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A PHARMACIST-LED PARADIGM FOR WERNICKE-KORSAKOFF SYNDROME: IMPROVING PREVENTION, DETECTION AND PATIENT ADVOCACY

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ABSTRACT

Wernicke Korsakoff Syndrome (WKS), a crippling neurological disorder brought on by a deficiency of thiamine (vitamin B1), frequently results in irreversible brain damage because it is frequently overlooked in its early stages. This review article advocates for a fundamental shift away from reactive treatment to an innovative, pharmacist-centered strategy emphasizing patient support, early detection and prevention. Pharmacists can play a crucial role because of their accessibility and frequent interaction with high-risk groups (such as patients with chronic alcohol consumption, poor nutrition or post bariatric surgery status). By identifying susceptible people and recommending preventative thiamine supplementation, pharmacists can spearhead prophylactic initiatives, according to the proposed model. The study also looks at the pharmacist's ability to quickly identify warning signs during patient consultations, which can lead to an urgent medical evaluation. Finally, it outlines the pharmacist's role as an essential patient advocate who verifies proper thiamine protocols, promotes medication compliance and collaborates with other medical specialists to enhance patients' long-term health. Adopting this pharmacist-driven framework represents a major advancement for patient wellness, community health by providing a potent method to reduce the frequency and severity of WKS.

KEYWORDS: Pharmacist-Led Care, Thiamine Deficiency Management, WKS Prevention, Early Symptom Recognition, Clinical Advocacy, Neurological Health, Community Pharmacy, Patient Safety.

INTRODUCTION

Wernicke-Korsakoff syndrome (WKS) is one of the most tragic but preventable neuropsychiatric conditions that physicians deal with, it is critical that healthcare professionals—pharmacists in particular—change the way that patient advocacy, detection and prevention are currently practiced. This illness, which is typically brought on by a severe thiamine (vitamin B1) deficiency, is a prime example of the terrible outcomes of wasted healthcare opportunities because early intervention could have saved many lives from irreversible cognitive and functional disability.[1] WKS is made up of two interrelated clinical entities: the chronic, irreversible Korsakoff syndrome and the acute, potentially fatal Wernicke encephalopathy. Even though they are often thought of as separate stages, they are both caused by the same thing: a lack of thiamine. Persistent alcohol abuse is the predominant cause of the syndrome; however, other factors such as, It can also happen because of malnutrition, eating disorders, constant vomiting or diseases that make it hard for the body to absorb nutrients.[2] Acute confusion, ataxia and ophthalmoplegia are symptoms of the first stage of Wernicke encephalopathy, which is a medical emergency. In the event that the acute symptoms are not identified and treated with high-dose thiamine, which is frequently given intravenously, Korsakoff syndrome may develop unavoidably. Often accompanied by significant functional deterioration, this phase is marked by acute memory impairment, confabulation and a startling inability to acquire new memories.[3]

WKS is particularly unfortunate because the irreparable consequences may usually be prevented with prompt identification and action. Unfortunately, many people go undiagnosed until irreversible cognitive damage has already occurred due to widespread underdiagnosis, especially in non-alcoholic populations.[4] According to data, only about 20–25% of patients who have Wernicke encephalopathy progress to Korsakoff syndrome reach full cognitive recovery; the remaining patients suffer from varied degrees of lifelong disability, and up to 25% of them die from disorder-related complications. Individuals, families, and healthcare systems are all burdened by the frequent need for long-term care and supervision. Delays in intervention often result in memory and learning deficiencies that cause many survivors to become chronically dependent on institutional care, even with rigorous therapy.[5]

WKS so great is its ability to stop things from happening. In therapeutic contexts, the fundamental cause, thiamine deficiency, can be discerned and easily rectified. Early, strong thiamine therapy can both fix Wernicke encephalopathy and stop it from getting worse. Many studies and clinical reviews say that Korsakoff syndrome can be treated, but only if it is given before neurological damage becomes permanent. Healthcare workers need to be well-trained, screened, watchful, especially when they are working with people who are at risk, such as those who are alcoholics, malnourished and have long-term conditions that make it hard for them to absorb nutrients.[6] When it comes to managing and stopping WKS, pharmacists are in a unique position to lead a change in thinking. Pharmacists are very helpful in promoting thiamine supplementation, making early detection protocols, telling patients, professionals about the dangers of thiamine deficiency because they are experts in medications, work with high-risk patients and their caregivers all the time. Not enough thiamine. The incidence of WKS could be markedly reduced by systematically integrating thiamine therapy into protocols for at-risk populations, including all patients presenting to the emergency room with malnutrition or altered mental status.[7]

The effects of not taking steps to prevent problems affect families and society as a whole, not just the person. When someone goes from having a treatable deficit to a permanent, debilitating cognitive disorder, they lose their independence and sense of self. This is a tragedy that could have been avoided. In today's healthcare system, it should

be easy to find information and resources to help prevent WKS.[8] These results are especially unfair because of this. So, it's clear that we need more pharmacists and other medical professionals. Being more careful, looking for problems early, acting quickly are not only clinical duties, but they are also the moral foundation of patient advocacy in WKS. With pharmacists at the forefront of coordinated, multidisciplinary efforts to promote prevention, ensure early detection, support patients, their families across the care continuum, significant change in the incidence and outcomes of Wernicke-Korsakoff syndrome will need to be achieved.[2]

Pathophysiology

A severe thiamine (vitamin B1) shortage is the cause of Wernicke-Korsakoff syndrome, a two- stage brain disease. In summary, the absence of thiamine causes a number of vital enzymes to malfunction, the brain cannot produce enough ATP, neurons and glia experience oxidative stress and energy failure, neurotransmitter systems become unbalanced and specific brain regions (mammillary bodies, thalamus, midbrain, cerebellar vermis) are harmed. If left untreated, this injury results in the acute Wernicke encephalopathy (confusion, nystagmus/ophthalmoplegia, ataxia) and the chronic Korsakoff amnestic syndrome (severe anterograde memory loss and confabulation).[9]

1. Biochemical base: the function of thiamine.

The active form of thiamine, thiamine diphosphate (ThDP), is a necessary cofactor for a number of enzymes that are critical to the metabolism of brain energy:

- By changing pyruvate into acetyl-CoA, pyruvate dehydrogenase (PDH) connects glycolysis to the Krebs cycle.
- α-Ketoglutarate dehydrogenase (α-KGDH), an enzyme essential to the Krebs cycle that maintains cycle flow and generates NADH.
- Transketolase, a component of the pentose phosphate pathway (PPP), is essential for the synthesis of nucleotides and NADPH.

