links between oxidative stress, hypertension, and CVDs.[40,41] Oxidative stress occurs when there is an imbalance between free radicals and the cellular antioxidant system, with pro-oxidant molecules overwhelming the system. Vascular oxidative stress is one of the leading factors for CVDs.[42,43] It is implicated in endothelial dysfunction, which is an initial step in the development of atherosclerosis and other CVDs. The generation of reactive oxygen species (ROS) and the degradation of nitric oxide are major outcomes of oxidative stress. This process promotes endothelial dysfunction by reducing endothelium-mediated vasorelaxation and disrupting the non-thrombogenic surface of the endothelium, exposing the vessel wall to thrombogenic components in the blood.[44,45] Impairment of endothelial vasodilation due to endothelial dysfunction disrupts the regulation of vascular tone, potentially resulting in paradoxical vasoconstriction, cardiac ischemia, heart failure, increased renal vascular constriction, sodium reabsorption, and hypertension.[40,44] In this study, serum levels of GSH, MDA, CAT, and SOD were examined as markers of oxidative stress in OVX rats fed TSO and TPO.

The findings of this study suggest that ovariectomy alone does not significantly impact oxidative stress. However, treatment with thermoxidized oils increases ROS production and disrupts redox balance, as revealed by the results of this study.

Treatment with ETD appeared to normalize lipid metabolism and reduce ROS production in both the TSO and TPO diet groups. These results support previous

findings where ETD was shown to offer protection against oxidative stress in OVX rats.[46,47] ETD reduces ROS production by downregulating mitogen-activated protein kinase activity and also decreases inflammatory markers and lipid peroxidation.[48,49]

In rats fed with TSO, treatment with EZE+ATV similarly restored SOD levels, while ATV treatment increased GSH, SOD, and CAT levels. Elevated expression of CAT inhibits the stimulation of ROS. As a crucial enzyme in the antioxidant defense system, CAT interacts with two molecules of hydrogen peroxide, breaking them down into water and oxygen[50] in a free radical scavenging process.

The results of this study suggest that ovariectomy alone contributes to dyslipidemia; however, ovariectomy does not independently lead to significant elevation in blood pressure or oxidative stress. However, dyslipidemia, which is a direct consequence of ovariectomy, is a well-established risk factor for CVDs. Furthermore, the consumption of thermoxidized oil exacerbates the effects of ETD withdrawal, resulting in elevated blood pressure, AI, lipid profiles, and oxidative stress markers.

The health effects of chronic consumption of TSO or TPO have been previously described.[51,52] Both have been shown to negatively impact lipid levels and general cardiovascular health. Based on their major fatty acid components, palm oil is classified as SFs, while soya oil is classified as a polyunsaturated fatty acid.[2] A recent systematic review showed the health impact of plant-derived SFs, such as palm oil, remains inconclusive, as both LDL-c and HDL-c levels increase following its consumption.[2]

TPO significantly elevated DBP, MAP, and SBP, while TSO raised SBP alone. Regarding their effects on ECG parameters, TPO increased heart rate and prolonged the QT interval, an effect not observed in the TSO group. Although TSO also had adverse health impacts, these results suggest that its impact is less severe than that of TPO. These results align with dietary guidelines advocating for the modification of dietary fats, specifically recommending reducing the intake of SFs and replacing them with unsaturated fatty acids to lower CVD risk.[2]

5. Conclusion

Our study demonstrates that the combination of menopause and thermoxidized oil consumption has a synergistically deleterious effect on cardiovascular health and the antioxidant system, with TPO exerting the most adverse impact. We propose that ETD supplementation and treatment with antihyperlipidemic drugs offer cardioprotective, antihyperlipidemic, and antioxidant benefits in OVX rats exposed to thermoxidized oils.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Olufunke E. Olorundare
Formal analysis: Joy T. Folahan, Abayomi M. Ajayi, Temidayo O. Omobowale
Investigation: Joy T. Folahan, Abayomi M. Ajayi, Olubunmi Atolani, Adeoye O. Oyewopo, Olumuyiwa A. Adejumobi
Methodology: Olufunke E. Olorundare
Writing – original draft: Joy T. Folahan, Abayomi M. Ajayi, Olubunmi Atolani
Writing – review & editing: Olufunke E. Olorundare, Abayomi M. Ajayi, Saheed O. Afolabi, Mary O. Ologe

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Ethical Review Committee of the University of Ilorin, Nigeria, under approval number UERC/ASN/2021/2038.

Consent for publication

Not applicable.

Availability of data

All data generated or analyzed during this study are included in this published article.

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MINI-REVIEW

Prescription digital therapeutics in obesity management: Present and future

Hara Prasad Mishra[1] and Shubhima Grover[2]*

[1]Koita Centre for Digital Health, Ashoka University, Sonepat, Haryana, India

[2]Department of Pharmacology, Lady Hardinge Medical College, University of Delhi, Delhi, India

Abstract

Prescription digital therapeutics (PDTs) are emerging as innovative solutions in the management of obesity, complementing traditional methods such as lifestyle interventions, pharmacotherapy, and surgery. This mini-review explores the current landscape and future potential of PDTs in obesity management. We begin by defining PDTs and examining key players and products in the market. These products exemplify the integration of artificial intelligence -driven personalized coaching and real-time data tracking to enhance user engagement and treatment efficacy. Clinical evidence supporting the effectiveness of PDTs in promoting weight loss and improving metabolic health is discussed, with an emphasis on the comparative studies with traditional interventions. The review also addresses challenges such as regulatory hurdles, user adherence, data privacy, and accessibility issues. Looking forward, advancements in technology, personalized medicine, and better integration with healthcare systems are poised to further enhance the impact of PDTs. This article underscores the potential of PDTs to revolutionize obesity management and calls for continued innovation and research in this field.

Keywords: Obesity; Digital therapeutics; Software; Prescription

***Corresponding author:**
Shubhima Grover
(shugrover@gmail.com)

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1. Introduction

Obesity is a persistent disease that is becoming more common and is now regarded as a worldwide epidemic, raising global public health concerns over the past five decades, owing to its adverse impacts on quality of life, the risk for other diseases, and healthcare expenses.[1] Epidemiological research has shown a connection between a high body mass index (BMI) and a wide array of chronic illnesses, including non-alcoholic fatty liver, cardiovascular disease, diabetes mellitus, various cancers, musculoskeletal disorders, chronic kidney disease, and mental health issues. These conditions negatively impact individuals' quality of life and drive up healthcare costs. The World Health Organization defines obesity as a state of excessive or abnormal fat accumulation that poses additional health risks. Overweight is defined as a BMI above 25 kg/m² and obesity as a BMI over 30 kg/m². The obesity epidemic that has spread across many regions in recent decades is largely attributed to a sedentary lifestyle and reduced overall physical activity, combined with the consumption of unhealthy diets, such as those high in sugar and refined carbohydrates. This is compounded by a variety of genetic, endocrine, metabolic, and environmental factors, which are now recognized as the primary common causes of this global health issue.[2]

Lifestyle intervention represents the cornerstone of treatment for obesity. It is a multicomponent strategy that encompasses lifestyle or behavioral training, dietary change, and an increase in physical activity. Apart from lifestyle intervention, a few drugs have been approved for the management of obesity, complementing lifestyle modifications. These drugs such as orlistat, naltrexone/bupropion, liraglutide, lorcaserin, and phentermine/topiramate work to strengthen the patient's urge to modify their eating behaviors and produce an energy deficit. However, these drugs pose the additional risk of side effects of which the patient should be aware. Apart from this, nowadays, patients have surgical options, such as gastric banding, sleeve gastrectomy, and Roux-en-Y gastric bypass. Since lifestyle intervention is the central pillar for managing obesity, digital therapeutics (DTx) with their key focus on improving the lifestyle of patients are gaining momentum.[3]

DTx refer to the application of high-quality software programs to prevent, manage, or treat a medical disorder or disease.[4] Recently, DTx has surfaced as a novel strategy for managing chronic diseases that are amenable to behavioral modifications. In response to the COVID-19 public health emergency, the U.S. Food and Drug Administration (FDA) has relaxed rules to expand access to digital health devices that can be used for remote monitoring and management of diseases.[5] Table 1 presents various definitions of DTx. At present, DTx products are mainly applied to conditions that are modifiable through behavior change, such as obesity and type 2 diabetes mellitus. For instance, Welldoc Communications offers diabetes management software for mobile phones that connects to web-based data analytics, creating an interactive platform for real-time information and analysis between patients and healthcare providers.[6] Other companies in the digital healthcare space for diabetes and weight management include Noom, Livongo, Omada, Voluntis, and Lark.

This mini-review examines evidence-based therapeutic interventions powered by high-quality software programs, excluding interventions that rely solely on short message services, telephone calls, or online web-based servers. The objective of this mini-review is to evaluate the current state and the future potential of prescription DTx (PDTs) in obesity management.

2. Current landscape of PDTs in obesity management

2.1. Definition and scope

2.1.1. PDTs

PDTs include a class of evidence-based, software-driven interventions designed to treat, manage, or prevent medical conditions. Unlike general wellness applications, PDTs require a prescription from a healthcare provider, underscoring the need for their clinical validation and regulatory oversight. These therapeutic applications deliver therapeutic interventions directly to patients using smartphones, tablets, and other digital devices, integrating seamlessly into daily life and offering continuous, personalized care.[11] The workflow of PDT solutions is depicted in Figure 1.

