Identifying, Assessing, and Treating Korsakoff Syndrome Patients

Updated Perspectives

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Abstract: Objectives consist of updating published reports on the recognition, assessment, and care of patients with Wernicke-Korsakoff syndrome (WKS). Methods included defining relevant terms, describing core clinical phenomena, conducting meaningful reviews for latter-day WKS publications, and selecting instructive case examples. Findings covered epidemiology, precipitants, neuroimaging studies, alternate learning strategies in WKS, adjunctive treatments, and promising research. In conclusion, patients, their family members, clinicians, and public health experts should benefit from this updated knowledge. Countries with substantial alcohol consumption should consider emulating Holland in designating WKS research centers, founding regional clinical facilities, and funding multidisciplinary expert teams.

Key Words: Alcohol use disorder, Wernicke-Korsakoff syndrome, epidemiology of WKS, pathophysiology of WKS, alternate learning methods in WKS, ethics in WKS care

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A century before the European neuropsychiatrists Carl Wernicke (Wernicke, 1881) and Sergei Korsakoff (Korsakoff, 1889) described Wernicke-Korsakoff syndrome (WKS), a fable regarding memory loss spread across central Europe and then North America. In the American version (Irving, 1819–1820), Rip Van Winkle spends 24 years drinking up his inheritance, then relocates to the Catskill Mountains to continue drinking a local beverage. There kinfolk find him 20 years later. Although Rip remembers them and his early life, he has no recall of many interim events such as the Revolutionary War or the first presidential election. In trying to explicate this extraordinary circumstance, people concluded that he had been sleeping over the previous 20 years, explaining his two-decade memory loss.

Wernicke and Korsakoff later published reports on the early course of this remarkable condition, as well as its pathophysiology in brain. WKS began suddenly, often with a period of confusion, and sometimes with ophthalmoplegia-nystagmus or ataxia. Among those dying acutely, small hemorrhages occupied gray matter in the mammillary bodies, an area of posterior-central midbrain subserving recent memory and binocular vision. Sentinel features encompassed thiamine deficiency, retrograde recent memory loss, and life-long anterograde memory loss, often portended by chronic alcohol consumption. The unique, concurrent loss of these two memory functions produced an ever-expanding extinction of event-related recall from WKS onset until death.

Our report updates knowledge on WKS from recent decades. The review emphasizes health-related findings, including changing WKS epidemiology, clinical presentation, rehabilitation, and public health implications. We have drawn on our own cases for clinical examples.

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METHODS

Terminology

"Wernicke syndrome" generally applies to thiamine deficiency without alcohol use; onset may not be remarkable. "Korsakoff syndrome" pertains to thiamine deficiency presaged by chronic alcohol use and acute, florid onset. Korsakoff syndrome patients typically try resuming drinking, rendering their care more challenging. WKS patients manifest such disparate presentations as amnesia (Blansjaar et al., 1992), delirium (Wijnia and Oudman, 2013), dementia (Ridley et al., 2013), encephalopathy (Isenberg-Grzeda et al., 2015), personality disorder (Plutchik and DiScipio, 1974), alcohol withdrawal (Trevisan et al., 1998), trauma (Brion et al., 2001), and psychosis (Ramayya and Jauhar, 1997). WKS patients with alcohol use disorder (AUD) may experience neuropathies, liver failure, esophageal varices, other brain disorders, infections, anxiety-depression, and AUD-related cancers (Westermeyer and Soukup, 2021).

Pathognomonic Signs and Course

WKS cases possess intact "archaic" recall despite the chronic interim amnestic impediments described in Table 1 (Cutting, 1978; Spiegel et al., 2020). Victor's WKS description as affecting memory and learning "out of all proportion to other cognitive functions in an otherwise alert and responsive patient" (Victor, 1989) succinctly captures its most distinctive features. Some observers aver that ataxia, peripheral neuropathy, and ophthalmological signs should be included in the syndrome, since Korsakoff's noted them in his original report 130 years ago (Caine et al., 1997). However, a 2007 study revealed that ataxia occurred in only 23% of acute WKS cases, and extraocular muscle paresis affected only 29% of WKS cases (Sechi and Serra, 2007). Ataxia from AUD-induced cerebellar vermis degeneration can occur independent of amnesia (Akbar and Ashizawa, 2015; Diener et al., 1984). Thus, neuropathies are often absent in WKS, can occur in AUD without WKS, and may remit with treatment while the core amnesias persist.