Lack of ThDP causes these enzymes to slow down or stop working, which lowers the amount of ATP and NADH produced in mitochondria and affects the PPP's ability to produce the NADPH required to detoxify reactive oxygen species (ROS). Increased oxidative damage and an energy crisis are the outcomes.[10]

2. Lack of ATP leads to selective susceptibility.

The brain is very dependent on the constant production of ATP. Mammillary bodies, medial thalami, periaqueductal gray, cerebellar vermis, portions of the hippocampus circuit are among the areas with high metabolic demand and restricted thiamine transport where energy failure initially manifests. Reduced PDH, α-KGDH activity causes lactate, pyruvate buildup, mitochondrial malfunction, ionic pump failure (Na+/K+ ATPase), cell swelling and eventually neuronal death in these zones. The impact on memory circuitry and oculomotor/coordination centers can be explained by this selective damage.[11]

3. Disruptions in neurotransmitters

Thiamine deficiency affects neurotransmitter synthesis, release and reuptake in several interrelated ways:

- **Acetylcholine:** Production of acetylcholine is decreased when PDH is compromised as Acetyl-CoA availability and choline acetyltransferase activity decline. Depletion of the cholinergic system, which is necessary for memory encoding and attention, contributes to the amnestic features of Korsakoff syndrome.[12]

- **Glutamate and GABA balance:** Extracellular glutamate accumulates when astrocytes, which require ATP, are unable to reabsorb glutamate due to energy failure. Excitotoxicity, calcium overload and cell death result from the activation of NMDA receptors by excess glutamate. Reduced or dysregulated GABAergic inhibitory tone can exacerbate network instability and disorientation.[13]
- **Monoamines and others:** Through altered metabolic flux and oxidative stress, thiamine deficiencies also indirectly impact the synthesis, metabolism of dopamine and serotonin, which contributes to mood and motivational symptoms observed in chronic instances.[14]

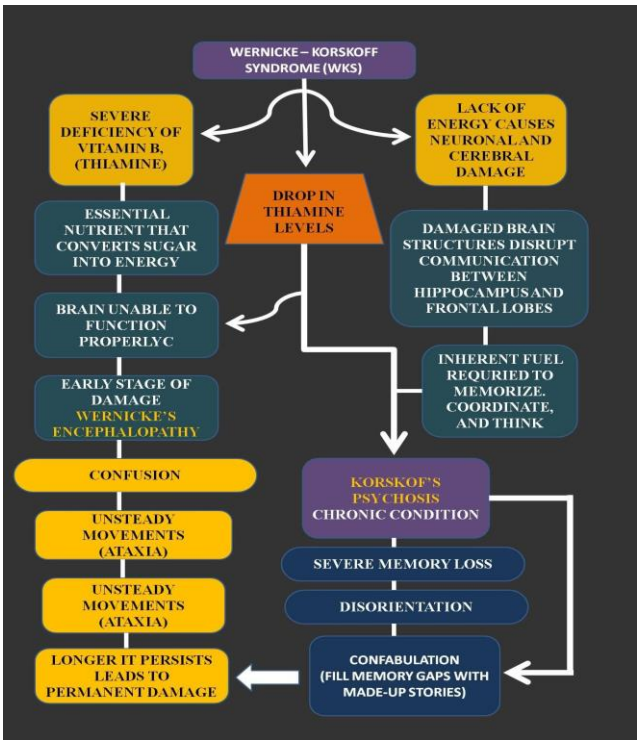
Together, these neurotransmitter alterations account for both the chronic severe memory impairment (hippocampal–mammillary–thalamic circuit breakdown), the acute confusion and eye movement symptoms (brainstem/diencephalic dysfunction).[15]

4. Oxidative stress, secondary damage and inflammation

Low transketolase activity, or a failed PPP, impairs glutathione recycling, lowers NADPH and which increases oxidative stress. Neuronal damage is exacerbated by oxidative damage, blood–brain barrier disturbance and microglial activation. Chronic alcohol consumption, which is prevalent in WKS, exacerbates damage by having direct neurotoxic effects and reducing thiamine absorption.[16]

5. Korsakoff to Wernicke

Many alterations are reversible if thiamine is administered quickly; symptoms can improve and ATP production returns. Neuronal cell loss and gliosis in memory circuits, particularly mammillary body atrophy, damage to the anterior thalamic nuclei and mammillothalamic tract, become permanent if insufficiency continues, resulting in the irreversible amnesia and confabulation typical of Korsakoff syndrome. These localized losses are correlated with the clinical picture by neuropathology and neuroimaging.[17]



Under-Recognized Non-Alcoholic Causes of Wernicke-Korsakoff Syndrome

Outside of the setting of alcoholism, thiamine deficiency is a disorder that is still very poorly understood. When ignored in a variety of medical situations, including bariatric surgery, chronic vomiting, several cancer therapies, it can have major negative effects on one's health.[18]

Thiamine Deficiency and Bariatric Surgery

The risk of thiamine deficiency is greatly increased by bariatric surgery, a common operation used to reduce weight in obese patients. This happens because gastrointestinal tract surgery decreases the absorption of thiamine, particularly in patients who have low nutritional intake or postoperative vomiting. Other risk factors include rapid surgical weight loss (more than 7 kg per month) and insufficient food supplements. Clinical symptoms may show up weeks after surgery, but they may potentially take years to materialize. Patients typically have prolonged nausea, vomiting, appetite loss in the beginning of their symptoms, which are often overlooked or mistakenly assigned to other reasons in routine practice. These symptoms can develop into serious neurological issues like Wernicke's encephalopathy (WE), ultimately, irreparable damage like Korsakoff's syndrome if prompt prophylactic thiamine supplementation is not taken.[19]

All candidates for bariatric surgery should take preoperative and preventive vitamin supplements, according to guidelines, since oral thiamine supplements might not be sufficiently absorbed after surgery, requiring parenteral delivery if a shortfall is anticipated. Even after restrictive surgeries like sleeve gastrectomy, cases have been documented where rapid post- surgical weight loss and vomiting directly resulted in neurologic symptoms and dry beriberi.[20]