2.2.2. Regulatory aspects and approval processes

The regulatory landscape for PDTs is rigorous, ensuring that these digital interventions meet high standards of safety and efficacy. In the United States, the FDA plays a pivotal role in the approval process of PDTs. The FDA's Digital Health Software Precertification (Pre-Cert) Program is designed to streamline the evaluation of software-based medical devices, fostering innovation while maintaining rigorous standards. This program assesses software developers based on five excellence principles: product quality, patient safety, clinical responsibility, cybersecurity responsibility, and proactive culture.[12]

To gain FDA approval, PDTs undergo a comprehensive evaluation that includes clinical trials to demonstrate their safety and effectiveness. This process is similar to that for traditional pharmaceuticals and medical devices. PDT

Table 1. Definitions of digital therapeutics based on institutions[7]

Institute	Definition of digital therapeutics
European data protection supervisor	DTx are evidence-based therapeutic interventions driven by software to prevent, manage, or treat a medical disorder or disease. In other words, DTx are patient-facing software applications that help patients treat, prevent, or manage a disease and that have a proven clinical benefit.[8]
Ministry of food and drug safety, South Korea	DTx are software, which can be used as a medical device to provide evidence-based therapeutic intervention to patients for prevention, control, or treatment of medical disabilities and/or diseases. DTx are applied to patients who require therapeutic intervention.[9]
Digital therapeutics alliance	DTx deliver medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders.[10]

Abbreviation: DTx: Digital therapeutics.

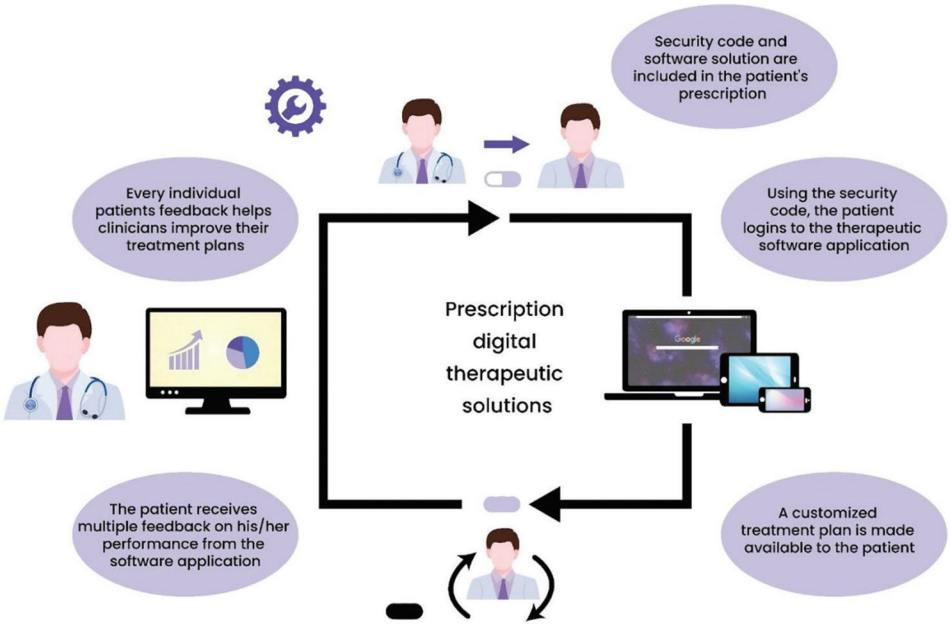

Figure 1. The workflow of prescription digital therapeutic solutions. Image is created by author.

developers must provide robust evidence from randomized controlled trials (RCTs) or other well-designed studies showing that the DTx achieve the intended health outcomes. In addition, the software must adhere to strict data privacy and security standards, ensuring the protection of patient information in compliance with regulations like the Health Insurance Portability and Accountability Act (HIPAA).[13]

Beyond the FDA, other regulatory bodies worldwide, such as the European Medicines Agency and various national health authorities, have established guidelines and frameworks for the approval and oversight of PDTs. These regulations ensure that PDTs can be safely and effectively integrated into healthcare systems globally, providing patients with reliable and clinically validated DTx options.[14]

In summary, PDTs represent a transformative approach in managing obesity, blending advanced technology with clinical rigor. The stringent regulatory pathways they navigate underscore their potential as powerful tools in modern healthcare, offering personalized and effective interventions to combat obesity and improve overall health outcomes. Figure 2 illustrates the uses of DTx.

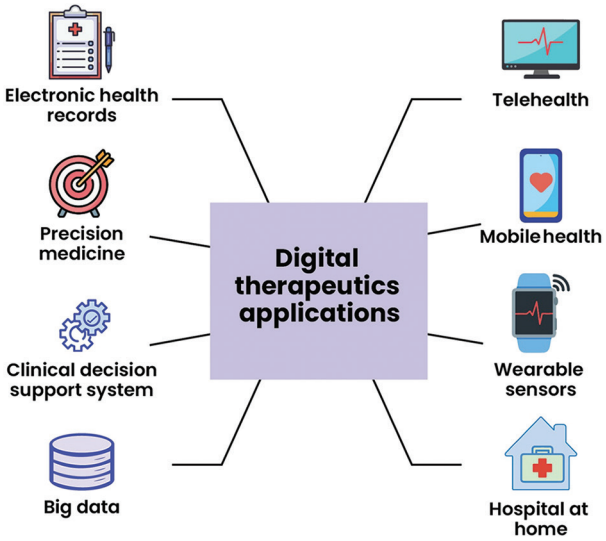

Figure 2. Uses of digital therapeutics. Image created by author.

3. DTx for obesity: An integrated and multidisciplinary approach

Diseases like obesity and eating behavioral disorders are complex in nature and require a mix of lifestyle changes and medical treatment for effective management.[15]

Addressing both physical and mental health is crucial for lifestyle modifications. High motivation is essential for adherence to these changes. Patients can develop stimulus control by managing eating-related cues, using cognitive techniques to address maladaptive thinking, and enhancing coping skills for emotional regulation and stress management.[3] These psychological mechanisms, vital for mental health, are closely linked to physical health and influence clinical outcomes. Consequently, mental health should be a key component of DTx for

obesity and eating-related problems. However, previous self-management DTx studies have often overlooked mental health, focusing instead on behaviors such as glucose and weight monitoring, medication adherence, food logging, and physical activity.[16,17] Most mobile health interventions have only shown improvements in physical health outcomes, such as hemoglobin A1c levels or body weight, but have not effectively addressed mental health issues.[18-20] Factors like motivation, depression, anxiety, and self-esteem are predictors of successful weight control. Therefore, developing practical DTx for obesity and eating behavior problems requires a multidisciplinary approach that includes psychological components.[21]

3.1. Key players and products

Omada Health is a prominent provider of DTx focused on obesity management and chronic disease prevention. The Omada Health program is built on a comprehensive, behavior change-oriented platform that integrates human coaching, peer support, digital tools, and data-driven insights. Key features include personalized health coaching, an interactive mobile app, and digital tracking tools for monitoring weight, diet, and physical activity. The user interface is designed to be intuitive and engaging, offering goal-setting capabilities, educational content, and progress tracking. The platform uses cognitive-behavioral techniques to help users develop lasting healthy habits. Participants receive wireless scales and activity trackers, which integrate their health data into the app for real-time feedback and personalized recommendations. Omada's evidence-based approach has proven effective in clinical trials, showing significant weight loss and improved health outcomes for participants.[22]

Noom is a well-known PDT that uses a psychology-based method to promote sustainable weight loss and manage obesity. At the heart of Noom's program is its mobile application, which offers various features to assist users on their weight loss journey. Notable features of Noom include customized meal plans, calorie tracking, and an extensive food database to aid users in making informed dietary decisions. The app incorporates cognitive-behavioral therapy techniques to address the psychological aspects of eating, fostering healthier habits and behaviors. In addition, Noom provides virtual coaching from trained professionals who offer guidance, motivation, and accountability. The user interface is designed to be intuitive and engaging, with daily lessons, quizzes, and progress tracking tools to keep users actively engaged in their health goals. By combining behavioral science, personalized coaching, and technology, Noom strives to offer a comprehensive and user-friendly solution for effective obesity management.[23]

WellDoc is a pioneering digital health company that offers BlueStar®, a comprehensive DTx platform initially developed for diabetes management and now expanded to address obesity and other chronic conditions. BlueStar® provides personalized, real-time guidance to users via a mobile app that integrates with various health data sources, including wearable devices, glucose monitors, and fitness trackers. The platform uses artificial intelligence (AI) to deliver customized coaching and educational content based on individual user data, assisting users in managing their diet, physical activity, medication adherence, and overall health behavior. The app features an intuitive and user-friendly interface with dashboards displaying health metrics, progress tracking, and actionable insights. Clinicians can access patient data through a dedicated portal, enabling better-informed treatment decisions and more personalized care. BlueStar® has been validated in multiple clinical studies demonstrating its effectiveness in improving health outcomes and is approved by regulatory bodies like the FDA, ensuring its credibility and reliability as a PDT.[24,25]

3.2. Mechanisms of action

PDTs leverage several mechanisms to effectively manage obesity. Central to their approach are behavioral interventions rooted in cognitive-behavioral therapy principles, which help users modify unhealthy eating patterns and adopt healthier behaviors. Gamification techniques further enhance user engagement and adherence by making the process more interactive and motivating. In addition, PDTs utilize data tracking and personalization through wearables and mobile apps, which monitor physical activity, dietary intake, and other health metrics, providing users with real-time feedback and personalized insights. Advanced technologies such as AI and machine learning play a critical role in this personalization, analyzing user data to create tailored treatment plans that adapt to individual needs and progress. Together, these mechanisms create a comprehensive and dynamic approach to obesity management, fostering sustained behavior change and improved health outcomes. The differences between conventional pharmacotherapy and DTx are shown in Table 2.