Thiamine treatment delayed even a day or two can result in partial recovery. If only partial response occurs, continued thiamine treatment and observation over months to a year can reveal slow, incremental recovery with some persisting amnesia. Even partial recovery cannot be assured if delays exceed a week or two, leading to permanent impairment (Thomson et al., 2012).

Immediate WKS recall lasts only several minutes. Factual details related to recent events with emotional recruitment (*e.g.*, a nearby electrical storm) are lost, although conditioned learning may evoke emotional responses to subsequent reminders of the startling event. Obliteration of recent events beyond several minutes undermines WKS patients' ability to chart a safe, secure life alone. Lack of awareness regarding the origins for current circumstances can produce faulty problem solving and dangerous judgments. Patients' responses to WKS disability range broadly, from calm indifference to demanding bullying. Irritability and disinhibition can foster violence (Gerridzen et al., 2018).

Archaic memory events from the person's pre-WKS era remain available, such as names, events, basic arithmetic, and spelling. Recall

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TABLE 1. Intact and Lost Memory Functions in WKS

Chronological Categories Related to Memory (With Usual Time Spans)	Intact and Failed Memory in WKS[a]
Immediate memory (duration: up to several minutes)	Intact: Once past early acute phase, patient functions normally on immediate aspects of mental status and psychometric examination.
Recent memory (duration: longer than several minutes to days) • Sometimes called "short-term memory"	Failed: Memory is lost for recent episodes and events that are personally experienced, plus recent episodes and events reported to patient by others. Memories that fail at this level cannot comprise remote memories.
Remote memory • Intermediate-term (duration: weeks to months) • Long-term (duration: years to decades)	Intact: Pre-WKS-onset memories for events and episodes (both experienced and learned from others) are retained. We refer here to this period as "archaic memory."[b] Failed: Post-WKS-onset memories involving episodes or events are lost, whether from one's own experience or other's reported experience (*i.e.*, nonexperiential learning). Intact: Post-WKS-onset retention may be emotion-related, state-dependent, and/or somatic in nature, rather than semantic or recalled as specific historical events.

[a]Surviving memory functions depends on the areas of brain still intact plus pre-WKS functional level. For example, patients with hippocampal, frontal lobe, or basal ganglia impediments or anatomic loss are not apt to have intact functions related to these areas.

[b]The term "archaic memory"—used for convenience in this manuscript—refers to the intact, pre-WKS-onset memories, which may last for decades depending on how long ago the WKS condition began. Although archaic memory may lapse with disuse over time in WKS, it can also remain rich compared with the limited recall from the patient's post-WKS era.

from archaic memory may become more strongly entrenched if revisited often, or they may be lost over time with disuse. Those who could swim, type, or drive a car before WKS can ordinarily still do so afterward, if they can practice the skill. However, retaining the skill does not guarantee sufficient judgment to use it safely. Earlier vocational training and advanced education can also persist, if practiced. WKS patients can sometimes continue employment in structured, supervised settings. Although mortality was apparently high a century ago, identified WKS patients now survive for years to decades (Sanvisens et al., 2017).

Literature Review

Our review began with a survey of PubMed articles from 1992 to 2020, using single terms (*e.g.*, Korsakoff, Wernicke, amnesia, confabulation, and thiamine) plus adjunctive terms (*e.g.*, ethanol, alcohol, neurotoxicity, and neuropathology). This led to 415 PubMed references, supplemented by 32 reports from our personal files, and another 8 articles obtained from the references, for a total of 455 references. We copied 142 manuscripts for further gleaning; 56 of these reports are cited here. We consulted a research librarian (see *Acknowledgment*) because our original search suggested that certain European journals, subspecialty journals, and recent articles available online might produce additional reports. This effort led to an additional 92 manuscripts (total 577), of which we obtained 76 copies (total 218). This process led to 33 additional citations (total 89).