The Underappreciated Cause of Vomiting

Persistent vomiting is a well-known but frequently overlooked cause of thiamine shortage, regardless of whether it is brought on by gastrointestinal disorders, drug side effects or surgical consequences. Vomiting causes the body to lose thiamine and other nutrients, thereby exhausting its reserves especially since thiamine is not stored in large quantities. Increased metabolic demands during the recovery phase following surgery or during systemic sickness exacerbate this depletion. Weakness, ataxia, neuropsychiatric symptoms and gastrointestinal issues can all be indicators of a thiamine deficiency. Diagnosing and treating the underlying illness can be more challenging when these symptoms coexist with its complications.[21]

Thiamine Deficiency and Cancer Treatments

The risk of thiamine deficiency is significantly increased by malignancies, especially those of the gastrointestinal tract, cancer treatments such as chemotherapy, radiation and major surgery. A number of variables put these patients at risk:

- Reduced oral consumption (caused by mucositis, nausea, vomiting, anorexia).
- Malabsorption due to treatment-induced gastrointestinal injury or direct tumor effects.
- Thiamine consumption is accelerated under hypermetabolic conditions such fever, systemic infection and fast cell turnover brought on by cancer.[22]

The need for caution is highlighted by the fact that cancer patients may have the deficit even if they are overweight and have normal levels of other B vitamins. Thiamine must be included in vitamin supplementation programs for hospitalized cancer patients, particularly if they are fasting, vomiting or receiving parenteral nourishment that is not

sufficiently fortified with vitamins.[23]

Additional Non-Alcoholic Reasons

Other situations that lead to underdiagnosed thiamine deficiency include:

- Excessive thiamine loss in the urine is a result of long-term diuretic therapy for heart and kidney disorders.[24]
- In patients receiving whole parenteral nutrition, supplements may be inappropriate or absent.[25]
- High fever, senior age, prolonged critical illness all raise the need for thiamine, which frequently surpasses what can be obtained from diet or supplements.[26]

Difficulties with Recognition

Non-alcoholic forms of thiamine insufficiency are underdiagnosed in clinical practice due to a number of factors:

- The symptoms can be easily linked to other causes, are non-specific and overlap with underlying diseases or surgical outcomes.
- Particularly when patients have normal weight or other vitamin levels, laboratory diagnosis is not frequently carried out.
- Provider awareness varies and many doctors still believe that alcohol abuse is the main cause of thiamine shortage.[27]

Management and Prevention

- Every patient undergoing cancer treatment, having gastrointestinal surgery, experiencing chronic vomiting should have a routine risk evaluation for thiamine deficiency.[28]
- If a deficiency is suspected, early and aggressive supplementation is recommended, ideally by parenteral administration in high-risk populations.[29]
- Patients who have had bariatric surgery should take a daily multivitamin supplement, patients, medical professionals should be informed about the warning signals and dangers of vitamin deficiencies.[30]

Pharmacology of Thiamine

Thiamine, often known as vitamin B_2, is a necessary water-soluble vitamin that mainly serves as a coenzyme for important metabolic enzymes such transketolase, α-ketoglutarate dehydrogenase and pyruvate dehydrogenase (in the form of thiamine pyrophosphate, TPP). The pharmacology of thiamine includes its chemical compositions, absorption, systemic distribution, transport into the brain and behavior under high-dose administration. Since humans are unable to synthesize thiamine, it must be acquired through diet.

1. Formulation of Thiamine

Thiamine hydrochloride is a freely soluble salt that is most frequently used in clinical and dietary applications. To improve bioavailability, lipid-soluble compounds have been created. Benfotiamine, an S-acyl thiamine precursor and disulfide derivatives like prosultiamine (thiamine propyl disulfide) are notable examples. In the gut, benfotiamine is dephosphorylated to more lipophilic S-benzoylthiamine, which enters the bloodstream, is primarily transformed back into free thiamine in the liver and erythrocytes by thioesterases.[31] Because free thiamine transport into the brain is rate-limited, benfotiamine effectively increases blood and liver thiamine levels in animal models but exhibits minimal rise in brain thiamine.[32] Similar to this, prosultiamine was created to overcome reliance on active intestinal transporters due to its exceptional lipid solubility.[33]

2. Absorption in the Gut

The proximal small intestine (upper jejunum) is where oral thiamine absorption mostly takes place. There are two mechanisms at work: a saturable, carrier-mediated active transport occurs at low (physiological) doses, while passive diffusion becomes more significant at increasing concentrations. Two high-affinity transporters, Thiamine Transporter-1 (THTR-1), encoded by SLC19A2, THTR-2, encoded by SLC19A3, mediate the carrier-mediated component.[34]

Thiamine absorption is saturable with a K_m of roughly 0.6 µM, strongly pH-dependent (driven by the proton gradient), competitively blocked by analogues like amprolium, according to studies conducted on human jejunal brush-border membrane vesicles (BBMVs).[35]

3. Systemic Distribution and Excretion

The average total body burden of thiamine for the general population is estimated at approximately 25mg-30mg. The physiological half-life of thiamine in the body is 9-18 days after ingestion. After absorption into body tissues, thiamine is distributed fairly uniformly throughout the body but it does not accumulate in significant amounts (i.e., large pools).[36] The brain, skeletal muscle, liver, kidneys and heart are the most common locations for distribution of a substance.[34] Thiamine is mainly excreted by the kidneys. THTR-1, THTR-2 (potentially other transporters such as OCTs) filter thiamine in renal glomeruli and reabsorb thiamine in the proximal tubule. As plasma thiamine levels rise, the kidneys transition from reabsorbing thiamine to actively excreting it (e.g. through OCTs and MATE proteins), resulting in improved clearance of thiamine from the body via renal excretion.[37]

4. Transport Across the Blood-Brain Barrier (BBB)

The brain has a constant and essential need for thiamine because neural tissue depends on TPP- dependent enzymes for energy consumption. Transport across the BBB is strictly controlled though BBB transport is carrier-mediated and saturable, with incomplete saturation even at high plasma levels, according to early animal research (rats) utilizing tracer thiamine. A two- component model with a high-affinity saturable transporter and a non-saturable (passive diffusion) component is suggested by kinetic analyses.[38] Additional research utilizing perfused rat brains revealed both substantial thiamine efflux and influx, suggesting a dynamic equilibrium at the BBB. It's interesting to note that efflux rates rise as vascular thiamine concentration rises, suggesting that the brain tends to strictly control intracellular thiamine levels.[39] At the BBB, thiamine monophosphate (ThMP) is also transported. Saturable transport with a J_{max} of ~27–39 $pmol \cdot g^{-1} \cdot min^{-1}$ and a K_m of ~2.6–4.8 µM is reported in in vivo rat investigations utilizing radiolabeled ThMP; nevertheless, affinity appears to be lower and capacity weaker than for free thiamine.[40] Thiamine (Vitamin B1) is transported into the cells—most notably, into brain endothelial cells of the blood-brain barrier (BBB) by two different types of molecular transporters, known as solute carrier (SLC) transporters, specifically SLC19A2 (ThTr1) and SLC19A3 (ThTr2).[41] Recent structural biology studies using advanced imaging, such as cryo- electron microscopy (EM), have also revealed the specific binding mechanisms for both thiamine (as well as other inhibitors) to their respective transporters, thereby providing insight into how some medications may inhibit the absorption of vitamins.[42] Notably, pathogenic mutations in SLC19A3 impede thiamine uptake, leading to neurodegenerative diseases (like ThTr2 deficiency) that react to high-dose thiamine therapy.[43]