3.3. Clinical evidence and effectiveness

3.3.1. Issues of DTx in obesity treatment

Based on the current status of the field, there as six major constructive issues currently facing the application of DTx in the management of obesity and eating-related problems (Figure 3).

3.3.1.1. Comprehensiveness of an individual's multifactorial health condition

As noted previously, obesity and eating behavior issues are complex and multifaceted in nature.[3] To thoroughly understand and monitor the progress of weight control

Table 2. Differences between conventional pharmacotherapy and digital therapeutics[7]

Category	Pharmaceutical	Digital therapeutics
Development cost	Very high cost (about $1.8B)	Comparatively low cost
Development period	Approximately more than 10 years	Approximately<10 years
Manufacturing	Continuous production required through manufacturing facilities	No additional manufacturing is required after initial development
Phases of clinical trials	Human pharmacology study (Phase 1) Exploratory study (Phase 2) Confirmatory study (Phase 3)	Exploratory study (Pilot, optional) Confirmatory study (Pivotal)
Regulation	Pharmaceutical law applicable	Medical device law applicable
Medication monitoring	Manual monitoring done	Real-time automatic monitoring done
Medication adherence	50%	80%
Prerequisites	Not required	Digital device, appropriate level of cognitive ability needed
Prescription	Mandatory (ETC only)	Mandatory (PDTs only)
Data security	Not applicable	Need cyber security and data protection solutions

Abbreviations: ETC: Essential-therapeutic-category; PDT: Prescription digital therapeutic.

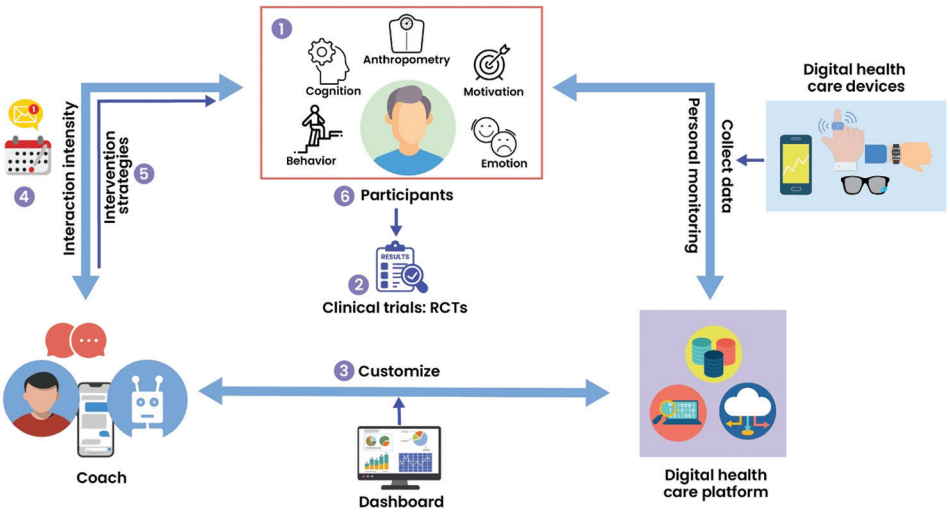

Figure 3. The workflow of digital therapeutics used in obesity management. Image created by author.
Abbreviation: RCTs: Randomized controlled trials.

and eating patterns, it is recommended to address multiple domains including behavioral, cognitive, emotional, motivational, and anthropometric aspects.[21] Since behavior styles and engagement with DTx are greatly influenced by cognitive structuring and emotional regulation, an integrated clinical approach that incorporates all these elements is essential for effectively addressing obesity-related challenges.

3.3.1.2. Efficacy of DTx in RCTs

The goal of RCTs is to evaluate the effectiveness of new treatments while reducing potential biases, such as the placebo effect. During the RCTs, both the efficacy and safety of treatments are established, which are critical factors for FDA approval. While many studies have investigated digital interventions for weight loss, not all have been structured as RCTs.[26] To conclusively demonstrate the effectiveness of new DTx, RCTs are essential. One of the most critical and challenging aspects of designing RCTs for DTx is creating an appropriate control group. Digital interventions encompass a wide range of features, such as self-monitoring, cognitive-behavioral therapy, user interface/user experience, and human coaching. This diversity makes it difficult to determine which specific features are effective and which should be compared in the trials.[27] Selecting the primary active ingredient of DTx and creating a specific active sham control group (an identical DTx platform without the primary active ingredient) presents

significant challenges. Achieving a fully blinded condition, akin to placebo-controlled trials for medications, is also difficult. Consequently, new RCT frameworks tailored to DTx have been developed. These include the multiphase optimization strategy, sequential multiple assignment randomized trials, micro-randomized trials, clustered RCTs, unequal allocation RCTs, and control optimization trials. Each of these designs addresses different research questions, aiming to provide gold-standard evidence in clinical medicine. In addition, due to the digital nature of these technologies, RCTs for DTx can employ fully digital, innovative designs, incorporating digital enrollment, digital intervention, and digital outcome phenotyping, potentially eliminating the need for on-site visits. Table 3 presents a summary of multiple clinical trials.

3.3.1.3. Individual feedback tailoring in DTx

Personalized PDTs have the capability to provide customized feedback using individualized data across various domains, as previously discussed. It has been demonstrated that this personalized approach is essential because it significantly impacts engagement with digital interventions and the potential for sustained lifestyle modifications over time.[21] However, the majority of interventions delivered through mobile applications employ standardized behavioral approaches (such as reminders for monitoring and appointments, and general health education), utilize content that is uniformly generated, or incorporate algorithms that are minimally customized and focus narrowly on domains like diet, physical activity, and body weight.[32,33] These approaches have demonstrated constraints in engaging participants in the intervention and sustaining treatment effectiveness. Therefore, utilizing tailored feedback and adaptive interventions based on baseline and/or real-time multifaceted assessments (including behavior, emotions, cognition, and motivation) can enhance both engagement and the overall efficacy of DTx. Moreover, incorporating additional factors such as genetic predispositions, social and economic circumstances, and coexisting health conditions could further optimize the development of personalized DTx solutions.

3.3.1.4. Temporal strategies for intervention frequency

The engagement rate in DTx is significantly influenced by temporal methods for intervention frequency. In general, an intervention can be applied at three different time points: daily, weekly, and monthly. Prior research using weekly or monthly interventions revealed high rates of attrition.[35] Given that DTx engagement rates impact clinical outcomes, it is imperative to take into account the level of contact between physicians and users. Higher involvement may be stimulated by daily interventions that are more intensive. However, users and coaches may find a too frequent intervention taxing or tiresome. By using cutting-edge digital technologies like AI and machine learning to replace tedious tasks with automated services, this can be lessened.[36]

3.3.1.5. Psychological theory for intervention strategies based on empirical evidence

While digital health technologies have advanced significantly, it is essential to evaluate the integration of evidence-based behavior change strategies and clinical protocols within these modalities. Evidence-based interventions refer to strategies supported by empirical evidence demonstrating their effectiveness and accountability. Key psychological interventions, such as cognitive-behavioral therapy, dialectical behavioral therapy, acceptance and commitment therapy, and mindfulness-based cognitive therapy, are well-established in clinical practice. Cognitive-behavioral therapy, particularly, is widely utilized across various mental health conditions, prompting researchers to explore its expansion through digital platforms. Incorporating these scientifically

Table 3. Summary of clinical trials and studies evaluating the effectiveness of prescription digital therapeutics in obesity management[28]

Study	Population	Intervention	Delivery digital device
Spring *et al.*[29]	Adults with obesity	Technology-supported	Smartphone, web portal
Nezami *et al.*[30]	Mothers with overweight and obesity, children aged 3 – 5 years	Smart group (mobile application-supported)	Smartphone
Spring *et al.*[31]	Adults aged 18 – 65 years	Temporally simultaneous intervention	Smartphone
Kim *et al.*[32]	Old adults with diabetes (mean age 60)	Mobile-based glucose diary	Smartphone
Fitzsimmons-Craft *et al.*[33]	Women with eating disorders	CBT-guided self-help	Smartphone
Lowe *et al.*[34]	Female and male adults with a BMI in the range of 27 – 43	Time-restricted eating	Smartphone, wearable devices
Kim *et al.*[21]	Overweight and obese women adults	Human-based digital CBT	Smartphone, web portal

Abbreviations: CBT: Cognitive-behavioral therapy; BMI: Body mass index.

validated intervention strategies into DTx is crucial for enhancing their efficacy.

In a study by Strombotne *et al.*,[37] 2 years of virtual coaching and ketogenic diet led to a significant reduction in BMI and monthly usage of diabetes medication in diabetic patients. In addition, involving healthcare professionals, including doctors, nurses, psychologists, and trainers, in the development of DTx can ensure the reliability and effectiveness of these interventions.