ORIENTATION TO WKS DIAGNOSIS

Diagnosis and Assessment

WKS recognition in clinical practice depends heavily on first considering the diagnosis and then on extensive clinical skills (Wijnia and Nieuwenhuis, 2011). Attending clinicians must devote time and ingenuity obtaining relevant information. Establishing a working WKS diagnosis requires history going back decades, mental status examination covering several cognitive realms, collateral sources of information, attempting to elicit confabulation, and performing a neurological examination—all in a potentially uncooperative patient. Screening for disorders besides AUD encompasses drug and nicotine dependence, eating disorders, behavioral addictions (*e.g.*, pathological gambling), and anxiety-mood disorders. Table 2 lists examinations and scales used for WKS evaluation, monitoring, and research. Identifying retained and

TABLE 2. Methods Relevant to WKS Studies and Clinical Evaluation

Method	Reference
Comparison groups: WKS patients versus others	
Normal controls	Pitel et al., 2009; Reed et al., 2003
AUD patients, uncomplicated	Brion et al., 2018a; Sullivan et al., 2000
Non-AUD Wernicke patients	Sullivan and Pfefferbaum, 2009
Lesions mimicking WKS amnesia	Rahme et al., 2007
Neuroimaging techniques	
Comparing regional metabolism	Reed et al., 2003
Computed tomography	Sullivan and Pfefferbaum, 2009
Diffusion tensor imaging	Nikolakaros et al., 2018
Fluorodeoxyglucose PET	Reed et al., 2003
Third ventricle volume	Visser et al., 1999
Volumetric magnetic resonance imaging analysis	Reed et al., 2003; Sullivan et al., 2000
Psychometric instruments	
Alcohol flanker test	Brion et al., 2018b
Autobiographical memory	El Haj and Nandrino, 2017; Robin et al., 2020
Clock angles spatial imagery	Robin et al., 2020
Learning tasks	Gorden and Zrull, 1991; Pitel et al., 2009
Montreal Cognitive Assessment	Oudman et al., 2014
Neuropsychiatric Inventory	Gerridzen et al., 2019
Patient Competency Rating Scale	Gerridzen et al., 2019
Tall/wilder visual imagery	Robin et al., 2020
Trail making A and B tests	Nikolakaros et al., 2019
Wechsler memory scale–III	Nikolakaros et al., 2019
Wisconsin card sorting test	Nikolakaros et al., 2019
Sociometric instruments	
Pattison Intimate Social Network	Favazza and Thompson, 1984; Westermeyer and Neider, 1988
Neurotransmitter studies (with controls)	
Choline/TMS relationship	Nardone et al., 2010
Rivastigmine	Luykx et al., 2008

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lost brain capacity lays the foundation for rehabilitation. This following case exemplifies today's challenges in recognizing and caring for WKS.

> *"A divorced, domiciled, pensioned man in his 50s had used alcohol heavily since adolescence, with periodic abstinence for detoxification, brief incarceration, hospitalization, and AUD treatment. He had graduated from high school, spent several years in military service, married, and held responsible jobs until his 40s. Over the previous year, police and ambulance services repeatedly brought him to several emergency departments (EDs) in the community, which then discharged him to the street or temporary shelters. On his first visit to our ED, the ambulance attendants reported his numerous ED visits and several brief hospitalizations over the previous year; the patient could recall none of these events. The ED physician admitted him, and a staff physician sought us for an addiction consultation. Ward nursing staff reported his repeatedly asking where he was. On interview, he provided detailed information regarding his life before 1 year ago. Despite several weeks of abstinence from alcohol, healthy nourishment, and parenteral high-dose thiamine, his anterograde and retrograde memory deficits remained."*

Differential Diagnosis of Memory Loss in AUD

WKS represents one of several alcohol-related and nutritional sources of amnesia (Cutting, 1978). These diverse conditions differ greatly in their pathophysiology, symptoms, signs, course, and outcome.

- Transient, reversible "blackout" amnesia accompanies heavy binge drinking, can begin early in AUD, and clears with some hours of abstinence.
- Memory loss associated with executive dysfunctions and disinhibition suggests frontal lobe atrophy, often occurring later in AUD or postfrontal trauma.
- Progressive all-sphere dementia from pan-cortical atrophy may resemble Alzheimer dementia, but beginning at an earlier age.
- Localized brain lesions can arise from alcohol-related complications including trauma, infection, cancer, and cardiovascular disorder.
- Nutritional deficiencies, especially other vitamin B or C or protein deficiency, can present with signs or symptoms overlapping with WKS (*e.g.*, pellagra, scurvy).

Medications for psychosis, alcohol withdrawal, depression, anxiety, and Alzheimer dementia do not alleviate core WKS dysfunctions. Still, other central nervous system conditions may co-occur with WKS, generating indications for these medications (Westermeyer and Soukup, 2021).