5. High-Dose Pharmacokinetics

It is important to understand how the body processes high-dose thiamine (Vitamin B1) because of its importance in several clinical situations including Wernicke's Encephalopathy, heart failure and metabolic diseases. The first study of

high-dose thiamine pharmacokinetics was done in healthy people, looked at escalating amounts of thiamine (100mg, 500mg and 1,500mg of thiamine hydrochloride) given orally. In this study, both the total amount of time thiamine is in the body (area under the curve ($AUC_{0-10}h$)) and the maximum concentration of thiamine at any one time (C_max) increased disproportionately with increasing dosage. The greatest increase in both $AUC_{0-10}h$ and C_max occurred with the lowest dose reflecting saturation of the carrier- mediated absorption system. Once the dose ascended above this saturation point, thiamine absorption shifted to passive transport resulting in a more rapid rise in thiamine blood levels.[44] This research clearly demonstrates that orally administering high doses of thiamine results in high plasma thiamine levels, supports the understanding that thiamine is able to be absorbed through both saturable and non-saturable pathways.[45] In addition to thiamine pharmacokinetics research, the pharmacokinetics of high-dose benfotiamine have also been studied. When benfotiamine was compared with thiamine hydrochloride, researchers found that using the two forms of thiamine in male, female participants who were healthy both as single doses, multiple dosages, showed benefits in the amount of thiamine available for the body and as a result the phosphorylated form of thiamine (TMP and TDP). According to the pharmacokinetic profile of benfotiamine, when fixed oral doses of benfotiamine were given to healthy participants, the amount of thiamine measured in the blood was over 1000% greater following benfotiamine than that measured following thiamine HCl. This indicates that although the amount of thiamine circulating in the body following benfotiamine is very high, this form of thiamine is not readily being transported into the brain.[46] This finding also corresponds with previous animal studies showing that benfotiamine has been shown to raise peripheral stores of thiamine, but not cerebral stores of thiamine.[47]

Current Treatment Guidelines: Gaps & Controversies (UK, US, India, WHO)

Clinical guidelines are critical to enhancing patient outcome and standardising clinical practice. While national organisations in the US, India, the UK adjust these recommendations for local context, international organisations, such as the World Health Organization (WHO), aim to provide evidence-based, globally applicable recommendations. However, because there are wide discrepancies across these three systems; there will inevitably be inconsistencies and disagreements about how to implement these recommendations in clinical practice.[48]

The WHO guidelines are designed primarily for low- and middle-income countries (LMIC), are intended to have international applicability, strong emphasis on accessibility, affordability and evidence-based medicine. However, in many instances, there are significant variations in national guidelines from WHO norms. For example, a global analysis of COVID-19 treatment guidelines showed that approximately 93% of national recommendations included an at least one treatment that could not be supported by WHO data, indicating significant differences in clinical decision-making.[49] These differences can often be attributed to differences in health system infrastructure, financial constraints or urgency of public health emergencies.

In the UK, NICE is responsible for developing guidelines on how to treat patients. They use a strict, open and measurable process for doing so. The guidelines are developed based on WHO recommendations and there is a general trend to follow these guidelines. NICE values high quality and cost-effectiveness in the studies that base their guidelines. For example, UK guidelines are cautious and use evidence to guide their treatment recommendations, with the minimum amount of medications prescribed to treat borderline personality disorder.[50] Even though using high-quality evidence reduces the difference between the studies that support UK guidelines and the use of those guidelines, this level of evidence can limit the possible scope of flexibility in clinical practice.

A decentralized approach to the development of US clinical guidelines has been taken by the National Institutes of Health (NIH) as well as the Centers for Disease Control, Prevention (CDC), specific medical specialties and many other groups. With this structure of distributed government, it is much easier to add and change guidelines as new information becomes available; however, because of the wide range of groups who develop their own independent guidelines there are many inconsistencies and thus define what is "correct" treatment. For example, the US and UK have markedly different protocols on the prescription of antibiotics. UK has much more stringent guidelines related to the prescribing of penicillin with a preference of using narrow-spectrum penicillins while the US guidelines promote the use of broad-spectrum antibiotics including cephalosporins and fluoroquinolones.[51] Consequently this variability in the prescribing of broad-spectrum antibiotics in the US as compared to other countries may contribute to the variability in the patterns of antimicrobial resistance.

Numerous groups create STGs (Standard Treatment Guidelines) for health systems in India, including the National Health Systems Resource Center (NHSRC) and the Indian Council of Medical Research (ICMR). Without an independent central authority to approve or endorse STGs, however, the result has been fragmentation and inconsistency across the country. One comprehensive review of Indian STG documentation found that a large number of guidelines are missing critical components such as detailed prescribing information, clearly defined diagnostic criteria and regular revision cycles.[52] Some of the guidelines evaluated in this review had a limited amount of evidence to support their recommendation, but NONE had an established schedule for revision. The missing elements contribute to a lack of clinician confidence that hinders their ability to use the guidelines consistently.

Adapting International standards to local conditions creates several problems in India. Impediments to the adaptation of norms include insufficient resources, inability to find adequate training for healthcare personnel and finding agreement (or consensus) for implementation among stakeholders.[53] Greater variability is compounded by the inconsistencies between WHO recommendations being applied throughout India, despite WHO's encouragement for these recommendations to be adapted; more variable clinical practices may result from a decentralized approach (i.e., India) when compared with a highly centralized approach (i.e., United Kingdom/NICE).

One of the major concerns is the balance between evidence-based advice and application. WHO and NICE give great weight to high-quality evidence; however, doctors in such situations of scarce resources might use methods that differ from these recommendations. For example, due to the need of the hour and scarce alternatives in the COVID-19 pandemic, some countries adopted treatments that had little to no evidence.[54] This is an example of the conflict between need and scientific evidence.