3.3.1.6. Target populations

Most DTx focusing on lifestyle modifications or eating-related issues have primarily concentrated on adults. Despite the correlation between childhood/adolescent obesity and adult metabolic diseases, there is a notable scarcity of studies examining DTx interventions in youths. For effective treatment of children and young adults, involving their caregivers or guardians in the intervention process is deemed more effective in achieving positive clinical outcomes. Similarly, involving families in interventions aimed at older adults, who often contend with existing metabolic or psychiatric conditions, is recommended to enhance the success of DTx approaches. In addition, clinicians are advised to tailor strategies according to specific target symptoms such as major depressive disorder, eating disorders, diabetes, or hypertension.

4. Challenges and limitations

4.1. Challenges

4.1.1. Regulatory and approval challenges

The regulatory landscape for PDTs in obesity management presents significant hurdles, varying widely across different regions. Obtaining approval involves navigating complex processes that differ in requirements and timelines between jurisdictions. Harmonizing these regulations globally is crucial for ensuring timely access to innovative therapies and fostering broader adoption in healthcare systems.

4.1.2. User engagement and adherence

Effective engagement and sustained adherence pose substantial challenges for PDTs in obesity management. Issues such as user motivation, interface design, and personalized feedback mechanisms influence long-term participation. Strategies incorporating behavioral science principles, real-time feedback, and gamification are being explored to enhance user engagement and promote adherence to PDTs.

4.1.3. Data privacy and security

Concerns regarding the privacy and security of patient data loom large in the adoption of PDTs. Compliance with stringent regulations like General Data Protection Regulation and HIPAA is essential to safeguarding sensitive health information. Robust encryption protocols, anonymization techniques, and transparent data handling practices are critical for maintaining patient trust and regulatory compliance.

4.1.4. Accessibility and equity

The accessibility of PDTs remains constrained by factors including cost barriers and varying levels of digital literacy among diverse populations. Addressing these disparities requires proactive efforts to reduce costs, improve user education, and ensure equitable access to DTx solutions. Collaboration between stakeholders in healthcare, technology, and policy sectors is essential for advancing accessibility and fostering inclusive healthcare delivery through PDTs.

4.2. Limitations with DTx use in hospital settings

Despite extensive efforts to develop various types of DTx, their integration into clinical settings remains incomplete due to several limitations. Presently, two significant concerns hindering the scalability and effectiveness of DTx are low user engagement and insufficient efficacy.[35] Next, akin to traditional pharmaceuticals, DTx must undergo RCTs as part of the approval process to confirm their safety and efficacy before they reach the market.[5] However, DTx software can be updated and adjusted in response to FDA guidance at any time, unlike traditional pharmaceuticals. Cybersecurity and data rights present additional challenges that hinder widespread adoption of DTx. One potential solution involves forming partnerships between industries and academic institutions; for instance, companies developing successful DTx collaborate with academic groups to ensure scientific rigor, in scenarios similar to how traditional pharmaceuticals are developed.

5. Future directions

The future of PDTs in obesity and diabetes management is poised for significant advancements, driven by emerging technologies and personalized medicine. Innovations in technologies such as AI, augmented reality (AR), and virtual reality (VR) are set to transform PDTs, offering more immersive and engaging interventions. AI can enhance the personalization of treatment plans by analyzing vast amounts of user data, while AR and VR can create interactive experiences that make lifestyle changes more engaging. Wearable technology is also advancing rapidly, providing continuous, real-time health data that can be seamlessly integrated with PDTs to offer more precise and timely interventions.

Personalized medicine is another promising avenue, with genetic insights allowing for highly individualized treatment strategies. The use of big data and advanced analytics will enable PDTs to deliver more tailored interventions, considering each individual's unique behavioral, emotional, and physiological profile. Big data is helpful for training of health models, which can be further leveraged to bring DTx solutions for chronic diseases into real life.[38]

Integrating PDTs into standard healthcare practices will be crucial for their widespread adoption. This will require strong collaboration between tech companies and healthcare providers to ensure that PDTs are effectively integrated into patient care plans. In addition, the future regulatory landscape will need to evolve, with advocacy for standardized regulations across regions to ensure the safety, efficacy, and accessibility of PDTs.

Overall, the future of PDTs in obesity management holds great promise, with technological innovations and personalized approaches driving more effective and engaging solutions. This progress will ultimately empower the affected individuals to take a more proactive attitude in managing obesity and improve the overall health outcomes.

6. Conclusion

PDTs have revolutionized the approach to obesity management by integrating advanced digital technologies with behavioral medicine. These innovative solutions, like WellDoc's BlueStar®, provide personalized health guidance and real-time support, significantly enhancing patient engagement and adherence. Clinical studies have validated the effectiveness of PDTs, underscoring their potential in improving health outcomes for individuals with obesity.

Despite their promise, PDTs face challenges such as regulatory hurdles, user engagement issues, data privacy concerns, and accessibility barriers. Addressing these challenges through improved regulatory frameworks, user interface enhancements, robust data security measures, and efforts to bridge the digital divide is essential for realizing the full potential of these digital interventions.

In future, the continued advancement of technology, including AI, wearable devices, and personalized medicine, will further drive the impact of PDTs in obesity management. Integrating these tools within healthcare systems and establishing standardized regulatory policies will be crucial for scaling their benefits. As PDTs evolve, they offer the promise of more effective obesity management and empower individuals to take proactive control of their health, adapting to the ever-evolving digital healthcare.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Shubhima Grover
Visualization: Hara Prasad Mishra
Writing–original draft: Hara Prasad Mishra
Writing–review & editing: All authors

Ethics approval and consent to participate

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ACCSCIENCE PUBLISHING

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SHORT COMMUNICATION

An observational study on the use of low-molecular-weight heparin for venous thromboembolism prophylaxis in acute stroke patients

Faizan A. Sandhu* and Revin Thomas

Department of Stroke Medicine, University Hospital North Durham, Durham, United Kingdom

Abstract

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) are common complications post-stroke. The UK stroke guidelines recommend the early use of intermittent pneumatic compression devices (IPCDs). At our center, we noticed poor compliance with the use of these devices and sought to develop a pathway for early implementation of low-molecular-weight heparins (LMWH) instead. We retrospectively analyzed the data of 2351 patients in two separate groups and compared both groups to check the incidence of PEs and DVTs as stated on the discharge documentation. Group A consists of 1599 patients who used IPCDs as VTE prophylaxis, whereas Group B involved 752 patients who were placed on the new VTE prophylaxis protocol, which involved the early use of LMWH with enoxaparin delivered subcutaneously. It was observed that IPCDs were not well tolerated by patients, leading to poor compliance with VTE prophylaxis in Group A. VTE compliance was noted to be better in Group B in which the patients were given LMWH in the hospital. Furthermore, symptomatic DVT and PE were not found to be higher in Group B patients, but in fact, the incidence of these conditions was lower in this group. In conclusion, compared to IPCDs, LMWH appears to be well tolerated by patients during the admission period owing to acute stroke. It was observed that the incidence of VTE was reduced in patients who started on early LMWH in the post-stroke period. However, the long-term effects of LMWH prophylaxis, in terms of mortality and morbidity, need to be delineated. Therefore, an additional large trial on the early use of LMWH in comparison to IPCDs is warranted.

Keywords: Low-molecular-weight heparin; Venous thromboembolism; Deep vein thrombosis; Pulmonary embolism; Acute stroke; Blood clots; Intermittent pneumatic compression device

***Corresponding author:**
Faizan Sandhu
(faizan.sandhu@nhs.net)

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1. Introduction

Venous thromboembolism (VTE), a term which encircles both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in stroke patients.[1] VTE is a considerable cause of morbidity, delayed hospital discharge, and potential increased health-care costs. It has been estimated to account for one-fourth of all deaths after stroke.[2] In the early post-stroke phase, the risk of VTE appears to be highest in

the initial few weeks.[3] Clinically, about 5% of hospitalized patients have definite DVT.[4] Similarly, about 1 – 2% of hospitalized stroke patients were clinically diagnosed with PEs, but in some studies, the incidence is about 10%.[5] Moreover, Warlow *et al.* revealed PE as an identifiable cause in about half of the patients dying after a stroke, based on data collected from a hospital where autopsies were more conventional.[6] Therefore, clinicians are expected to assess VTE risk among stroke patients and provide the most effective and safe prophylaxis.