Confabulation as Adaptation

Korsakoff syndrome patients can become adept at filling memory gaps in recent and remote memory. Asked about pseudoevents earlier in the day, they may endorse the events and add pseudoinformation or falsely reported sensory perceptions. Eventually, WKS patients spontaneously cease confabulating in sensory spheres. However, they may continue confabulating conceptually to explain events for which they are amnestic—especially AUD patients accustomed to explaining brief "blackout" memory lapses. Those patients trained to cope with their WKS disability may in time respond, "I cannot remember that situation due to my memory problem." Eventually, those in the person's immediate environments should cease asking questions to which the WKS person cannot accurately respond (and may then revert to confabulating). As people around the patient stop provoking confabulation, WKS patients typically stop practicing it.

LITERATURE SEARCH REVIEW

Epidemiology: WKS Rates and AUD Comorbidities

WKS annual mortality studies have depended upon autopsy findings of hemorrhage into the mamillary body midbrain area. An Australian study based on 2212 sequential autopsies, conducted among decedents aged 15 years and older over a 2-year period, revealed 25 cases, or 1.1% of all deaths (Harper et al., 1998). Among the 25 cases, only four people (16%) had been diagnosed while alive, indicating extreme WKS underdiagnosis. Importantly, the 1.1% WKS rate had decreased from 2.1% a decade earlier, when thiamine-supplemented bread became mandatory in Australia (Harper et al., 1989). Earlier European and Australian WKS mortality rates in the mid-1990s, also based on autopsies, ranged from 0.4% to 2.8% in alcohol-using countries (Harper et al., 1995). Around the same time, clinical investigators in the Netherlands (Kok, 1991) and Scotland (Ramayya and Jauhar, 1997) reported upsurges in the WKS clinical prevalence rates.

In 2010, expert AUD clinicians from several European countries estimated their national lifetime WKS prevalence rates among people with AUD—a difficult rate to determine, as it is based on indirect future extrapolations from current and past demographic and epidemiologic data. They estimated that WKS affected approximately 10% of heavy drinkers (Galvin et al., 2010). Since the mid-1990s, age-specific WKS rates have peaked among older people aged 55 to 75 years (Van Dam et al., 2020). Increased per-capita alcohol consumption among middle-aged and elderly people worldwide has raised concern regarding rising WKS incidence rates with advancing age (Blazer and Wu, 2011), especially among middle-class drinkers (Wong et al., 2007).

Recent neuropsychiatric studies have compared "WKS + AUD patients" and "non-WKS AUD-only patients." These useful studies have shown that the two groups show comparable rates of affective prosody (Brion et al., 2018a), executive dysfunction (Brion et al., 2014), impaired spatial and visual imagery (Bermejo-Velasco and Ruiz-Huete, 2006; Robin et al., 2020), and amnesia for specific earlier life events (Pitel et al., 2009). These findings indicate that certain AUD brain comorbidities may affect WKS patients in rates similar to matched AUD patients without WKS.

Precipitants

Occasional cases of WKS syndrome seem to begin gradually outside of clinical observation, with no apparent precipitants. In mass outbreaks of Wernicke syndrome—for example, among prisoners-of-war and fleeing refugees—other signs and symptoms may occur in addition to amnesia (*e.g.*, fatigue, apathy, high-output beriberi congestive heart failure). WKS onset in AUD patients commonly involves precipitants that exhaust marginal thiamine stores, resulting in mitochondrial dysfunction, impaired cell oxidation, and decreased neural energy (Thomson et al., 2012). Common precipitants, each with characteristic presentations, include the following:

- Severe alcohol withdrawal, such as delirium tremens (Brion et al., 2001);
- Severe sepsis, pneumonia, urinary tract infections (Wijnia et al., 2016);
- Organ failure, for example, pancreas, liver, heart, kidneys (Wijnia et al., 2016); and
- Tissue trauma, for example, surgery, head injury, fractures (Brion et al., 2001).

The common pathways by which these diverse maladies affect thiamine are unclear. However, alcohol withdrawal increased the cortisol levels in one study conducted during "medically assisted" withdrawal treatment (Keedwell et al., 2001). Compared with controls, the mean area under the curve cortisol levels in nine AUD patients exceeded levels in normal controls by 5.3 times on day 1, descending to 3.0 times on day

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7 ($p < 0.001$). More severe withdrawal produced a trend for greater cortisol levels.