Guideline adherence is another contentious issue. Compliance varies greatly, even in cases where there are explicit guidelines. Implementation issues are not exclusive to developing nations, as evidenced by a comparison study on surgical antiseptic techniques that revealed worse adherence to WHO guidelines in the UK compared to India.[55]

Clinician preference, institutional regulations and resource availability are some of the factors that affect adherence.
The parameters for treatment also differ due to economic reasons. While the parameters may include costly and sophisticated treatments that may not be feasible in LMICs, the WHO and Indian guidelines may recommend cost-effective treatments that can be adopted for a large number of people. Hence, differences in healthcare outcomes and access. Moreover, various governmental guidelines, especially from high-income nations, have been attributed to

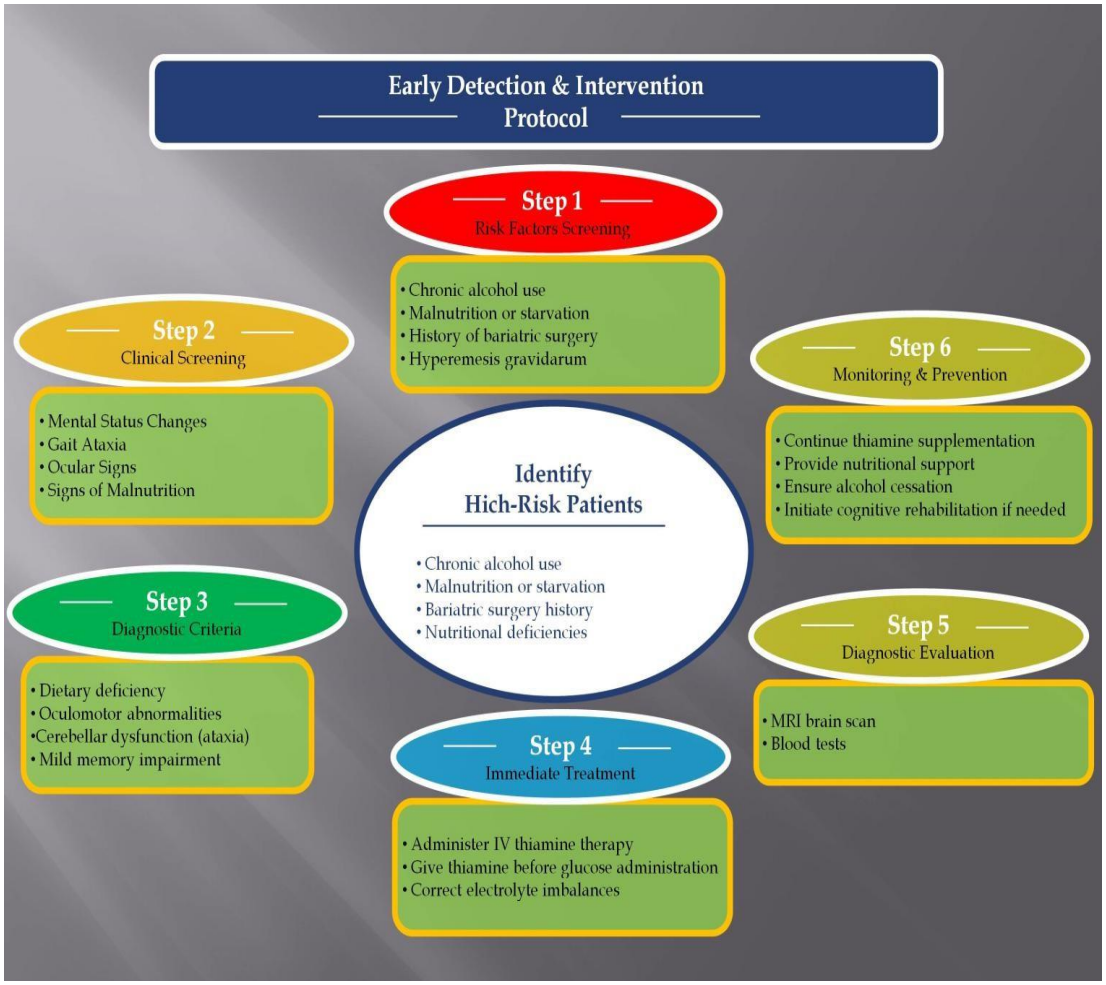
the influence of the pharmaceutical industry.[56]

In all, a large number of differences and disagreements can be seen between the WHO, UK, US, Indian guidelines for the treatment of the disease, which include a lack of consistency, unequal application of the evidence, poor execution and unequal access to resources. Even though the WHO has a framework for the entire world, the country-specific changes lead to variations in the guidelines. While the US model offers freedom at the expense of consistency, the UK model points to the advantages of a centralized approach to the creation of guidelines based on evidence. Systemic limitations are a problem in the country.[57]

Protocol for Early Detection

A deficiency in thiamine (vitamin B1) produces Wernicke-Korsakoff syndrome (WKS), a neuropsychiatric disorder composed of both acute Wernicke's Encephalopathy (WE) and chronic Korsakoff Syndrome (KS). While KS can lead to permanent cognitive dysfunction with delayed diagnosis, identification of WE is crucial as the condition (WE) is reversible / curable.[58,59] Sadly, 80%+ of patients who are diagnosed with WKS have no treatment. Therefore, it is imperative to require comprehensive screening protocols.[60]

Clinical suspicion is vital in this case because only a small percentage of patients display the usual triad of symptoms, which include confusion, ophthalmoplegia, and ataxia. It is therefore important to have a system for early detection that includes screening.



Protocol Components

1. Risk-Based Screening

The first step in early detection is identifying those who are at high risk. Although non-alcoholic reasons like starvation and bariatric surgery are becoming more widely acknowledged, chronic alcohol use is still the most common cause.[62] Research highlights the need for therapeutic monitoring to go beyond situations involving alcohol.[63]

2. Low-Threshold Clinical Suspicion

Experts advise a "low threshold" approach, where even one symptom should raise suspicions due to the classical triad's weak sensitivity.[64] The first symptom is frequently mental disorientation, which is followed by anomalies in movement and vision.[61]

3. Use of Caine Criteria

When compared to the traditional triad, the Caine criteria greatly increase diagnostic sensitivity. In clinical practice, the presence of two or more criteria improves diagnostic accuracy and is often advised.[59,65]

4. Immediate Empirical Thiamine Therapy

"Treat first, confirm later" is a fundamental tenet of early detection procedures. Treatment delays may result in permanent damage to neurons. Since oral absorption may be compromised, high- dose intravenous thiamine is the standard.[64]

In addition:

- To avoid a deepening shortage, thiamine must be administered before glucose.
- Multivitamin supplementation is frequently necessary.