Hemorrhagic transformation (HT) is another common complication in acute ischemic stroke, and its rate of occurrence can range from <1%.[7-9] The severity of hemorrhage may range from a few petechiae to a large hematoma with or without space-occupying effects. Based on the classification by the European Cooperative Acute Stroke Study, each HT category is divided into two subtypes, with each featuring distinctive characteristics (Table 1).[10]

HT does not usually have a significant impact on patient prognosis,[11] but massive parenchymal hematoma, albeit rare, is life-threatening.[12] The mechanism of HT formation during ischemic stroke is thought to be related to the early disruption of the blood–brain barrier (BBB).[13] The BBB is a physiological barrier between the brain parenchyma and brain circulation that nourishes brain tissue. It filters various substances from the brain to the blood and protects the brain.[14,15] The other factors that might influence HT are histological changes, vascular occlusion, collateral circulation, and infarct size.[16,17]

Post-stroke VTE prophylaxis can be achieved with non-pharmacological and pharmacological strategies. Non-pharmacological or physical methods consist of graduated compression stockings (GCSs) and intermittent pneumatic compression devices (IPCDs). The use of blood thinners such as low-molecular-weight heparin (LMWH) and unfractionated heparins (UFH) come under pharmacological interventions. HT should be taken into account when the timing for anticoagulation initiation in cardioembolic strokes has to be established.[18] The European Stroke Organization (ESO) guidelines recommend that prophylactic anticoagulation with UFH and LMWH should be considered in immobile patients with ischemic stroke in whom the benefits of reducing the risk of VTE are significant enough to offset the increased risk of intracranial and extracranial bleeding.[4] This was also suggested by Khan et al. following a systemic review of literature on deep vein thrombosis in acute stroke; LMWH was effective in reducing DVT and PE in patients with stroke at the cost of a slightly increased risk of intracerebral and extracranial bleeding.[19]

Table 1. ECASS classification of hemorrhagic events

Category	Subtype and characteristic
Hemorrhagic infarction	HI-1: Small petechiae along the margins of the infarct. HI-2: Confluent petechiae within the infarcted area but no space-occupying effect.
Parenchymal hemorrhage	PH-1: Blood clots in 30% or less of the infarcted area with some slight space-occupying effect. PH-2: Blood clots in more than 30% of the infarcted area with substantial space-occupying effect.

ECASS: European Cooperative Acute Stroke Study, HT: Hemorrhagic transformation

The CLOTS 1 and 2 trials showed that GCSs were ineffective in preventing VTE or improving functional outcomes in stroke.[20] The CLOTS 3 trial showed that intermittent pneumatic compression (IPC) using sequential compression with venous refill technology in immobile patients in the first 30 days after stroke is an effective treatment for reducing proximal DVT and improves survival but not functional outcomes.[21]

It is challenging for patients with a high risk of VTE and low risk of bleeding to use anticoagulants in a selective manner after stroke because the factors that predict VTE and those predicting bleeding risk overlap.[22,23] According to Geeganage *et al.*, LMWH minimizes the risk of recurrent ischemic stroke, DVT, and PE; however, on the other hand, they increase the risk of symptomatic intracranial and extracranial hemorrhage.[24] In stroke, the benefits of LMWH are often offset by its harms; according to the data from randomized controlled trials of subcutaneous heparins, there was no noticeable effect of anticoagulants on death or disability measured several months after stroke.[25-27]

1.1. Study justification

Poor compliance with IPCDs among admitted patients with acute stroke was common at our unit. The poor compliance can be described as patients not tolerating the device, increased risk of falls, patients being ignorant that they attempt to stand without support with the IPCDs still on, and forgetfulness in reattaching IPCDs after care (*e.g.*, showering or hygiene) or therapy.

Thus, we reviewed the adherence to VTE prophylaxis plans formulated for our stroke unit by auditing compliance with IPCD use in 2021. The auditing process was completed in two parts:

(1) Audit 1: Review of compliance of VTE prophylaxis prescription using IPCDs in acute stroke patients within 72 h of admission
(2) Audit 2: Review of compliance of VTE prophylaxis prescription using IPCDs in acute stroke patients,

after the initial 72 h of admission, but within 1 month of stay.

In Audit 1, we found that generally, following admission to the acute stroke unit, stroke patients and staff demonstrated a high level of compliance in using IPCDs for VTE prophylaxis, with only 8% of patients not using their prescribed IPCD. However, Audit 2 showed that compliance with using IPCDs greatly reduced as patients continued with their stroke recovery in the rehabilitation unit, with 87% of patients found not to be wearing their prescribed IPCDs despite staff recommendations. There was a variety of reasons recorded in the notes, *e.g.*, patients reporting pain or discomfort while using IPCDs and patients reporting difficulty with transfers.

Following these two auditing processes, discussions on finding ways to improve compliance with IPCDs or considering alternative methods to deliver VTE prophylaxis in the stroke unit were held. After a series of discussions at governance meetings, we introduced a new protocol in July 2022, recommending the early use of LMWH prophylaxis in acute stroke patients as a VTE prophylaxis strategy. This was done using enoxaparin 20 – 40 mg (based on weight), delivered subcutaneously. Acute stroke patients were prescribed LMWH prophylaxis based on their stroke type (ischemic vs hemorrhagic) and stroke severity (mild: Lacunar stroke [LACS]; moderate: Partial anterior circulatory stroke [PACS]; severe: Total anterior circulatory stroke [TACS]) (Figure 1).

2. Study objectives

The purpose of this work is to evaluate the incidence of DVTs or PEs in patients treated with a new protocol for early use of LMWH prophylaxis. The secondary objective of this study is to examine if the same patient group is vulnerable to a higher incidence of symptomatic HT of ischemic stroke.

3. Method

The data of 2351 stroke patients admitted between January 1, 2021, and July 31, 2023, were evaluated retrospectively. In our analysis, these patients were subdivided into two groups:

- Group A consists of 1599 patients admitted between January 1, 2021, and July 31, 2022 (19 months). The patients in this group used IPCDs as VTE prophylaxis during the admission period for acute stroke

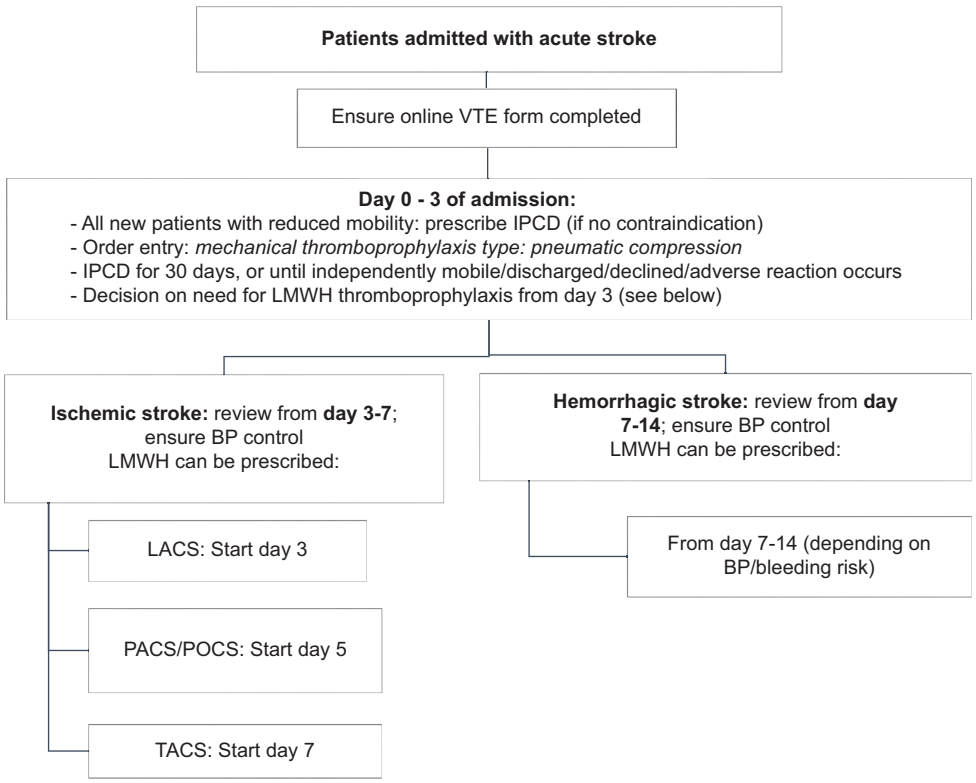

Figure 1. Flowchart for venous thromboembolism (VTE) prophylaxis with low-molecular-weight heparin (LMWH) therapy based on acute stroke presentation conducted in our hospital
Abbreviations: BP: Blood pressure; IPCD: Intermittent pneumatic compression device; LACS: Lacunar stroke; PACS: Partial anterior circulatory stroke; POCS: Posterior circulation stroke syndrome; TACS: Total anterior circulatory stroke.

- Group B consists of 752 patients admitted between August 1, 2022, and July 31, 2023 (12 months). The patients in this group used LMWH (enoxaparin 20 – 40 mg delivered subcutaneously, dose adjusted for weight) as VTE prophylaxis during the admission period for acute stroke.

In each of the groups, the patients who developed PE, DVT, or symptomatic HT within 3 months of their stroke were identified. They were investigated if they presented with clinical symptoms or were suspected of PE/DVT or symptomatic HT. The diagnosis of ischemic stroke, PE, DVT, and HT was confirmed by radiological means such as computed tomography (CT) of the head, CT pulmonary angiogram, and Doppler ultrasound.

The electronic VTE risk assessments (Appendix A1) and IPCD/LMWH prescriptions for patients were gathered from the hospital's electronic prescribing platform.

4. Results

The electronic VTE risk assessments of all the patients were completed at admission. This highlights that the admitting stroke team was aware of performing stroke VTE prophylaxis and the need to ensure the patients were adequately treated. We found that the early use of LMWH was associated with 100% compliance to VTE prophylaxis once the new protocol was implemented, as compared to 91.6% compliance during the admission period when the acute stroke patients were using IPCS (Figure 2).

In Group A, the incidence of PE and DVT is about 0.75% (12 patients) and 0.12% (Two patients), respectively. Among the 12 patients who developed PE, four cases were directly related to stroke, whereas the remaining eight cases were linked to other risk factors. In Group B, the incidence of PE is about 0.79% (six patients) and no case of DVT was identified. Among the six patients, only one patient was symptomatic, whereas the rest were found to have incidental PE based on the findings from other tests or investigations (Figures 2 and 3). None of the two groups have any reported cases admitted with symptomatic post-stroke HT in 3 months' time (Figure 3).