Neuroimaging Studies

Fluorodeoxyglucose PET research has shown mammillary body hypometabolism during WKS syndrome (Reed et al., 2003), with widespread hypermetabolism occurring in nearby white matter. These findings suggest cell death in recent memory storage areas with compensatory axonal activity. Volumetric magnetic resonance imaging (MRI) analyses demonstrated atrophy not only in mammillary bodies but also in other thalamic areas and frontal lobes. WKS studies (Sullivan et al., 2000; Sullivan and Pfefferbaum, 2009; Visser et al., 1999) plus studies of non–alcohol-related neurological conditions mimicking WKS amnesia (Kahn and Crosby, 1972; Rahme et al., 2007) have revealed numerous other lesions, that is, thalamic nuclei, pons, frontal lobe, cingulate cortex, hippocampus, amygdala, cerebellum, and fornix. Lesions in these areas may exacerbate or mimic mammillary body lesions. In addition to thiamine deficiency, WKS-like amnesia has accompanied the following conditions:

- Localized brain lesions due to vascular (Rahme et al., 2007), neoplastic (de Falco et al., 2018), and traumatic lesions (Brion et al., 2001; Kahn and Crosby, 1972);
- Malnutrition associated with general cachexia from starvation (DeWardener and Lennox, 1947), pellagra and thiamine deficiency beriberi (Di Marco et al., 2018), and psychogenic food refusal (Hargrave et al., 2015);
- Gastrointestinal malabsorption and fluid problems due to gastric bypass and gastrointestinal malfunction (Fandiño et al., 2005), celiac disease (Sahu et al., 2020), excessive protein pump treatment (Miyanaga et al., 2020), and hyperemesis gravidarum (Ashraf et al., 2016); and
- Cancer with low serum thiamine, low oral intake, weight loss, and gastrointestinal and hematologic malignancies (Isenberg-Grzeda et al., 2016).

Alternative Means of Learning

Intact Brain Functions

The sentinel learning deficit in WKS involves recall of events, also known as episode amnesia (Pitel et al., 2009). These episodes or events fail to register in short-term memory stores after WKS onset—a liability that prevents the selective entry of new events and semantic information into long-term memory. Therefore, before launching into extensive rehabilitation, clinicians serving WKS patients obtain multidisciplinary assessments to identify intact versus damaged brain structures and functions. Depending on the patient, these assessments might include consultations with neurology, neuroimaging, neuropsychology, primary care, addiction psychiatry, addiction nursing, and psychosocial rehabilitation (Van Dam et al., 2020).

> "*A WKS patient with extensive frontal lobe vascular damage required 1 year of behavioral therapies to address addictive behaviors besides AUD (e.g., pathological gambling, online pornography, nicotine dependence). Another WKS patient with earlier Agent Orange exposure had extensive basal ganglia lesions, parkinsonian tremors, and parkinsonian-gait ataxia. He responded to antiparkinsonian medications and physical therapy for his gait. Both patients have since lived at home with their families for several years.*"

After adequate assessments have been completed, with strengths and deficits identified, a treatment team can plan appropriate, often staged interventions. The latter rely extensively on language-free approaches, such as emotional arousal, state-dependent paradigms, and other approaches that typically remain operational in WKS.

Operant Conditioning

The link between a causal behavior and its consequential effect underlies operant conditioning. Addiction processes follow the principles of operant conditioning (Koob, 2017), which usually survives WKS onset and can contribute to learning, adaptation, and recovery from addiction. People with WKS rapidly learn the location of bathrooms in buildings, heated areas in cold weather, and places to rest after strenuous activity. Caregivers can foster operant learning by observing what pleases the WKS patient.

> *"A WKS patient enjoyed the hospital cafeteria where his quarterly clinic visits occurred. He could locate the cafeteria from most areas of the building. His spouse could find him in the cafeteria if they became separated during the day."*

Classical Conditioning

This method involves pairing a natural reward to a desirable new behavior (O'Brien et al., 1992). The new behavior may be desired by the patient, family, or caregiver. For example, breakfast may be available for a reasonable period after a morning alarm, to establish daily schedules and avoiding oversleeping, or an after-dinner treat for clearing the table and helping to clean up can elicit participation in household chores.