5. Diagnostic Evaluation

Supportive testing for WKS include the following, even though it is essentially a clinical diagnosis:

- MRI: displaying symmetrical lesions in the thalamus and mammillary bodies
- Laboratory testing may aid in diagnosis but have a low sensitivity.
- Neuropsychological testing: helpful in identifying cognitive impairment in its early stages However, treatment shouldn't be postponed due to reliance on imaging.[62]

6. Monitoring and Long-Term Management

Patients who receive treatment early may see a quick improvement in their confusion and ocular symptoms, but if treatment is postponed, memory impairments frequently continue.[64] Chronic forgetfulness and functional impairment are the outcomes of Korsakoff syndrome progression. Among the preventive tactics are:

- Nutritional assistance
- Giving up alcohol
- Preventive thiamine in groups at high risk

Important Gaps This Protocol Addresses

- Overcomes underdiagnosis through screening based on risk
- Uses an empirical treatment-first approach to reduce delay.

- Increases sensitivity by applying Caine criteria
- Combines interdisciplinary management.[66]

WKS is still an underdiagnosed yet avoidable illness. Early risk detection, low-threshold screening, prompt thiamine administration and organized follow-up are highlighted in the suggested flowchart. By putting such measures into place, morbidity can be greatly decreased and the development of irreversible Korsakoff syndrome can be stopped in emergency, primary care and hospital settings.[67]

Underdiagnosis and Lack of Reliable Early Diagnostic Markers in Wernicke–Korsakoff Syndrome

Due to the lack of accurate early diagnostic indicators and reliance on non-specific clinical symptoms, Wernicke–Korsakoff syndrome (WKS) continues to be one of the most underdiagnosed but avoidable neuropsychiatric illnesses. WKS includes both chronic Korsakoff syndrome and acute Wernicke's encephalopathy (WE), both of which are caused by a thiamine shortage. While delayed diagnosis results in irreparable neurological damage, early detection is crucial because WE is reversible with quick treatment.[68,69]

Underdiagnosis: An Enduring Clinical Problem

WKS is still not given due consideration in day-to-day life despite advancements in clinical management. Research carried out by conducting autopsies has shown time and again that a significant percentage of patients remain undiagnosed during their lifetime, indicating a major flaw in clinical diagnosis. Even though the incidence of WE in autopsy series varies between 0.4% and 2.8%, it is found to be much lower in clinical diagnosis methods.

The dependence on the traditional trinity of symptoms of confusion, ataxia, and ophthalmoplegia, which only affects a small percentage of patients, is also a significant contributor. Research has shown that only 10% to 20% of patients have all three characteristics that might lead to unusual presentations. In addition to that, co-existing conditions that include alcohol intoxication and withdrawal symptoms or other forms of metabolic encephalopathies make diagnosis more complicated.[72]

According to recent evaluations, WE often presents non-specific and unusual symptoms that can be easily overlooked in clinical settings. Such symptoms include delirium, apathy and slight cognitive impairment. Underdiagnosis and delay in intervention are mostly due to the diversity of WE presentations.

Limitations of Current Diagnostic Approaches

1. Clinical Diagnosis and Its Limitations

The clinical diagnosis of WKS remains largely in place, often employing standards like the Caine criteria. However, these have the disadvantage of being limited by the subjectivity of interpretation and the clinical knowledge employed, although the standards are more sensitive than the classical trio. This knowledge, however, may not be readily available in many healthcare facilities, especially in those with minimal resources.[74]

In addition, the early stages of the condition are difficult to diagnose due to the absence of pathognomonic clinical characteristics. As a result of this, doctors often fail to diagnose WE until the brain damage has occurred.[75]

2. Neuroimaging Limitations

Although magnetic resonance imaging (MRI) is frequently employed as a supplementary diagnostic technique, it is not very useful for early diagnosis. According to studies, MRI has a sensitivity of about 53%, meaning that over half of the instances could go unnoticed. Computed tomography (CT) is also inadequate for screening due to its much lower sensitivity (around 13%).

MRI has a high sensitivity (~93%), but its usefulness as a screening tool is limited by its incapacity to consistently identify early-stage illness. Crucially, normal MRI results do not rule out the diagnosis of WKS, which emphasizes the need for more advanced diagnostic techniques.[76]

Furthermore, although modern imaging methods like MR spectroscopy, functional MRI (fMRI) have demonstrated potential in research settings, their cost, availability and patient-related constraints make them unsuitable for normal clinical usage.[77]

3. Biochemical Markers: Current Gaps

The diagnosis of WKS is seriously impeded by the lack of reliable biochemical markers. Thiamine-dependent enzyme activity, for instance, and blood thiamine levels are used in research settings. However, they have a number of drawbacks.

- Standardized reference ranges are absent.
- There is little association with clinical severity.
- Limited accessibility in situations of emergency
- A delayed response time.[78]

The diagnosis is further complicated by the fact that normal thiamine levels do not rule out WKS.

Potential biomarkers such cerebrospinal fluid lactate, microglial activation markers and neurotransmitter metabolites have been investigated in recent research, although they are still in the experimental stage and have not been approved for use in clinical settings.

Emerging Biomarker Research: Future Directions

In an effort to get beyond the drawbacks of clinical diagnosis, recent research has focused on finding objective and early diagnostic biomarkers. Some of these are:

1. Neuroinflammatory and Metabolic Biomarkers

There is evidence that the pathophysiology of WKS involves both neuroinflammation and microglial activation. Potential early signs include biomarkers like CSF lactate levels and CD68- positive microglial cells.[79]

Moreover, metabolic alterations resulting from impaired thiamine-dependent pathways may offer opportunities for the development of biomarkers.[80]

2. Advanced Neuroimaging Biomarkers

Diffusion-weighted imaging, magnetic resonance spectroscopy and functional imaging are some of the advanced imaging techniques that can be used for the purpose. The imaging techniques can detect minor changes in the brain

before actual lesions appear. However, because of technical limitations, the usefulness of these techniques is still limited.