5. Discussion

Few studies have reported the use of early anticoagulation in acute stroke. Most studies have used LMWH as the anticoagulant agent and two of them used unfractionated heparin and a particular direct thrombin inhibitor, *i.e.*, argatroban.[28-30] The International Stroke Trial (IST) compared the administration of subcutaneous UFH versus aspirin within 48 h of onset of ischemic stroke symptoms. This randomized trial involved 19,435 patients from 467 hospitals in 36 different countries. The study revealed that

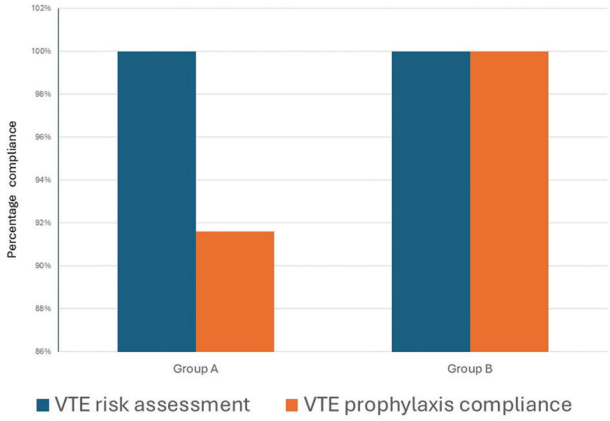

Figure 2. Venous thromboembolism risk assessment and prophylaxis compliance

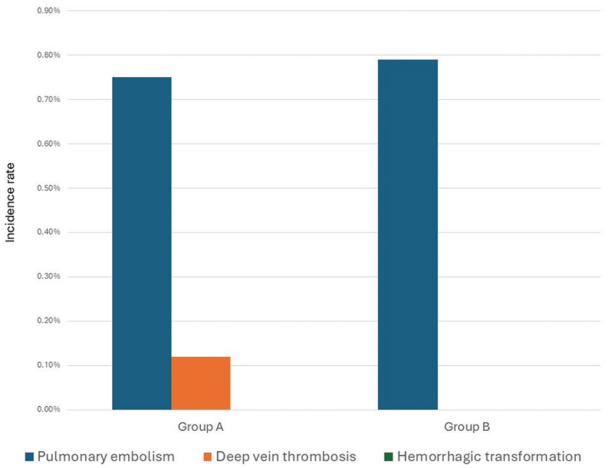

Figure 3. Incidence of pulmonary embolism, deep vein thrombosis, and hemorrhagic transformation. The incidence rate of hemorrhagic in Group A is 0, while the incidence rate of deep vein thrombosis and hemorrhagic transformation in Group B is 0

patients treated with heparin had a significantly lower recurrence of ischemic stroke within a 14-day period.[31] According to a FISS-tris trial involving patients with large-artery occlusive disease, nadroparin calcium was compared with aspirin. The therapy was initiated within 48 h of symptoms onset and patients were followed up until 6 months after the ischemic stroke. The results showed no significant benefit of nadroparin over aspirin in the patients assessed, and further investigation of anticoagulation in large-artery atherosclerosis patients was recommended.[32]

We observed the non-compliance of IPCD among stroke patients in 2021, despite that they were recommended to use the device. The reasons recorded include patients reporting pain or discomfort using IPCDs, staff and patients forgetting to effectively use the IPCDs after

therapy sessions, and patients reporting difficulty with transfers or positioning in bed. These situations were discussed in the local stroke governance meetings, and measures were taken to improve VTE compliance, *e.g.*, staff checking IPCD compliance during each nursing and medical ward round. At our institute, we followed the UK Stroke Guidelines 2016 (now replaced by the 2023 version, with the same document title). Accordingly, "patients with immobility after acute stroke should be offered IPC within 3 days of admission to hospital for the prevention of DVT. Treatment should be continuous for 30 days or until the patient is mobile or discharged, whichever is sooner."[33.p.60] However, despite staff checking, compliance was still found to be lacking with IPCD use.

Following discussions at governance meetings, we introduced a new protocol in July 2022, recommending the early use of LMWH prophylaxis in acute stroke patients as a VTE prophylaxis strategy. This was done using enoxaparin 20 – 40 mg (based on weight), delivered subcutaneously. Acute stroke patients were prescribed LMWH prophylaxis based on their stroke type (ischemic and hemorrhagic) and stroke severity (mild: LACS from day 3; moderate: PACS from day 5; severe: TACS from day 7) (Figure 2). Following this new protocol for VTE prophylaxis, we noted an improvement in VTE compliance among patients admitted to the stroke ward, probably due to regular monitoring done on the patients receiving VTEs prophylaxis and the LMWH being better tolerated by the patients. Furthermore, the incidence of DVT in stroke patients reduced, as no cases have been identified since the implementation of the new protocol. Both Groups A and B have more cases of asymptomatic incidental PE compared with DVTs. Relatively, the incidence of PE was slightly increased in Group B as compared to Group A, after taking into consideration their cohort size (Figure 3). This is probably due to the lower number of patients in Group B being analyzed (752 vs 1599 patients), which is a pitfall of this analysis. However, there was only a small proportion of patients with post-stroke PE in Group B who became symptomatic with shortness of breath or reduced blood oxygen saturation levels (Figure 4). Interestingly, one of the cases, who was admitted with a posterior circulatory stroke (POCS), showed no reduced mobility even if IPCD was prescribed. The patient later, on day 4 of admission, developed symptomatic PE.

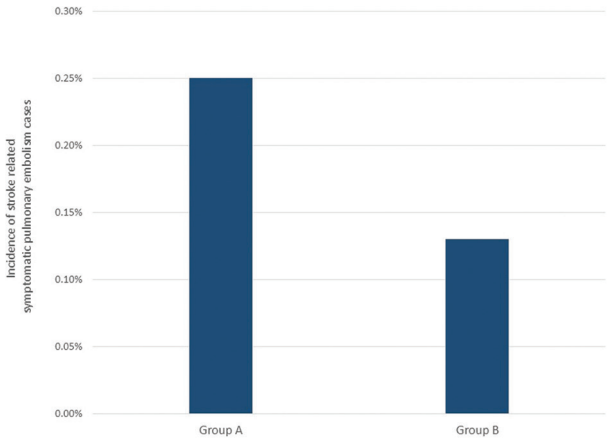

Figure 4. Incidence of stroke-related pulmonary embolism

In this study, we observed that being male with age around 71 – 80 years and/or having health issues such as diabetes mellitus, hypertension, and cardiac problems are

Table 2. Demographics of the patients from Groups A and B with pulmonary embolism and deep vein thrombosis

	Group A (*n*=14)	Group B (*n*=6)	N (number)	Percentage
Gender				
Male	8	5	13	65
Female	6	1	7	35
Age group				
51 – 60 years	2	1	3	15
61 – 70 years	3	2	5	25
71 – 80 years	5	2	7	35
81 – 90 years	4	1	5	25
Thromboembolism risk factors				
Hypertension	5	3	8	40
Diabetes mellitus	5	2	7	35
Ischemic heart disease or heart failure	3	1	4	20
Chronic illness or malignancy	5	1	6	30

the risk factors in both Groups A and B. Strangely, a small number of the population assessed tend to have cancer of various organs that may also contribute to VTE formation. Table 2 shows the patient demographics of all 20 patients from Groups A and B with DVTs and PEs.

The current study had several limitations. One apparent shortcoming of this analysis is that potential risk factors, including obesity, dehydration, and family history of thromboembolism, were not covered in this study. Another pitfall is that Group B consisted of a small number of subjects (only 752 patients), who were recruited over a shorter period of time (12 months versus 19 months in Group A), preventing us from exploring the long-term significance of LMWH in reducing mortality and morbidity. Finally, although no definite cases of symptomatic HT were detected in either Groups A or B, this observational study was not statistically powered enough to ascertain the significance of the findings.

6. Conclusion

There are numerous controversies over the utilization of VTE prophylaxis in the management of acute ischemic stroke. According to our analysis, early use of LMWHs was better tolerated as a form of VTE prophylaxis. However, given the short-term nature of this project, we cannot establish the long-term significance of LMWH in reducing death and disability rates, and thus, additional large trials are warranted to validate the efficacy of earlier use of LMWH.

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The authors declare they have no competing interests.

Author contributions

Conceptualization: Revin Thomas
Formal analysis: All authors
Investigation: Faizan A. Sandhu
Methodology: All authors
Writing – original draft: Faizan A. Sandhu
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

Data are available from the corresponding author upon reasonable request.