> *"A WKS patient who owned rental property had enjoyed making repairs and upgrades to his property prior to WKS onset. Post-WKS-onset, he started three complex projects, each of which led to a large mess and expensive repairs when he could not complete them. Subsequently, his spouse hired skilled workman to undertake challenging projects. The WKS spouse happily served as an assistant in the process, anticipating the tools and supplies that workmen needed and assisting with clean-up. Paired with a teenaged grandson, the spouse was able to undertake simpler, repetitive chores, such as repairing a fence or doing gardening chores."*

Aversive Conditioning

This approach involves negative or unpleasant consequences linked to unhealthy or dangerous behavior. For example, WKS patients, despite their grave disability, can be amazingly persistent and creative in pursuing alcohol and other addictions. Access to even small, infrequent volumes of alcohol can goad WKS patients to devote time and ingenuity to this pursuit, with painful consequences.

> *"Within weeks of onset, a WKS patient began creatively collecting funds to purchase alcohol. He saved church and hospital Bingo winnings, searched furniture cushions for loose change, took coins from unattended purses, and spent a family coin collection. The attending physician and the patient's legal guardian (his spouse) agreed to administer monitored disulfiram on a daily basis, beginning after they informed the patient and providing him with written materials. Although he agreed to the intervention, he forgot the details and tried drinking. Since that single alcohol-disulfiram reaction, he has not attempted alcohol use during the intervening decade."*

Metronidazole, an antiprotozoal drug that produces a milder acetaldehyde reaction, can be used in patients whose health contravenes disulfiram use.

Ethical analyses must be considered in aversive conditioning to ensure that the goal is recovery and not punishment, with reasonable risk and equity (Sullivan et al., 2008). Bioethical committees in clinical settings can help in addressing these concerns and devising a humane conditioning protocol. When caretakers fail to interrupt alcohol use, WKS patients usually enter a crisis-ridden period ending in liver failure within a few years.

Contingency Contracting

Contractual agreements can entail a therapeutic exchange between a patient and a friend, relative, spouse, or employer (Sullivan et al., 2008).

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For example, a family might shelter an alcohol-addicted member willing to take monitored disulfiram daily. The federal government can assign payment of federal pension funds through a representative payee, who ensures that alcohol or drug purchases do not replace expenditures for food, shelter, and clothes.

Errorless Learning

Training so as to prevent learning errors has been helpful in learning disabilities. This approach requires extra time and nuance, but it reduces negative corrections and provides more pleasant learning experiences. It has helped WKS patients with nonsemantic learning (Rensen et al., 2019).

Affective Recruitment

Pairing affective responses with successfully achieving learning objectives is key to this approach. It does not favor new learning if the same positive outcome occurs regardless of the patient's behavior. Emotional experiences can assist WKS patients in learning to distinguish categories (Labuddha et al., 2010). Social network support for abstinence has facilitated recovery in non-WKS AUD (Galanter et al., 1990) and appears therapeutic for WKS patients.

Schedules, Structures, and Keeping on Track

WKS patients retain the ability to read and comprehend written material, despite inability to retain new semantic materials. The key lies in enabling them to access an external data source when anxious or confused. For example, providing a daily schedule can reduce caregiver burdens imposed by repeated questions regarding "what comes next." Bulletin boards, smart phones, or iPads can help patients implement a daily plan. WKS survivors become motivated by rewarding outcomes when checking the daily plan (*e.g.*, obtaining lunch) and driven by negative outcomes when not consulting them (*e.g.*, missing lunch). These resources can also help WKS patients manage unexpected problems (*e.g.*, becoming lost).

Becoming lost comprises a common WKS problem, which caregivers can address by using structure, schedules, and anticipation. The following case exemplifies how some WKS patients become rigid homebodies and how to reverse this dilemma.

> *"A man with recent-onset WKS walked away from his family's newly acquired residence. He wandered through the night into a forested rural area. He was found several miles away from home, dehydrated, with scratches and torn clothes. Although unable to describe his experience, he subsequently became anxious away from home. As a vehicular passenger on a shopping trip or clinic visit, he became visibly agitated and shouted every several minutes 'Where are we? Where are we going?' Responses to these queries reassured him for some minutes until the reassurance slipped from his immediate memory. The resolution lay in providing him before each trip with 1) the destination and rationale for the current trip and 2) a map with the route denoted. Over time, these documents relieved his anxiety with assuring reorientations to his location, the destination, and the purpose for the trip."*

The following vignette, observed years apart in two patients from different states, epitomizes the panicky "flight" scenario that can erupt in lost WKS patients.