3. Blood-Based Biomarkers

The search for fast, accessible, and reliable blood-based biomarkers is gaining popularity. Among the potential candidates, the following can be listed:

- Metabolites of thiamine, like thiamine monophosphate, etc.
- Markers of oxidative stress
- Cytokines that cause inflammation

However, at the moment, there is no enough information to prove the diagnostic potential of the above-mentioned substances.[82]

Clinical Implications of Underdiagnosis

The implications of this underdiagnosis are severe. Consequences of undiagnosed or delayed diagnosis include:

- Development of irreversible Korsakoff syndrome from reversible WE
- Persistent memory loss and impairment
- A higher cost of healthcare

The importance of early detection is emphasized by the fact that thiamine treatment is capable of reversing the disorder and arresting further damage.[83]

Need for a Paradigm Shift in Diagnosis

A paradigm shift to a "biomarker-based diagnosis" is necessary because of the limitations of the present diagnostic techniques. For future research, emphasis should be placed on:

- Developing screening tools that are highly sensitive
- Validating biomarkers for imaging and biochemistry
- Incorporating multiple diagnostic techniques
- Routinely screening high-risk groups for WKS

These developments are likely to significantly improve clinical outcome and early diagnosis of WKS.[84]

Future of Wernicke–Korsakoff Syndrome (WKS) Management

Wernicke-Korsakoff syndrome (WKS), often associated with long periods of alcoholism and malnutrition, is still considered an important neuropsychiatric disorder caused by thiamine deficiency. Parenteral thiamine therapy is available; nevertheless, due to delayed diagnosis, absorption problems, as well as irreversible damage to neurons, the results remain suboptimal. Some of the promising innovations in diagnosis and treatment of WKS include artificial intelligence-based diagnostic tools, transdermal delivery methods, as well as nano-technology formulations.

1. Nano-formulations for Thiamine Delivery

One of the major disadvantages of conventional thiamine therapy is its low bioavailability and limited penetration into the blood-brain barrier. Overcoming these obstacles requires an advanced drug delivery system in the form of nano-

formulations. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, etc., are examples of such carriers that can improve the stability of drugs, increase their circulation time and target particular regions of the brain.

Nanotechnology-based thiamine delivery methods can offer sustained release of thiamine in sufficient intracellular concentrations in target regions of the brain. This is particularly significant because thiamine deficiency leads to neuronal damage and apoptosis, which is critical in cerebral energy metabolism and mitochondrial function.[85]

Additionally, nanoparticle- mediated delivery of thiamine can increase blood-brain barrier permeability by passive diffusion as well as receptor-mediated transport.

Based on recent advancements in nanomedicine in the context of neurodegenerative diseases, these approaches can potentially reduce oxidative stress, neuroinflammation, and neuronal loss— processes that are critical in WKS pathogenesis.[86] These approaches, by shifting focus from symptomatic treatment to neuroprotection using nano-technology-based formulations, still in their preclinical stages, hold great promise to revolutionize WKS treatment in the future.

2. Transdermal Thiamine Delivery Systems

The development of transdermal thiamine drug delivery systems, which aim to develop a method for continuous and non-invasive drug delivery, is another new method being used. Some of the drawbacks of traditional drug delivery methods include poor patient compliance, lack of absorption, especially in alcohol abusers and the need for hospitalization.

Patches, microneedles, wearable devices are examples of transdermal drug delivery systems that may help bypass absorption difficulties and provide sustained plasma levels of thiamine for long periods of time. Individuals suffering from malabsorption syndromes, such as post-bariatric surgery or gastrointestinal disease, may benefit most from this method.[87]

Advances in wearable biosensors further support this method. Transdermal alcohol sensors, for example, have already been designed and developed, proving that continuous and non-invasive biochemical monitoring is possible.[88] Similar devices may be designed to measure biochemical indicators or thiamine levels in real time.

In individuals at risk for Wernicke's encephalopathy, such as those suffering from alcohol dependence, where patient compliance to oral thiamine supplements is low, this method may help improve patient compliance. This method is thus in line with WKS's increasing focus on patient-centered and long-term management techniques.

3. Artificial Intelligence (AI)-Based Diagnosis

Underdiagnosis and delayed detection of WKS represent major obstacles in dealing with WKS because conventional clinical characteristics of WKS are often absent or ambiguous. AI-based diagnostic tools are proving to be effective solutions to this problem. Large databases of information, such as neuroimaging results like MRI scans, clinical parameters, biochemical parameters, can be analyzed by machine learning and deep learning algorithms to identify early signs of WKS. MRI scans can reveal unique signs of WKS in the thalamus and mammillary bodies of the brain even though it is not very sensitive (53% sensitivity).[89] AI-based diagnostic tools can improve diagnostic accuracy by better identifying these minute changes.

AI-based neuroimaging diagnostic tools have shown high accuracy in early diagnosis and prediction of disease progression in various neurodegenerative diseases such as Alzheimer's disease.[90] These tools can also be used to diagnose WKS early before any damage occurs to neurons.

In addition, AI can help to develop a risk prediction model by integrating multi-modal data, including test results, trends of drinking alcohol, nutritional condition, which can help clinical decision support systems to alert doctors to begin thiamine therapy as soon as possible, even in unclear circumstances.

In the same way, AI can help to improve the results of personalized medicine, which can reduce morbidity and improve the outcome of cognitive functions in the long run by tailoring the treatment according to the patient's risk profile, genetic predisposition and therapeutic response.

4. Integration with Emerging Therapies

Probably in the future, it will be possible to treat WKS by employing a multi-modal approach that uses state-of-the-art medication delivery methods in conjunction with regenerative and rehabilitative approaches. For example, by stimulating regenerative processes in neurons and synaptic plasticity, stem cell therapy has shown promise in reversing damage to the brain resulting from thiamine deficiency.[91] These approaches might prove beneficial in treating chronic Korsakoff syndrome in combination with nano-formulated thiamine.

Wearable devices and mobile apps are examples of digital health technologies that can aid in early detection as well as monitoring of WKS. These devices can interface with AI systems to provide feedback in real-time, arresting disease progression.[92]

5. Challenges and Future Directions

There are still some hurdles to overcome with the aforementioned promising developments. Clinical validation of transdermal systems, nano-formulations needs to be performed to ensure cost-effectiveness, safety and efficacy. The aforementioned technologies may also need to go through lengthy and complex regulatory procedures.