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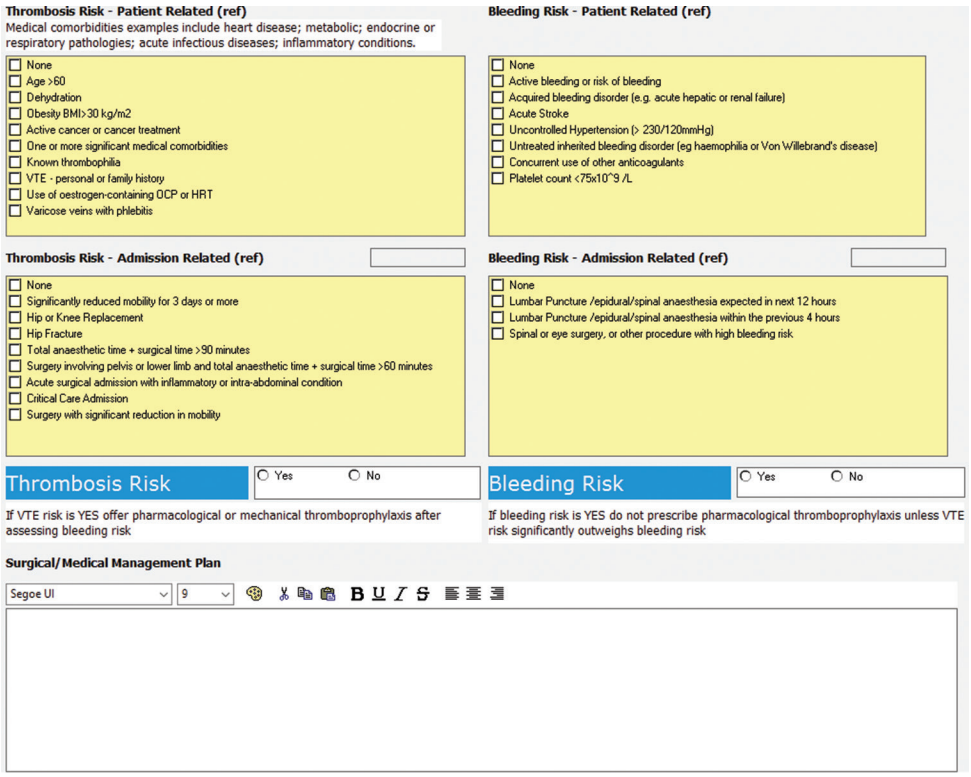
Appendix



Appendix A1. Venous thromboembolism risks assessment form used at our hospital

ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

CASE REPORT

Managing atropine-induced psychosis in organophosphate poisoning: A case report

Mohammed Misbah Ul Haq*, Juveria Almas, Soha Amreen, and Mohammed Zabeeruddin

Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, India

Abstract

Atropine-induced psychosis, though rare, is a critical adverse effect that can arise during the treatment of organophosphate (OP) poisoning, necessitating swift recognition for optimal patient care. This case report describes the presentation of a 45-year-old male with a history of chronic alcoholism and smoking, admitted for OP intoxication, who developed acute psychosis after atropine administration. The symptoms included hallucinations, agitation, and delirium, with diagnostic evaluation confirming atropine-induced psychosis according to DSM-IV-TR criteria. The treatment approach involved discontinuing atropine and providing supportive care, which resulted in symptom resolution within several days. In addition, benzodiazepines were administered to manage agitation and anxiety. This case highlights the need for careful monitoring of drug reactions, particularly in patients with risk factors, such as chronic alcoholism. It underscores the importance of individualized treatment strategies and the critical role of healthcare professionals in recognizing and addressing atropine-induced psychosis. Further research is warranted to better understand the underlying mechanisms and risk factors associated with this complication.

Keywords: Atropine-induced psychosis; Organophosphate poisoning; Adverse drug reactions; Psychiatric manifestations; Management strategies

***Corresponding author:**
Mohammed Misbah Ul Haq
(drmdmisbah@outlook.com)

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1. Background

Organophosphate (OP) insecticide poisoning remains a significant global health challenge, contributing to an estimated 100,000 deaths annually worldwide.[1] These compounds exert their toxic effects by inhibiting acetylcholinesterase, leading to the accumulation of acetylcholine at cholinergic synapses and resulting in acute cholinergic syndrome.[2] Atropine, a naturally occurring alkaloid extracted from plants such as deadly nightshade (*Atropa belladonna*), is commonly employed as an antidote in the management of OP poisoning. However, high doses of atropine can cause adverse effects, including the rare but serious complication of atropine-induced psychosis.[3]

Atropine functions by antagonizing the muscarinic effects of acetylcholine in both the central and peripheral nervous systems, blocking neurotransmitter actions on post-ganglionic nerves and smooth muscles.[4] Common side effects, such as xerostomia, photophobia, blurred vision, and tachycardia, typically occur at or below therapeutic doses. However, at toxic doses, more severe adverse effects, including dilated pupils, marked palpitations, restlessness, tremors, delirium, hallucinations, and fatigue, can

occur.[5] Among these, atropine-induced psychosis is a rare phenomenon characterized by symptoms such as restlessness, excitement, hallucinations, and delirium following atropine administration.[4] Although atropine administration for OP poisoning is generally well-tolerated, allergic or toxic reactions, including atropine-induced psychosis, are infrequently reported in the literature.[6]

Atropine-induced psychosis, though rare, is a potentially serious adverse effect observed following atropine administration, particularly in the context of OP poisoning.[7] While the exact mechanisms underlying this psychosis remain unclear, several hypotheses have been proposed, including disruption of central cholinergic neurotransmission, altered dopaminergic signaling, and modulation of glutamatergic and GABAergic pathways.[8] Clinically, this condition resembles acute psychotic disorders, such as schizophrenia or substance-induced psychosis, and is marked by hallucinations, delusions, agitation, confusion, and disorientation.[9] Patients may exhibit erratic behavior, paranoia, and perceptual disturbances, often requiring close monitoring and intervention to ensure their safety and prevent harm.[4,10]

Several factors may pre-dispose individuals to atropine-induced psychosis, including advanced age, pre-existing psychiatric disorders, substance abuse, polypharmacy, and underlying medical comorbidities.[6,11] Elderly patients are particularly vulnerable due to age-related changes in drug metabolism, altered blood-brain barrier permeability, and reduced tolerance to anticholinergic effects.[7,12] Comorbidities such as dementia, Parkinson's disease, cerebrovascular disease, and cardiovascular disorders may further increase susceptibility by disrupting neurotransmitter balance or impairing cognitive function.[13] The concomitant use of medications with anticholinergic properties, such as antipsychotics, antidepressants, antihistamines, and antiparkinsonian agents, may also heighten the risk of psychosis.[14]

Diagnosing atropine-induced psychosis requires a comprehensive clinical assessment, including a detailed patient history, mental status examination, physical evaluation, and exclusion of other causes.[15] The DSM-5 criteria for substance-induced psychosis include the onset of psychotic symptoms related to substance use, the absence of a primary psychotic disorder, and the resolution of symptoms following cessation of the substance.[8,14] Laboratory tests and neuroimaging may be necessary to rule out other conditions that could contribute to psychosis, such as metabolic disturbances, infections, or drug intoxication.[11] Toxicology screening for serum or urine levels of atropine can provide supportive evidence for diagnosis.[16]

Management of atropine-induced psychosis involves a multifaceted approach, including the discontinuation of atropine, supportive care, pharmacological interventions, and psychosocial support. Prompt recognition and cessation of the offending drug are crucial to preventing further complications.[17,18] Supportive measures, such as providing a calm environment and close supervision, are essential for managing agitation and behavioral disturbances.[17-19] Pharmacological treatments may involve the use of antipsychotic medications, such as haloperidol, risperidone, or olanzapine, as well as benzodiazepines to manage acute agitation and anxiety.[20] Psychosocial interventions, including psychoeducation, cognitive-behavioral therapy, and family support, play a key role in recovery and rehabilitation.[20] Close monitoring of clinical responses, side effects, and the risk of relapse is important to optimize outcomes and prevent recurrence.[19,20]

OP poisoning and atropine-induced psychosis present complex clinical challenges, especially in elderly patients with comorbidities. Effective management requires a multidisciplinary approach, integrating expertise in toxicology, pharmacotherapy, psychiatry, and geriatric medicine to address the various complications associated with OP exposure and anticholinergic therapy. By promoting early recognition and implementing evidence-based interventions, healthcare providers can improve outcomes for elderly individuals at risk of OP poisoning and atropine-induced psychosis. Continued research and collaboration are needed to better understand the pathophysiology, risk factors, and treatment strategies of these conditions, ultimately improving care for vulnerable populations.

We present a case report illustrating atropine-induced psychosis during the treatment of OP intoxication. Through this report, we aim to elucidate the clinical presentation, diagnostic approach, management strategies, and outcomes of this rare adverse drug reaction, emphasizing the importance of vigilance in monitoring and managing complications associated with atropine therapy in OP poisoning.

2. Case presentation

A 45-year-old male presented to the General Medicine unit of OHRC, Hyderabad, India after ingesting 250 – 500 mL of phenthoate insecticide at his residence. He was initially treated at a local hospital, where atropinization and gastric lavage were performed. The details of the patient are summarized in Table 1.

Upon transfer to a tertiary care facility, a repeat gastric lavage was performed, and the patient received 1 g of pralidoxime (PAM) along with an atropine infusion at 30 mL/h. Hit treatment regimen also included ceftriaxone (1 g IV *Bis die* [BD]), thiamine (100 mg IV BD),

pantoprazole (40 mg IV BD), ondansetron (4 mg IV BD), a multivitamin (1 amp IV *Omni die*), sucralfate (10 mL oral *Ter in die*), and haloperidol (5 mg IM) (Table 2).