> *"Family caretakers of two employed WKS patients eventually allowed them to drive alone to and from work, after having ensured that they could drive safely along the same route. This system worked for years until road repairs resulted in detours off the usual route. Each man became lost but continued driving through the night until they ran of fuel. The next day, police located each stranded man over a hundred miles from home."*

Helping WKS patients to avoid becoming lost requires strategic planning. The plan might involve a cell phone, a list of instructions, or localizer-transmitters manufactured for trekkers who might become lost. Caregivers can limit such crises by considering how their WKS relative or patient might use their still partially intact but amnestic brain to manage various problems, along with access to printed materials and modern technology. Experienced caregivers, once oriented to alternative learning principles, may acquire dependable intuitions on such matters. Predictably, a longitudinal study has shown that WKS patients do better in small-scale, individualized, homey residences than in large, more impersonal hospitals or boarding institutions (Cutting, 1978).

Calendars and Smart Phones

Chronological and geographic aids have improved WKS patients' management skills and functionality (de Joode et al., 2013; Lloyd et al., 2019). Time, effort, training, and on-going technological support are needed to achieve practical computer-based utility. Modern technologies can facilitate the constant supervision so often needed, while alleviating the spatial and temporal constraints that can restrict WKS patients and their caregivers.

Day Programs

Attendance at day programs can aid rehabilitation for AUD patients facing major life changes (Favazza and Thompson, 1984). Day programs likewise enable WKS patients to expand their daily routines, adapt to another place and different activities, and reexpand their intimate social network back toward normal (Westermeyer and Neider, 1988). These forays involve trying out new emotion-challenging roles (*e.g.*, reading a newspaper to the group, preparing or serving a meal, leading chair exercises). Programs range from 2 to 6 hours daily, and from one to several sessions weekly.

Our WKS patients have done well in day programs designed for other diagnostic groups, such as Alzheimer dementia or Parkinson disease. WKS patients can rely on other patients for recent memory support, while contributing abilities that other patients lack. Day programs can replicate the multigroup affiliation of intimate social networks that are central to human well-being (Pattison, 1977) and to AUD recovery (Gorden and Zrull, 1991). Programs also relieve primary caregivers from constant supervisory duties and burnout.

Adjunctive Treatments

Neural Transmission

Rivastigmine, a cholinergic medication beneficial in some dementias, has not been effective in a controlled study of WKS patients (Luykx et al., 2008). Transcranial magnetic stimulation has not been correlated with cholinergic activity in WKS syndrome, suggesting that reduced choline does not cause WKS's amnesia (Nardone et al., 2010). Antidepressants and other medications can relieve depression, anxiety, Parkinson disease, Alzheimer dementia, psychosis, or insomnia associated with WKS, but they do not relieve uncomplicated WKS amnesia.

Alcoholics Anonymous

Wernicke syndrome and Korsakoff syndrome patients share certain core brain lesions, but they do not share previous addiction. Familiarity with both Wernicke and Korsakoff syndromes can abet clinicians who treat either disorder. Our Wernicke cases consisted of refugees, combatants, and prisoners of war encountered in Asia and Minnesota (Westermeyer, 1982; Westermeyer, 1989; Williams and Westermeyer, 1986). By definition, Wernicke syndrome patients do not typically require intervention for AUD. Therein lies an enormous difference.

Korsakoff syndrome patients can cathect readily to AA groups. Using their intact archaic memory, they can identify with AA members who have similar life experiences. AA affiliation can contribute another

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group to the WKS patient's recovery-oriented social network (Hall and Nelson, 1996). Orienting the sponsor and the AA group to WKS pathophysiology (see Table 1) helps to understand and relate to their WKS member.

Avoiding AUD Recurrence

Some families and guardians erroneously believe that memory losses erase addiction from the WKS brain. Others aver that their relative "deserves a drink now and then" after years of sobriety. More malignant motivations may emerge if an inheritance is involved.

> *"A married man continued working for several years following onset of WKS syndrome. During that time, he received monitored disulfiram treatment, but no AA or other recovery interventions. When he reached retirement age, his wife and adult offspring discussed his resuming alcohol use, believing that they could limit his intake to one standard drink daily. Contrary to their expectations, the patient began obsessing about alcohol and finding means to obtain it. He died 2 years later from liver failure."*

> *"A single man was placed in an abstinence-oriented adult foster home following diagnosis of WKS syndrome. The patient requested that his court-appointed guardian transfer him to a program where he could resume drinking. His guardian ignored clinical recommendations and approved transfer to a 'wet' setting, where the patient received a cash sum weekly and was permitted to leave the premises to purchase beverage alcohol. He resumed daily drinking and died within 1 year from bleeding esophageal varices and liver failure."*

Courts handling WKS cases might consider appointing two guardians, one for person and the other for property, so that these interests can be separated, monitored, and arbitrated when necessary. Courts can add convenances for vulnerable adults at mortal risk to self and others if readdicted.