In the same context, data standards, interpretability, issues such as algorithmic bias and patient privacy must also be addressed for AI-based diagnostic tools. A collaborative approach must be taken by clinicians, researchers and regulatory authorities to incorporate the aforementioned tools into clinical practice.[93]

However, the significance of early diagnosis, specific treatment and patient individualization is increasing for the management of WKS. The impact of the aforementioned debilitating yet avoidable disease may be mitigated with the help of nanotechnology, non-invasive delivery and artificial intelligence.[94]

CONCLUSION

Wernicke-Korsakoff syndrome (WKS) is still a critical neuropsychiatric condition that can be prevented in most cases. This condition highlights the shortcomings of modern healthcare systems. Although the cause of thiamine deficiency is well understood, this condition has always been underdiagnosed, undertreated and not prevented properly. This situation underlines the urgent need for a paradigm shift where pharmacists are at the core of patient advocacy, early detection, prevention and treatment optimization.

The underdiagnosis of this condition, which is attributed to the lack of specific, sensitive diagnostic biomarkers and the heterogeneous presentation of this syndrome, is a significant factor that contributes to the poor outcome of this condition. Only a few patients with this syndrome present with the classic triad of symptoms, which includes disorientation, ataxia and ophthalmoplegia. Therefore, this condition can be underdiagnosed if clinicians rely on these symptoms alone. Studies have shown that delays in diagnosing this condition are common. In fact, patients are often subjected to lengthy examinations before receiving the right thiamine medication. This medication causes irreparable damage to the brains of these patients. In addition, clinicians often fail to recognize the prodromes of thiamine deficiency, especially in high-risk patients with alcohol dependence, malnutrition and cancer.

The lack of defined biomarkers further complicates diagnosis. Cerebrospinal fluid lactate levels, microglial cell activation markers like CD68+ cells and neurotransmitter metabolites are some of the potential markers that have been explored. However, none have gained sufficient clinical relevance and standardization. The need for a high index of suspicion and empirical treatment is further emphasized by the lack of clarity in diagnosis. This is particularly true in vulnerable populations. Pharmacists can play a vital role in the identification of patients who are at risk, can emphasize the importance of thiamine supplementation in drug evaluation and risk stratification.

The role of pharmaceutical monitoring in the management of WKS is significant in this scenario. In the current scenario of varied clinical standards, the role of pharmacists is vital in ensuring that thiamine supplementation is carried out effectively in terms of dose, route and duration. Even though intravenous thiamine is the gold standard in acute settings, its underuse and varied dose regimens indicate that implementation is lacking. This can be bridged by promoting evidence-based practices, monitoring drug response and preventing medication errors.

New technology in the future holds promise in enhancing WKS management by addressing its shortcomings. These include thiamine nano-formulations. Low bioavailability and blood-brain barrier penetration are two shortcomings of conventional thiamine therapy that might cause less than optimal recovery of patients. Stability of drugs in the body, blood-brain barrier penetration, delivery of these drugs to damaged areas of the brain might all be enhanced by using nanotechnology in drug delivery, including liposomes and polymeric nanoparticles. Such enhanced delivery of drugs might greatly improve therapy results because thiamine deficiency is known to interfere with critical enzymatic activities in cerebral energy metabolism, resulting in damage to neurons. WKS therapy might be transformed into proactive therapy by using nano- formulations; however, these formulations are still in experimental stages.

The design of transdermal thiamine delivery devices, which can help to circumvent the major difficulties associated with the oral and parenteral route, is another creative approach. The absorption of thiamine is generally impaired in patients with gastrointestinal symptoms or those with a history of excessive drinking and the compliance rate with the oral medication is still low. The transdermal delivery system, which circumvents the gastrointestinal barrier, improves patient compliance, can provide sustained and controlled delivery of the drugs. In line with the overall goal of preventing the progression of the disease from Wernicke encephalopathy to Korsakoff syndrome, the transdermal delivery system can be useful for long-term prevention and outpatient management of the patients.

The use of AI-based diagnostic instruments in clinical settings is also revolutionary. Neurological images, metabolism-related markers, clinical features are just a few of the numerous, complex parameters that AI can process to identify the earliest and subtlest signs of WKS. AI-based models can potentially lead to the earliest identification and intervention

of WKS because conventional diagnostic instruments like MRIs have low sensitivity and are often used after the beginning of symptoms. AI can also be used to develop risk prediction models by using parameters like co-morbid conditions, alcohol intake and nutritional status. This approach also supports the ideas behind personalized medicine and can lead to the best treatments for patients to achieve favorable outcomes.

Most importantly, a supportive and effective interprofessional collaboration system should be in place to incorporate these advancements. In order to effectively treat WKS, medical professionals like doctors, pharmacists, nurses, dietitians and mental health professionals should work together. In this regard, pharmacists have a vital role to play in bridging different fields by promoting patient-centered care, medication management and continuity of care. In addition to medication management, they also participate in public health campaigns, educational activities and patient compliance to prevent thiamine deficiency in vulnerable populations.

Another important factor associated with a pharmacist-led paradigm involves patient advocacy. This is because some of the groups at increased risk of developing WKS are often characterized by vulnerable groups, including people with financial issues, alcoholism and mental illnesses. These groups are often stigmatized and lack proper nutritional support and access to healthcare services. By educating people about the condition, supplement availability, and harm reduction strategies, pharmacists can play a crucial role. In this case, community pharmacy services provide a unique opportunity for the early management and education of patients.

Despite these developments, there are still some issues that need to be addressed to fully actualize the future of WKS management. Validation, regulatory approvals, cost-effectiveness are important for the transfer of transdermal systems and nano-formulations from the bench to the bedside. Similarly, data collection, validation across different demographics, consideration of ethical issues like algorithm bias and data privacy are important when using AI-based applications.

In other words, the above-mentioned condition of Wernicke-Korsakoff syndrome is just one of the many manifestations of disorders in which the proper and timely treatment of the condition has the potential to prevent the onset of irreversible morbidity. However, the best results are also being hindered by the systemic gaps that are in place. The first step in this process is to fill the gap of underdiagnosis, overcome the dearth of reliable biomarkers, adopt the latest technology in the treatment and diagnosis of the condition. Pharmacists have the opportunity to lead the way in bringing about the kind of revolutionary change in the delivery of healthcare in this ever- changing environment by bridging the gap between the long-term treatment, detection and prevention of the condition.

The way forward in the treatment of the condition of Wernicke-Korsakoff syndrome is through a proactive and technologically advanced approach in the hands of the pharmacist. This has the potential to take healthcare systems closer to the eradication of the condition of WKS and to improving the quality of life of the people afflicted with the condition through the bolstering of pharmacological vigilance and the interprofessional collaboration in the treatment of the condition.

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