Table 1. Case details

Category	Details
Patient information	45-year-old male
Presentation	Ingestion of 250 – 500 mL phenthoate insecticide
Initial treatment (local)	Atropinization and gastric lavage
Treatment on transfer	Repeat gastric lavage, 1 g pralidoxime, atropine infusion (30 mL/h)
Medications	As per the treatment chart (Table 2)
Clinical monitoring	Drug interactions and adverse reactions monitored by clinical pharmacists
Key drug interactions	• Pralidoxime enhancing atropine effects • Additive anticholinergic effects with antipsychotics
Patient counseling	Focused on: • Medication adherence • Lifestyle modifications (stress management, fasting, physical activity, social engagement, meditation)
Special considerations	• Administer atropine before pralidoxime for muscarinic symptoms • Use benzodiazepines for seizure management
Trauma protocols	Airway management emphasized
Atropine-induced psychosis management	• Discontinue atropine • Consider alternative muscarinic agents (physostigmine, glycopyrrolate, scopolamine) • Use haloperidol and benzodiazepines for symptom control
Anticholinergic selection	Tailored based on receptor targeting

Clinical pharmacists closely monitored the patient for potential drug interactions and adverse reactions, paying particular attention to the enhancement of atropine's effects by PAM and the additive anticholinergic effects when combined with antipsychotics. Patient counseling focused on medication adherence and lifestyle modifications, emphasizing stress management, fasting, physical activity, social engagement, and meditation.

Administering atropine before PAM was highlighted to mitigate muscarinic-mediated symptoms, and benzodiazepines were recommended for seizure management. Trauma protocols, particularly those emphasizing airway integrity, were followed, and anticholinergic selection was tailored based on receptor targeting. Management of atropine-induced psychosis involved discontinuing atropine and considering alternative muscarinic agents, such as physostigmine, glycopyrrolate, or scopolamine. Antipsychotics, such as haloperidol and benzodiazepines were also recommended for symptom control.

3. Discussion

Atropine-induced psychosis is a rare but clinically significant adverse effect observed in the management of OP poisoning. While atropine is a cornerstone treatment for OP toxicity due to its potent anticholinergic properties, its use, particularly at high doses, can lead to adverse reactions, including psychosis. This discussion delves into recent case studies, management strategies, and adverse drug reactions associated with atropine-induced psychosis. Recent case studies have highlighted the occurrence and management of atropine-induced psychosis. For instance, a study of 292 cases of phenthoate (the World Health Organization Class II OP insecticide) self-poisoning reported less severe

Table 2. Treatment chart

Medication	Dose	Route	Frequency	Indication	Special Notes
Atropine	Infusion at 30 mL/h	IV Infusion	Continuous	Management of muscarinic symptoms	Administered before pralidoxime to mitigate muscarinic effects
Pralidoxime	1 g	IV	BD	Antidote for organophosphate poisoning	Enhances the effect of atropine; repeat dosing at BD intervals
Ceftriaxone	1 g	IV	BD	Prophylaxis for potential infections	Broad-spectrum antibiotic
Thiamine	100 mg	IV	BD	Nutritional support	Prevents Wernicke's encephalopathy
Pantoprazole	40 mg	IV	BD	Gastric protection	Proton pump inhibitor
Ondansetron	4 mg	IV	BD	Nausea and vomiting control	Antiemetic
Multivitamin	1 amp	IV	OD	Nutritional support	Single daily dose
Sucralfate	10 mL	Oral	TID	Gastric mucosal protection	Protects against gastric irritation from ingested substances
Haloperidol	5 mg	IM	As needed	Management of atropine-induced psychosis	Antipsychotic; used for symptom control

Notes: amp: Ampoule; BD: *Bis die* (twice daily); OD: *Omni die* (once daily); IM: Intramuscular administration; IV: Intravenous administration; TID: *Ter in die* (3 times a day).

poisoning compared to other OP insecticides, with a case fatality rate of 6.5%.[1] Notably, while most patients presented fully alert, a minority exhibited impaired consciousness.[1] This variability in clinical presentation underscores the need for individualized treatment approaches based on the severity of poisoning.

Atropine's potent pharmacological effects make it widely used in the management of OP poisoning. However, adverse effects, including psychosis, can occur, necessitating prompt recognition and intervention. The diagnosis of atropine-induced psychosis aligns with the DSM-IV-TR criteria, with patients often meeting at least three of the four criteria for drug-induced psychosis.[2] Management strategies involve discontinuing the causative agent, adjusting the dose, and providing symptomatic treatment.

In cases of atropine-induced psychosis, discontinuation of atropine and substitution with alternative muscarinic agents such as physostigmine, glycopyrrolate, or scopolamine have been effective in alleviating psychotic symptoms.[3] In addition, antipsychotics, such as haloperidol and benzodiazepines, such as diazepam or lorazepam, are viable treatment options.[3] It is crucial to note that adverse drug reactions can occur with atropine therapy, particularly when administered intravenously, emphasizing the importance of vigilant dose management and early cessation of the offending drug to prevent further complications.[4]

Recent advancements in understanding atropine-induced psychosis have elucidated its pathophysiological mechanisms and pre-disposing factors. Hypotheses regarding the underlying mechanisms include disruption of central cholinergic neurotransmission, altered dopaminergic signaling, and modulation of glutamatergic and GABAergic pathways.[5] Pre-disposing factors such as advanced age, pre-existing psychiatric disorders, substance abuse, polypharmacy, and underlying medical comorbidities increase susceptibility to atropine-induced psychosis.[4] Moreover, the concomitant use of other medications with anticholinergic properties, such as antipsychotics, antidepressants, antihistamines, and antiparkinsonian agents, may potentiate the risk of psychosis.[6] Close monitoring and comprehensive clinical assessment are essential for accurate diagnosis and timely intervention.

4. Conclusion

Atropine-induced psychosis remains a rare but potentially serious complication in the management of OP poisoning. Recent case studies provide insights into its occurrence and management strategies, emphasizing the need for vigilant monitoring and individualized treatment approaches. Understanding adverse drug reactions, pathophysiological mechanisms, and pre-disposing factors are critical in managing this complex clinical condition. Continued research efforts are warranted to further elucidate its underlying mechanisms and optimize treatment outcomes, ultimately improving patient care and safety.

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Author contributions

Conceptualization: All authors
Formal analysis: All authors
Investigation: All authors
Writing-original draft: All authors
Writing-review and editing: All authors

Ethics approval and consent to participate

This case report is exempt from institutional review. Per our institutional guidelines, case reports of three or fewer patients do not require institutional review board approval. Verbal consent was obtained from the patient.

Consent for publication

Verbal consent to publish his data was obtained from the patient.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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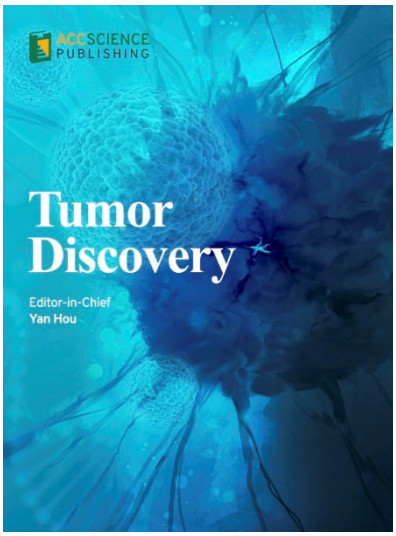
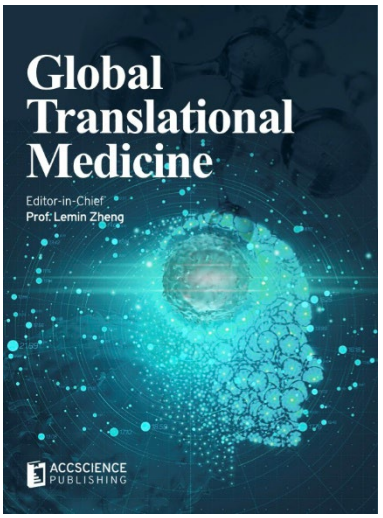


Tumor Discovery is a peer-reviewed and open-access journal that aims to present new cancer research with strong emphasis on fundamental and translational studies. *Tumor Discovery* covers topics, including but not limited to the following:

- Etiology and pathogenesis of cancer
- Mechanisms and molecular pathways underlying cancer initiation and progression
- Tumor metastasis
- Tumor evolution and heterogeneity
- Tumor microenvironment and tumor-host interactions
- Cancer genetics and genomics
- Cancer characterization using omics approaches
- Discovery and validation of cancer biomarker
- Discovery of new therapeutic targets
- New approaches of diagnostic and treatment modalities
- Statistical methods in cancer research

Global Translational Medicine is a quarterly journal that focuses on medicine, biological sciences, and biomaterials engineering. The goal of *Global Translational Medicine* is to provide a platform to researchers for showcasing their latest research works in translational medicine so as to advance the field towards the betterment of human health. Despite the advancement of omics and new technologies, the process of transforming these technologies and scientific research results into effective therapies and putting them into clinical use still has a long way to go. *Global Translational Medicine* provides a platform to fill the gaps in preclinical and inter-disciplinary research, to promote clinical translation of scientific research results, and to contribute to the conception of new and improved preventive measures as well as diagnostic and therapeutic techniques of diseases.

Global Translational Medicine covers the following themes: cardiovascular disease, metabolism/diabetes/obesity, neuroscience/neurology, cancer, biomaterials and their applications in medicine, proteomics/metabolomics, pharmacogenomics, biomarkers, bioinformatics and data mining, animal and clinical research, and medical methods arising from interdisciplinary crossover.



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