Comorbid Brain Conditions

Additional brain lesions in WKS may ensue from falls, fights, obstructive sleep apnea, alcohol-drug overdoses, disuse atrophy of neglected brain centers, infections, and neoplasms. Among 63 hospitalized WKS patients, 13 (or 21%) also had alcohol dementia (Cutting, 1978). A 2-year longitudinal study demonstrated that WKS-only patients maintained stable cognition and function over time, whereas Alzheimer and vascular dementia patients with WKS experienced progressive decline (Oslin and Cary, 2003).

WKS Research

Unique aspects of WKS pathophysiology present opportunities for creative research. One team compared two autobiographical interviewing methods to facilitate optimal assessment in WKS versus controls (Rensen et al., 2017). The two methods did not differ within the WKS subsample, although differences did exist between WKS patients versus controls.

Surgical decompression of supracellar masses producing acute WKS syndromes in four patients rapidly reversed the syndrome (Savastano et al., 2018), enhancing knowledge regarding WKS pathophysiology. A translational rodent model showed neuroanatomical substrates for memory loss resembling, although not wholly replicating human WKS (Savage et al., 2012). A European center found that WKS patients started on supplemental vitamin D within the previous year had a higher cancer rate than other WKS patients at $p < 0.011$ (Wijnia et al., 2019). Logistic regression analysis further revealed that tobacco smoking and length of stay significantly increased the odds ratios for cancer in WKS patients (respectively, odds ratio = 2.74 and 1.68). An in vitro study of cancer cells indicated that, after hypoxic stress, supplemental thiamine increased cancer cell growth—an effect that may theoretically be reversed by cell-permeable antioxidants (Jonus et al., 2018). The ability to conduct ethical studies among large numbers of WKS patients has begun to guide their treatment.

Clinical and research protocols increasingly use specific test batteries for WKS (see Table 2). Some tests have shown minimal or no pathology in some WKS cases; the Montreal Cognitive Assessment is an example. Such exploratory work holds promise for improved understanding and care of WKS patients.

DISCUSSION

Historical Changes

Underdiagnosis of WKS poses a worldwide problem today (Barata et al., 2020; Donnelly, 2017; Nikolakaros et al., 2018; Sechi and Serra, 2007; Wijnia et al., 2014). The Australian autopsy study suggests that 80% to 90% of WKS decedents are not identified premortem (Harper et al., 1998). Clinicians miss WKS diagnoses among patients presenting to privileged settings where AUD and WKS are not anticipated (Isenberg-Grzeda et al., 2012; Westermeyer and Soukup, 2021). In addressing this issue, Holland furnishes an outstanding model, with a national WKS research center (Wijnia et al., 2016), regional clinical centers (Gerridzen et al., 2021), and world-class experts in several fields of WKS study and service (Wijnia et al., 2014).

If the life-time WKS incidence were 1% and their mean survival time was one decade, then the 331 million people living in the United States during mid-2020 would produce 3.3 million WKS cases and 33.1 million years of WKS morbidity over their lifetimes. Although these data are not based on known information, neither are they exorbitant based on extrapolations from Australia and Europe.

Limitations, Implications, and Opportunities

Without sufficient epidemiological understanding, targeted health planning remains stymied. Several health measures suggest a serious and evolving problem worldwide in countries like ours. These data include increasing alcohol consumption among middle-class people aged 50 to 70 years and case reports of missed diagnoses in otherwise first-class medical facilities. The stigma associated with AUD can sway many people toward secrecy even when the diagnosis is known.

Training in WKS prevention, early diagnosis, and timely care needs to expand into the several disciplines that nowadays provide acute health care for AUD patients, that is, nursing, social work, psychology, physician assistants, police, and jail guards. Within clinical services, instruction on WKS prevention and care should involve emergency departments, consultation-liaison services, anesthesiology, surgical specialties, infectious disease and gastroenterology medicine, neurology, psychiatry, and addiction medicine (Barata et al., 2020; Donnelly, 2017; Donnino et al., 2007). Perhaps most heartrending, every new case of WKS syndrome creates a costly tragedy that could have been prevented by timely administration of a vitamin.

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DISCLOSURE

The authors declare no conflict of interest.

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